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SYNTHESIS AND AMINOMETHYLATION OF IODINE-CONTAINING TRIAZOLE DERIVATIVES

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Abstract: Four iodine-containing triazolethiones and two iodine-containing triazolones have been synthesized from 2-(3-methoxyphenyl)acetic acid and 2-(3,4-dimethoxyphenyl)acetic acid through a reaction sequence. In the first stage, the aromatic ring of these starting materials was substituted with iodine using *N*-iodosuccinimide as iodination agent, then the acids were converted into the corresponding esters, which were next transformed into the related hydrazides. Reaction of these two hydrazides with phenyl isothiocyanate and with allyl isothiocyanate led to the expected thiosemicarbazides, which afforded triazolethiones upon cyclocondensation using KOH. Similarly, reaction of these hydrazides with phenyl isocyanate followed by ring closure of the intermediate semicarbazides yielded triazolones. Mannich reaction of triazolethiones with morpholine as the amine reagent provided access to the N^1-aminomethylated iodine-containing triazole derivatives with good yields.

***Keywords*:** Iodination; Ring closure; Triazolethione; Aminomethylation; Mannich base

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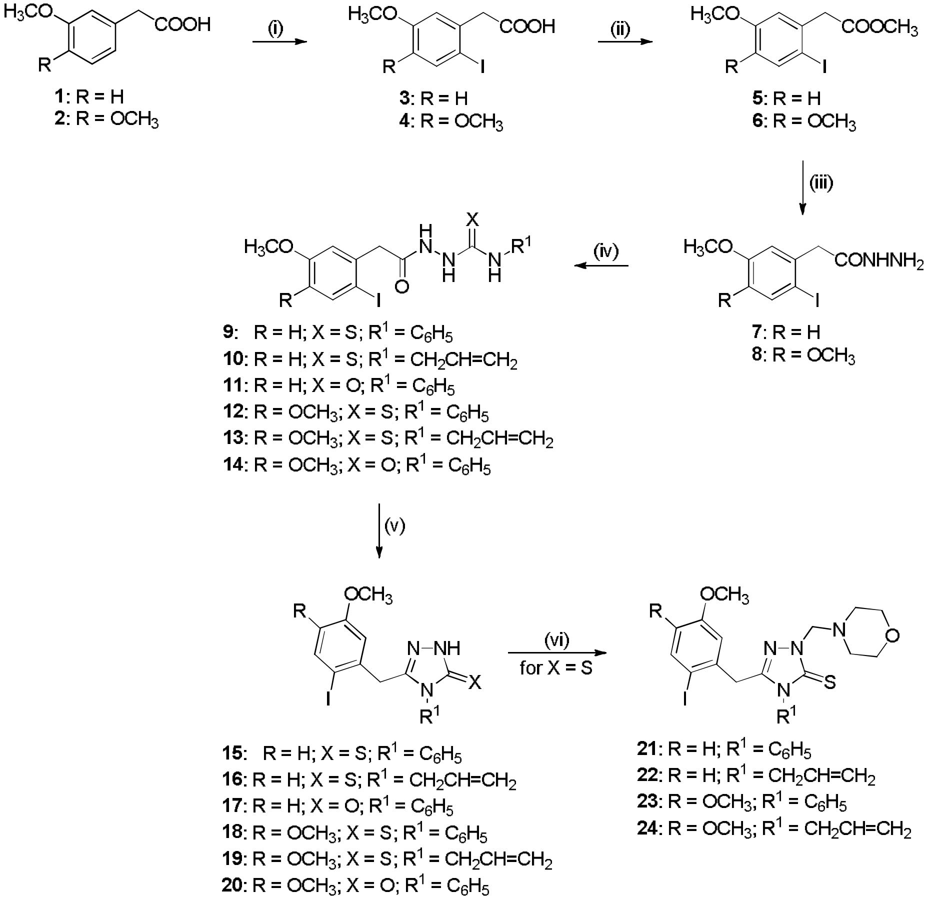
Introduction

The triazole ring, either as 1,2,3-triazole or its isomer 1,2,4-triazole, can be identified as a core structural feature in a large number of biologically active compounds with antimicrobial, anti-inflammatory, analgesic, antiepileptic, antiviral, antineoplastic, antihypertensive, antimalarial, local anesthetic, anti-anxiety, antidepressant, antihistaminic, antioxidant, anti-tubercular, anti-Parkinson's, anti-diabetic, or anti-obesity activity.[1] Their particular physicochemical properties (such as weak basicity, diverse polarity, significant dual hydrogen bond acceptor and donor capabilities, along with their metabolic stability, metal-binding capacity, ability to mimic various functional groups such as amides and esters or to act as less lipophilic bioisosters to phenyl or homologous azines) make them attractive for drug design and development.[2] A particular type of triazole derivatives is represented by 3,4-disubstituted-1,2,4-triazole-5(4*H*)-thiones (commonly referred to as triazolethiones), whose significant contribution to medicinal chemistry can also be gleaned from the large number of reports on this topic, many of these compounds being mentioned in reviews[3-9] that have been published within the last decades. In particular, this specific type of 1,2,4-triazoles have been recently reported in a number of studies describing their anti-diabetic potential,[10] fungicidal,[11] antimicrobial[12] or anti-*Mycobacterium*[13] profile, anti-inflammatory action,[14] anticancer activity through inhibition of human epidermal growth factor receptor[15] or of sirtuins[16] as target proteins, their efficiency in the treatment of toxoplasmosis,[17] or their inhibitory activity toward various enzymes such as butyrylcholinesterase,[18] α-carbonic anhydrase of *Helicobacter pylori*,[19] influenza neuraminidase,[20] VIM-type metallo-β-lactamase,[21] or protein DCN1 (Defective in Cullin Neddylation 1) involved in pathological cardiac remodeling.[22] The related oxygen-containing analogs (3,4-disubstituted-1,2,4-triazole-5(4*H*)-ones, trivially known as triazolones) have also been reported to be useful in cancer therapy through their inhibitory activity of chemokine receptor 2,[23] or as hybrids obtained from conjugation of an androgen receptor antagonist with a heat shock protein 90 inhibitor that may improve the therapy of castration-resistant prostate cancer,[24] or as inhibitors of dihydroorotate dehydrogenase in the treatment of acute myelogenous leukemia,[25] or as binders to bromodomain-containing protein 9 with very good passive permeability profile and significant selectivity profile towards leukemia cells.[26] 1,2,4-Triazolones have also been found to act as agonists of peroxisome proliferator-activated receptor α with efficiency in nonalcoholic fatty liver disease,[27] to present anti-HIV-1 activity comparable to known non-nucleoside reverse transcriptase inhibitor drugs,[28,29] or to exhibit synergism with fluconazole toward resistant *Candida* strains owing to dual inhibition of heat shock protein 90 and histone deacetylase.[30]

A large number of 1,2,4-triazolethiones and 1,2,4-triazolones have been synthesized so far, the structural diversity in this class of compounds deriving primarily from the nature of the organic moieties at positions 3 and 4 of the triazole ring. A search of the literature has revealed that the information on such compounds having at least an iodo substituent in the aforementioned organic residues is quite limited, with only a handful of compounds that are dispersed in a few reports.[31–33] Therefore, we have set out to prepare a small library of iodine-containing 1,2,4-triazoles using synthetic approaches commonly employed for the generation and chemical modification of 1,2,4-triazolethiones and 1,2,4-triazolones.[34]

Results and Discussion

One of the reaction sequences that are usually employed to prepare 1,2,4-triazolethiones and 1,2,4-triazolones from simpler compounds uses either a carboxylic acid or a derivative (such as an ester or an acid chloride) as starting material, while a N^1,N^4-disubstituted (thio)semicarbazide is the open-chain key intermediate that leads to the desired triazole derivative under suitable ring closure conditions.[34] With a view to synthesize hitherto unknown iodine-containing 1,2,4-triazolethiones and 1,2,4-triazolones, less common, preferably not commercially available, yet easily accessible iodo-substituted carboxylic acids were central to this endeavor. As direct iodination is particularly facile in the case of electron-rich, activated aromatic substrates,[35,36] two methoxy-substituted phenylacetic acids (**1**) and (**2**) have been chosen as starting materials (Scheme 1). However, iodine is a rather poor electrophile, and it requires activation by an oxidant in order to perform well in aromatic iodination.[37] Alternatively, the use of *N*-iodoamides (a type of iodination agent where iodine has a more electrophilic character) in combination with strong protic acids affords good results even in the case of mildly deactivated aromatic substrates.[38] Therefore, 2-(3-methoxyphenyl)acetic acid (**1**) was reacted with an equimolar amount of *N*-iodosuccinimide in acetonitrile in the presence of trifluoroacetic acid (Scheme 1). Inspection of the progress of iodination by thin layer chromatography showed that unreacted substrate was still present after eight hours, but the reaction reached completion after 24 hours. According to NMR analysis of the solid material that had been isolated from this process, iodination of acid (**1**) under these conditions afforded a mixture of the 2-(2-iodo-5-methoxyphenyl)acetic acid (**3**) as the major component and an isomeric iodine-substituted 2-(3-methoxyphenyl)acetic acid as the minor component. Considering the orientation effects of the substituents in the aromatic ring, it was hypothesized that the minor component is 2-(4-iodo-3-methoxyphenyl)acetic acid, and this hypothesis was confirmed by the analysis of the NMR spectrum of the mixture, which presents a set of signals for this compound that is typical for a 1,3,4-trisubstituted phenyl ring (one doublet of doublets, and two doublets having different coupling constants). The ratio between the isomers varied slightly in the three distinct experiments conducted for the iodination of acid (**1**) using this method, but the content of the minor component was always lower than 10 %. Given its low content in the mixture of isomers, 2-(4-iodo-3-methoxyphenyl)acetic acid has been removed conveniently and in an inexpensive manner through recrystallization from 2-propanol of the crude solid material. The proton spectrum of the pure acid (**3**) presents three sets of signals in the aromatic region, whose initial assignment to the three corresponding protons based on their distinctive splitting pattern was later confirmed using correlation spectroscopy. The “heavy atom on light atom effect” of iodine reflects in the carbon NMR spectrum of acid (**3**) through the presence of a resonance signal for the carbon atom directly attached to iodine at 90.1 ppm.



Scheme 1. Reaction sequence leading to iodine-containing triazole derivatives. Reaction conditions: (i) *N*-iodosuccinimide, trifluoroacetic acid, acetonitrile, rt, 24 h; (ii) methanol, $SOCl_2$, rt, 3 h for acid (**3**) or 24 h for acid (**4**); (iii) hydrazine hydrate, 2-propanol, reflux, 4 h; (iv) phenyl (or allyl) isothiocyanate, 96 % ethanol, reflux 1 h, or phenyl isocyanate, tetrahydrofuran, reflux, 1 h; (v) KOH, distilled water, reflux, 3 h; (vi) morpholine, 36 % aq. formaldehyde, ethanol, rt, 2 h, then reflux, 1 h.

Next, iodination of 2-(3,4-dimethoxyphenyl)acetic acid (**2**) was examined under the conditions previously established for the reaction and isolation of the crude product in the iodination of 2-(3-methoxyphenyl)acetic acid (**1**) (Scheme 1). This approach provides a very good yield of a crude product that was devoid of any isomeric iodine-substituted by-products, making it suitable for use in the next step without purification. The proton and carbon spectra of acid (**4**) are in agreement with the literature data,[39] thus confirming its identity.

For the conversion of acids (**3**) and (**4**) into the corresponding esters (**5**) and (**6**), a variant of the Fischer–Speier esterification in which thionyl chloride is employed for the *in situ* generation of the hydrogen chloride required as catalyst was preferred to the classical version using concentrated sulfuric acid as catalyst. Whereas the reaction is completed in a short period of time in the case of acid (**3**), the detection of unreacted acid (**4**) by TLC after 3 h led to an extension of the reaction time to 24 h in this case. The reaction proceeds almost quantitatively to afford the desired esters with satisfactory purity (according to their proton NMR spectra) to allow their use in the next stage as such. A comparison of the spectra for compound (**5**) with the reported literature data[40] confirmed its identity. In the case of ester (**6**), a comparison between its proton spectrum and the one of starting acid (**4**) showed that the former presents an additional singlet integrating for three protons at 3.72 ppm, which was assigned to the hydrogen atoms in the ester methyl group. The carbon atom in the same methyl group appears in the ^{13}C NMR spectra of compound (**6**) at approximately 52 ppm, thus supporting its structure.

Reaction of esters (**5**) and (**6**) with an excess of hydrazine monohydrate in refluxing 2-propanol produced the required hydrazides (**7**) and (**8**) in a facile manner and with excellent yields (Scheme 1). Because of the multi-gram amounts of hydrazides, and owing to the very good purity (according to NMR analysis) of the crude hydrazides isolated from the reaction mixture, only a small sample of 100 mg was recrystallized from 96 % ethanol with a view to obtain an analytical sample. The absence in the proton spectra of hydrazides (**7**) and (**8**) of the singlet associated with the hydrogen atoms in the methyl ester group, and the presence of a broad singlet integrating for two protons at approximately 4.2 ppm along with a singlet integrating for one proton at chemical shifts greater than 8 ppm (which correspond to the protons in the $–NH–NH_2$ group of these hydrazides) confirms the existence of the hydrazine function in the structure of compounds (**7**) and (**8**).

Next, each of hydrazides (**7**) and (**8**) were subjected to separate reactions with phenyl isothiocyanate and allyl isothiocyanate. When hydrazide (**7**) was heated at reflux temperature in 96 % ethanol with phenyl isothiocyanate, a colorless solid started to separate after 5 min. After 1 h, the solid was isolated and analyzed by proton NMR spectroscopy. The ^1H NMR spectrum of crude thiosemicarbazide (**9**) recorded in DMSO-d_6 at room temperature showed, in addition to the signals for the eight aromatic protons, the three protons in the methoxy group, and the two protons in the methylene group, three peaks between 9.60 and 10.21 ppm corresponding to the three NH protons. However, low intensity resonance signals with chemical shifts close to those assigned to the protons in thiosemicarbazide (**9**), that may be indicative for the presence of a compound with similar chemical structure to thiosemicarbazide (**9**), have also been identified in the spectrum. According to integration of these signals, the molar ratio between thiosemicarbazide (**9**) and this minor component is approximately 1 to 0.1. On the other hand, analysis using proton NMR spectroscopy of a sample obtained by recrystallization of a small amount of crude compound (**9**) as a solution in DMSO-d_6 at room temperature led to a spectrum that was in any respect identical to the one obtained from the crude compound under similar experimental conditions. As a change in ratio between the content of the components in a mixture after recrystallization is often observed, a possible explanation would be that the minor component in the material isolated at the end of the reaction time is not an impurity. Additional NMR experiments that were performed with a sample of the crude material isolated from the reaction dissolved this time in $CDCl_3$ (a solvent in which the solid had low solubility) led to the proton spectrum in Figure 1a. The sample was then recovered by allowing $CDCl_3$ to evaporate, then the resulting solid was redissolved in DMSO-d_6 in order to record its proton spectrum (Figure 1b).

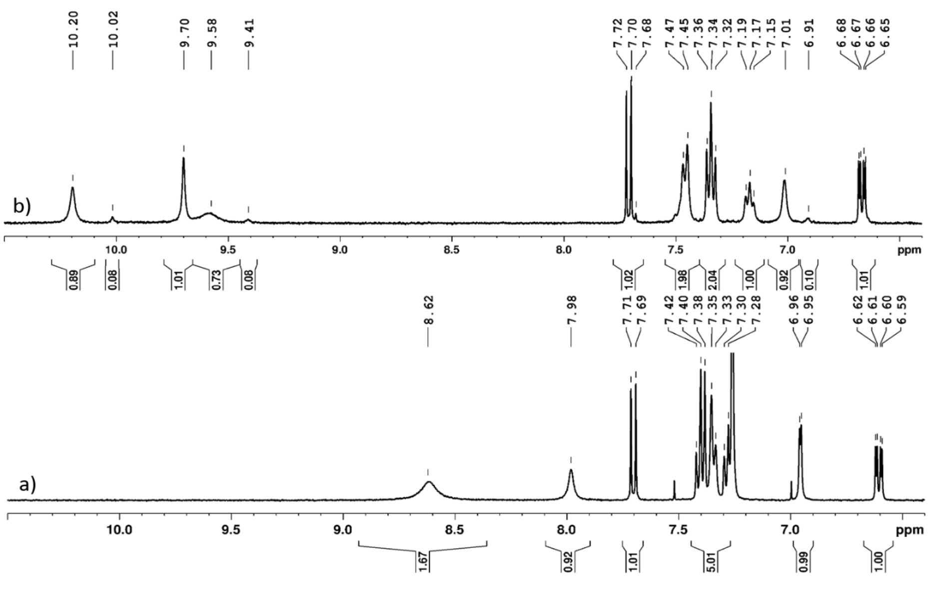


Figure 1. Detail of the aromatic region of the ^{1}H NMR spectra for the same sample of the crude material isolated from the reaction of hydrazide (**7**) with phenyl isothiocyanate first in $CDCl_3$ (a), then in DMSO-d_{6}.(b).

For the same sample, the spectrum in $CDCl_3$ shows peaks for a single compound, whereas the one in DMSO-d_6 shows resonance signals for a mixture of two components, suggesting that the crude material isolated from the reaction is actually pure and consists of only one species, namely thiosemicarbazide (**9**), but compound (**9**) undergoes a change in a DMSO-d_6 solution. Moreover, the ^{1}H NMR spectrum of the same sample in DMSO-d_6 that was recorded at 70° C (Figure 2) also presents peaks for a single compound.

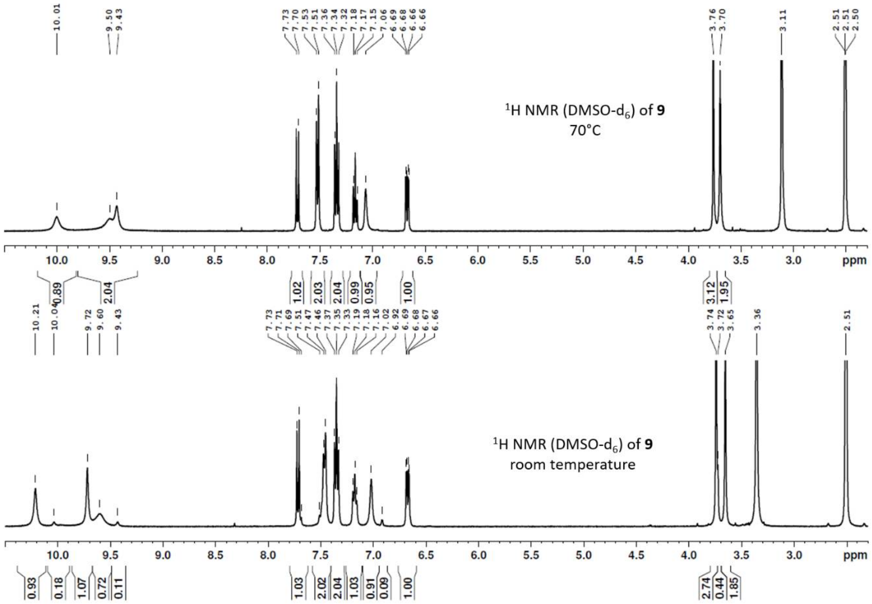
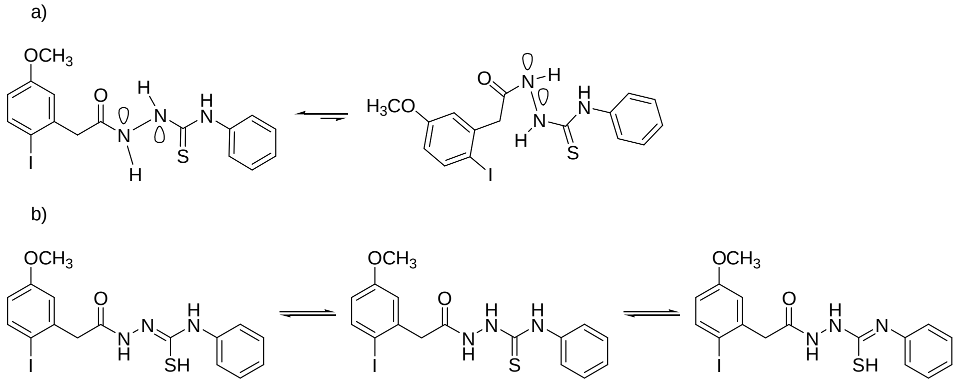


Figure 2. ^{1}H NMR spectra for compound (**9**) in DMSO-d_6 recorded at room temperature and at 70 °C.

Therefore, the presence of the minor resonance signals in the spectrum in DMSO-d_6 at room temperature can be tentatively explained by the presence of an equilibrium between different stereoisomers (such as those depicted in Scheme 2a) owing to the conformational changes in the fragment –CO–NH–NH–CS–NH–, in a manner similar to that observed for the simpler fragment –CO-NH-NH_2 in hydrazides.[41] The equilibrium evidenced between these conformers in DMSO-d_6 shifts towards the more stable conformer with increasing temperature, whereas the conformational change is fast in $CDCl_3$, and the NMR spectrum has in these cases only one set of peaks corresponding to a single conformer. Also, one cannot exclude the contribution of thioamide–iminothiol tautomerism (as exemplified in Scheme 2b) to the existence of different species in solution that would ultimately result in the presence of distinct resonance signals in the proton spectrum for a given hydrogen atom. As the nature of the solvent plays an important role in the tautomerization of organic molecules,[42–44] the presence of extra resonance signals that could be correlated with the existence of such tautomers in DMSO-d_6 and the absence of similar signals in $CDCl_3$ may be interpreted as an indication that tautomerism of compound **9** also contributes to the unusual behavior of this compound in NMR experiments.



Scheme 2. Illustration of conformational isomerism (a) and tautomerism (b) that could be responsible for the existence of distinct resonance peaks in the ^1H NMR spectrum of compound **9** for the protons in the thiosemicarbazide fragment.

Moreover, an exploratory small-scale experiment aiming at transforming the crude material isolated from the reaction of hydrazide (**7**) with phenyl isothiocyanate into the corresponding 1,2,4-triazolethione (**15**) afforded a crude reaction product that contained (based on the results from proton NMR analysis) only the expected triazole derivative, and it was free of any by-products that could have been potentially derived from a hypothetical impurity in the crude thiosemicarbazide (**9**).

Next, in a similar manner, addition of hydrazide (**7**) to allyl isothiocyanate and also of hydrazide (**8**) to phenyl isothiocyanate and allyl isothiocyanate gave crude reaction products (**10**), (**12**) and (**13**), respectively, which were analyzed using proton NMR spectroscopy in DMSO-d_6. All the spectra of each of these crude compounds presented approximately 10 % of a minor conformer or tautomer, while the same results were obtained for samples of these compounds that had been recrystallized prior to analysis. Therefore, it appears that the presence of a minor conformer or tautomer in DMSO-d_6 solutions is common for this type of *N*,*N′*-disubstituted thiosemicarbazides. To the best of our knowledge, this unusual behavior for *N*,*N′*-disubstituted thiosemicarbazides has not been previously mentioned in literature studies dealing with the synthesis and NMR characterization of this particular type of compound.

In addition to isothiocyanates, phenyl isocyanate was also employed as reagent in reaction with hydrazides (**7**) and (**8**) with a view to generate *N*,*N′*-disubstituted semicarbazides (**11**) and (**14**), as illustrated in Scheme 1. Because isocyanates are significantly more reactive toward alcohols than isothiocyanates, the reaction was not performed in ethanol, but rather in tetrahydrofuran at reflux temperature. Under these reaction conditions, similarly to the structurally related thiosemicarbazides (**9**) and (**12**), semicarbazides (**11**) and (**14**) have been isolated with yields close to 90 %. Unlike the corresponding thiosemicarbazides, the proton NMR spectra of crude semicarbazides (**11**) and (**14**) in DMSO-d_6 at room temperature do not present extra peaks that could be attributed to conformers or tautomers, but the presence of unwanted by-products was clearly noticeable. For characterization purposes, a small amount of each crude semicarbazide was recrystallized from 96 % ethanol to give pure compounds (**11**) and (**14**), whose proton NMR spectra were devoid of signals pertaining to the by-products previously noticed in the spectra of crude semicarbazides, indicating that the signals in the crude compounds (**11**) and (**14**) came from impurities, and not from conformers or tautomers. Moreover, in these NMR spectra, the singlets of the nitrogen-bonded protons in semicarbazides (**11**) and (**14**) were sharp, while the signals associated with same protons in thiosemicarbazides (**9**) and (**12**) were broad in the corresponding spectra. The same is also true when the peaks in the ^{13}C spectra of semicarbazides (**11**) and (**14**) of the two carbon atoms of the carbonyl functions are compared with the resonance signals in the carbon spectra of thiosemicarbazides (**9**) and (**12**) that are were attributed to the two carbon atoms that are double-bonded, one to oxygen and the other to sulfur.

Ring closure of thiosemicarbazides (**9**), (**10**), (**12**) and (**13**) in aqueous KOH solution leads to 1,2,4-triazole-5-thiones (**15**), (**16**), (**18**) and (**19**), respectively (Scheme 1). Given that the crude thiosemicarbazides do not appear to contain any impurities, the products isolated from the reaction of hydrazides and isothiocyanates were employed as such in these cyclizations, affording very good yields (usually over 90 %) of crude heterocycles, that were considered pure based on proton NMR spectroscopy, but were recrystallized mostly to secure samples suitable for elemental analysis. Fortunately, these cyclic compounds are fairly soluble in hot ethanol compared to the acyclic thiosemicarbazides, while the recovery of the desired compound from this purification process is excellent. Ring closure of thiosemicarbazides to 1,2,4-triazole-5-thiones led to significant changes in the proton spectrum of the latter compared to those of the former. Thus, the broad signals of the nitrogen-bonded protons for both the major and the minor isomeric forms of thiosemicarbazide **9** are no longer present, while a sharp singlet at chemical shifts greater than 13 ppm that may be attributed to the proton at *N*-1 is now noticeable. Also, the broad signals in the carbon spectra corresponding to the two carbon atoms that are double-bonded (one to oxygen, and one to sulfur) in the structure of thiosemicarbazides have now resolved into sharp peaks at approximately 150 ppm (*C*-3) and 166 ppm (*C*-5).

A similar ring closure reaction was performed using semicarbazides (**11**) and (**14**). Unlike their sulfur-containing analogs, these semicarbazides do not dissolve readily in the aqueous KOH solution, even at boiling point; addition of 96 % ethanol, however, led to the formation of a homogenous reaction mixture. In contrast to triazolethiones, only moderate yields (about 55 %) of crude triazolones were obtained upon treatment of the cooled reaction mixture with dilute acetic acid, and recrystallization from ethanol lowered the yields of pure triazolones (**17**) and (**20**) even more. In the proton spectra of these triazolones, only one singlet associated with a labile proton can be noticed, albeit at lower chemical shift value (close to 11.7 ppm) than the singlet assigned in the spectra of triazolethiones to the proton at *N*-1. Carbon atoms *C*-3 and *C*-5 in the newly formed triazole ring resonate in the ^{13}C NMR spectra at around 154 ppm and 145 ppm, respectively.

Among the several chemical modifications that these 1,2,4-triazolethiones and 1,2,4-triazolones may undergo, aminomethylation represents one of the most important transformations that takes place at the unsubstituted *N*-1 atom of the triazole ring,[45–49] leading to pharmacologically interesting 1,2,4-triazole-derived *NH*-heterocyclic

Mannich bases.[50] According to a literature survey, aminomethylation of 1,2,4-triazolethiones with secondary aliphatic amines such as morpholine or piperidine appears to proceed fast even at room temperature, as reaction times as brief as 0.5 h are often employed to provide good yields of aminomethylated products. However, the nature and the amount of the solvent seem to be important for a straightforward process leading to the expected results. While the large majority of similar Mannich reactions normally take place in ethanol or methanol, the literature survey showed that sometimes the reaction has been performed in dioxane or even in *N*,*N*-dimethylformamide. The use of these solvents particularly for the aminomethylation of substrates such as Schiff bases of 4-amino-1,2,4-triazolethiones points to the significance of the substrate’s solubility in the solvent of choice for a good outcome of the reaction. Because triazolethiones (**15**), (**16**), (**18**) and (**19**) have been recrystallized from 96 % ethanol with excellent recovery, they must have a limited solubility in this solvent at room temperature. An initial aminomethylation experiment conducted with 1 mmole of triazolethione (**19**) in 10 mL 96 % ethanol as solvent led to isolation of a solid that was shown by NMR analysis to be a mixture of the desired Mannich base (**24**) and the starting triazolethione (**19**) in an approximate ratio of 1 to 0.1, respectively. Removal of the unreacted substrate (**19**) from this mixture through repeated recrystallization was cumbersome, thus emphasizing the importance of appropriate reaction conditions in aminomethylation of these triazolethiones. Luckily, an increase of the volume of 96 % ethanol from 10 mL to 15 mL in a second identical experiment afforded in the end a solid that contained only the aminomethylated product (**24**). The remaining three Mannich bases (**21**)–(**23**) were also prepared in pure form and with good yields when

15 mL 96 % ethanol were employed as solvent for 1 mmole of each substrate. A consequence of the aminomethylation of these triazolethiones is the disappearance in the proton spectra of the signal in the off-set, which is associated with the proton at *N*-1 that was substituted with the morpholinomethyl group. The signals of the protons in the aforementioned fragment can be identified in the ^{1}H NMR spectra of Mannich bases (**21**)–(**24**) as the singlet integrating for two hydrogen atoms at approximately 5 ppm (the methylene group bridging the two nitrogen atoms – one in triazolethione and the other in morpholine) and as the two triplets, each integrating for four hydrogen atoms, corresponding to the protons in the methylene groups in the morpholine residue (the one at about 2.6-2.7 ppm belongs to the protons in the methylene groups adjacent to nitrogen, while the one at about 3.5-3.55 ppm belongs to the protons in the methylene groups adjacent to oxygen). In the carbon spectra of Mannich bases (**21**)–(**24**), the resonance signal at approximately 68 ppm is assigned to the carbon atom in methylene group linking the triazolethione scaffold with the morpholine fragment, while those at approximately 66 ppm and 50 ppm are associated with the carbon atoms in the morpholine residue that are adjacent to the oxygen atom and to the nitrogen atom, respectively.

Experimental

Materials and Methods

All chemical reagents and solvents were obtained from Merck–Sigma–Aldrich (Schnelldorf, Germany). Melting points were taken on a Mel-Temp II apparatus and are uncorrected. NMR spectra were recorded on a Bruker Avance NEO spectrometer at 400 MHz, with a 5 mm probe for direct detection of H, C, F, and Si, at room temperature (298 K). The residual signals of the deuterated solvents were used as internal standard ($CDCl_3$: δ = 7.26 ppm for ^{1}H and δ = 77.01 ppm for ^{13}C; DMSO-d_6: δ = 2.51 ppm for ^{1}H and δ = 39.47 ppm for ^{13}C). CHN elemental analysis was performed on a Vario-EL-III elemental analyzer.

Synthesis

2-(2-Iodo-5-methoxyphenyl)acetic acid (**3**)

A solution of 3-methoxyphenylacetic acid (**1**, 1.66 g, 10 mmole), *N*-iodosuccinimide (2.25 g, 10 mmole) and trifluoroacetic acid (1.14 g, 0.76 mL, 10 mmole) in acetonitrile (15 mL) was stirred at room temperature, under the exclusion of light for 24 h. The reaction mixture was poured under rapid stirring into distilled water (500 mL), and then the resulting suspension was kept in a refrigerator for 24 h. The solid material was filtered, washed with distilled water (3 × 20 mL), air-dried, and recrystallized from 2-propanol to afford off-white crystals (2.05 g, 70 %), mp 129 – 130 °C (Iit.[39] mp 124 – 126 °C). ^{1}H NMR (DMSO-d_6, 400.1 MHz), δ (ppm): 3.67 (s, 2H), 3.73 (s, 3H), 6.66 (dd, *J* = 3.0 and 8.8 Hz, 1H), 7.00 (d, *J* = 3.0 Hz, 1H), 7.69 (d, *J* = 8.8 Hz, 1H), 12.38 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100.6 MHz), δ (ppm): 45.5, 55.2, 90.1, 114.7, 117.4, 139.2, 139.5, 159.4, 171.3.

2-(2-Iodo-4,5-dimethoxyphenyl)acetic acid (**4**)

The procedure detailed above was also employed for the iodination of 3,4-dimethoxyphenyl)acetic acid (**2**, 3.92 g, 20 mmole), the crude reaction product that was isolated in a similar manner being deemed sufficiently pure by NMR analysis. Light tan crystals (5.79 g, 90 %), mp 165 – 166 °C (Iit.[39] mp 162 – 164 °C; Iit.[51] mp 165 – 166.5 °C). The recorded ^{1}H and ^{13}C NMR spectra were in agreement with the reported data.[39]

Methyl 2-(2-iodo-5-methoxyphenyl)acetate (**5**)

To a well-stirred solution of 2-(2-iodo-5-methoxyphenyl)acetic acid (**3**, 5.84 g, 20 mmole) in absolute methanol (90 mL) that is cooled in an ice bath, thionyl chloride (5.95 g, 3.67 mL, 50 mmole) was added dropwise over 5 min. The resulting solution was stirred at room temperature for 3 h, then the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (120 mL), and the solution was washed with aqueous 10 % Na_2CO_3 (20 mL). The aqueous phase was extracted with fresh ethyl acetate (20 mL), then the combined organic phases were washed with water (30 mL) and brine (10 mL). The organic phase was dried over anhydrous Na_2SO_4, the drying agent was filtered, and the solvent in the filtrate was removed under reduced pressure to afford an oil that turned upon cooling into a yellowish solid mass. The solid (5.88 g, 96 %), which was deemed sufficiently pure by NMR analysis, melted at 43 – 44 °C. The recorded ^{1}H and ^{13}C NMR spectra were in agreement with the reported data.[40]

Methyl 2-(2-iodo-4,5-dimethoxyphenyl)acetate (**6**)

The previous procedure was employed for the synthesis of ester (**6**) from 2-(2-iodo-4,5-dimethoxyphenyl)acetic acid (**4**, 5.16 g, 16 mmole), absolute methanol (70 mL) and thionyl chloride (4.76 g, 2.85 mL, 40 mmole), but the reaction time was extended overnight. Similar work – up of the reaction mixture afforded an an oil that solidified into a light tan mass. The solid (5.11 g, 95 %) was deemed sufficiently pure by NMR analysis and melted at 71 – 72 °C (Iit.[51] mp 72 – 72.5 °C). ^{1}H NMR ($CDCl_3$, 400.1 MHz), δ (ppm): 3.72 (s, 3H), 3.74 (s, 2H), 3.85 (s, 6H), 6.81 (s, 1H), 7.23 (s, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz), δ (ppm): 45.6, 52.1, 55.9, 56.1, 88.8, 113.2, 12.7, 129.9, 148.7, 149.4, 171.3.

2-(2-Iodo-5-methoxyphenyl)acetohydrazide (**7**)

A mixture of methyl 2-(2-iodo-5-methoxyphenyl)acetate (**5**, 5.2 g, 17 mmole) and hydrazine monohydrate (3.4 g, 68 mmole) in 2-propanol (20 mL) was heated at reflux temperature for 4 h. The reaction mixture was allowed to reach room temperature, then it was further cooled in a freezer for 3 h. The solid was filtered, washed with a mixture of hexanes – isopropanol (3 × 15 mL, 9:1 v/v) and air-dried to give a colorless solid (4.99 g, 96 %) that was deemed pure by NMR analysis. An analytical sample (mp 179 – 180 °C) was obtained by recrystallization of a small portion of crude material from 96 % ethanol. ^{1}H NMR (DMSO-d_6, 400.1 MHz), δ (ppm): 3.47 (s, 2H), 3.83 (s, 3H), 4.27 (br s, 2H), 6.64 (dd, J = 3.2 and 8.8 Hz, 1H), 6.92 (d, J = 3.2 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 9.15 (s, 1H); ^{13}C NMR (DMSO-d_6, 100.6 MHz), δ (ppm): 44.8, 55.2, 89.8, 114.4, 116.9, 139.3, 140.1, 159.4, 168.4.

2-(2-Iodo-4,5-dimethoxyphenyl)acetohydrazide (**8**)

The previous procedure was employed for the synthesis of hydrazide (**8**) from methyl 2-(2-iodo-4,5-dimethoxyphenyl)acetate (**6**, 4.70 g, 14 mmole), hydrazine monohydrate (2.8 g, 56 mmole) and 2-propanol (20 mL). Similar work – up of the reaction mixture gave a colorless solid (4.42 g, 94 %) that was deemed pure by NMR analysis. An analytical sample (mp 191 – 192 °C) was obtained by recrystallization of a small portion of crude material from 96 % ethanol. ^{1}H NMR (DMSO-d_6, 400.1 MHz), δ (ppm): 3.44 (s, 2H), 3.72 (s, 3H), 3.73 (s, 3H), 4.21 (br s, 2H), 6.64 (dd, J = 3.2 and 8.8 Hz, 1H), 6.94 (s, 1H), 7.24 (s, 1H), 8.38 (s, 1H); ^{13}C NMR (DMSO-d_6, 100.6 MHz), δ (ppm): 44.3, 55.5, 55.8, 89.2, 114.1, 121.4, 131.3, 148.1, 148.8, 168.7.

2-[2-(2-Iodo-5-methoxyphenyl)acetyl]-N-phenylhydrazinecarbothioamide (**9**)

To a boiling solution of 2-(2-iodo-5-methoxyphenyl)acetohydrazide (**7**, 918 mg, 3 mmole) in 96 % ethanol (25 mL), phenyl isothiocyanate (405 mg, 3 mmole) in 96 % ethanol (5 mL) was added, and then the mixture was heated at reflux temperature for 1 h. The mixture was allowed to reach room temperature, the solid was filtered, washed sequentially with 96 % ethanol (5 mL), 2-propanol (10 mL), and hexanes (2 × 10 mL), and air-dried to yield colorless crystals (1.15 g, 87 %). The analytical sample (mp 177 – 178 °C) was obtained by recrystallization of a small portion of crude material from a mixture of 96 % ethanol – chloroform (3:1 v/v). ^{1}H NMR (DMSO-d_6, 400.1 MHz), δ (ppm), major isomer: 3.65 (s, 2H), 3.74 (s, 3H), 6.68 (dd, J = 2.8 and 8.8 Hz, 1H), 7.02 (br s, 1H), 7.17 (t, J = 7.2 Hz, 1H), 7.34 (t, J = 7.6 Hz, 2H), 7.46 (d, J = 7.6 Hz, 2H), 7.71 (d, J = 8.4 Hz, 1H), 9.60 (br s, 1H), 9.72 (s, 1H), 10.21 (s, 1H); ^{13}C NMR (DMSO-d_6, 100.6 MHz), δ (ppm), major isomer: 45.0, 55.3, 90.1, 114.7, 116.6, 125.0, 125.4 (br), 128.1, 139.0, 139.3, 139.6, 159.4, 168.8, 180.9 (br).

N-Allyl-2-[2-(2-iodo-5-methoxyphenyl)acetyl]hydrazinecarbothioamide (**10**)

A mixture of 2-(2-iodo-5-methoxyphenyl)acetohydrazide (**7**, 918 mg, 3 mmole) and allyl isothiocyanate (327 mg, 3.3 mmole) in 96 % ethanol (15 mL) was heated at reflux temperature for 1 h. The mixture was allowed to reach room temperature, the solid was filtered, washed sequentially with 2-propanol (10 mL) and hexanes (2 × 10 mL), and air-dried to yield colorless crystals (1.03 g, 85 %), mp 182 – 183 °C.

^{1}H NMR (DMSO-d_6, 400.1 MHz), δ (ppm), major isomer: 3.59 (s, 2H), 3.73 (s, 3H), 4.12 (t, *J* = 4.8 Hz, 2H), 5.05 (dd, *J* = 1.6 and 10.4 Hz, 1H), 5.12 (dd, *J* = 1.6 and 17.2 Hz, 1H), 5.78 – 5.88 (m, 1H), 6.66 (dd, *J* = 2.8 and 8.8 Hz, 1H), 6.97 (d, *J* = 2.8 Hz, 1H), 7.70 (d, *J* = 8.8 Hz, 1H), 8.47 (br s 1H), 9.38 (s, 1H), 10.01 (s, 1H); ^{13}C NMR (DMSO-d_6, 100.6 MHz), δ (ppm), major isomer: 44.9, 45.8, 55.3, 90.0, 114.7, 115.3, 116.6, 134.8, 139.2, 139.6, 159.4, 168.8, 181.8 (br).

2-[2-(2-Iodo-5-methoxyphenyl)acetyl]-N-phenylhydrazine-carboxamide (**11**)

A mixture of 2-(2-iodo-5-methoxyphenyl)acetohydrazide (**7**, 612 mg, 2 mmole) and phenyl isocyanate (238 mg, 2 mmole) in tetrahydrofuran (20 mL) was heated at reflux temperature for 1 h. The cooled reaction mixture was filtered, the solid was washed sequentially with 2-propanol (10 mL) and hexanes (2 × 10 mL), and air-dried to yield colorless crystals (780 mg, 92 %). The analytical sample (mp 218 – 219 °C) was obtained by recrystallization of a small portion of crude material from 96 % ethanol. ^{1}H NMR (DMSO-d_6, 400.1 MHz), δ (ppm): 3.60 (s, 2H), 3.75 (s, 3H), 6.66 (dd, *J* = 2.8 and 8.4 Hz, 1H), 6.95 (t, *J* = 7.2 Hz, 1H), 7.06 (d, *J* = 3.2 Hz, 1H), 7.26 (t, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 8.8 Hz, 1H), 8.13 (s, 1H), 8.69 (s, 1H), 9.94 (s, 1H); ^{13}C NMR (DMSO-d_6, 100.6 MHz), δ (ppm): 44.8, 55.2, 89.9, 114.7, 116.7, 118.4, 121.9, 128.6, 139.2, 139.5, 139.7, 155.2, 159.5, 169.1.

2-[2-(2-Iodo-4,5-dimethoxyphenyl)acetyl]-N-phenylhydrazinecarbothioamide (**12**)

A mixture of 2-(2-iodo-4,5-dimethoxyphenyl)acetohydrazide (**8**, 1.01 g, 3 mmole) and phenyl isothiocyanate (415 mg, 3 mmole) in 96 % ethanol (30 mL) was heated at reflux temperature for 1 h. The mixture was allowed to reach room temperature, the solid was filtered, washed sequentially with 2-propanol (10 mL) and hexanes (2 × 10 mL), and air-dried to yield colorless crystals (1.2 g, 85 %). mp 182 – 183 °C. The analytical sample (mp 181 – 182 °C) was obtained by recrystallization of a small portion of crude material from 96 % ethanol. ^{1}H NMR (DMSO d_6, 400.1 MHz), δ (ppm), major isomer: 3.61 (s, 2H), 3.73 (s, 3H), 3.74 (s, 3H), 7.01 (br s, 1H), 7.17 (t, J = 7.2 Hz, 1H), 7.28 (s, 1H), 7.34 (t, J = 8.0 Hz, 2H), 7.46 (d, J = 7.6 Hz, 2H), 9.58 (br s, 1H), 9.69 (s, 1H), 10.14 (s, 1H); ^{13}C NMR (DMSO-d_6, 100.6 MHz), δ (ppm), major isomer: 44.5, 55.6, 55.8, 89.5, 113.8, 121.4, 125.0, 125.6, 128.1, 130.8, 139.0, 148.2, 148.9, 169.2, 181.0 (br).

N-Allyl-2-[2-(2-iodo-4,5-dimethoxyphenyl)acetyl]hydrazinecarbothioamide (**13**)

A mixture of 2-(2-iodo-4,5-dimethoxyphenyl)acetohydrazide (**8**, 1.01 g, 3 mmole) and allyl isothiocyanate (327 mg, 3.3 mmole) in 96 % ethanol (25 mL) was heated at reflux temperature for 1 h. The mixture was allowed to reach room temperature, the solid was filtered, washed sequentially with 2-propanol (10 mL) and hexanes (2 × 10 mL), and air–dried to yield colorless crystals (1.07 g, 82 %). The analytical sample (mp 185 – 186 °C) was obtained by recrystallization of a small portion of crude material from 96 % ethanol. ^{1}H NMR (DMSO-d_6, 400.1 MHz), δ (ppm), major isomer: 3.56 (s, 2H), 3.72 (s, 3H), 3.74 (s, 3H), 4.11 (s, 2H), 5.05 (dd, J = 1.6 and 10.4 Hz, 1H), 5.13 (dd, J = 1.6 and 12.6 Hz, 1H), 5.78 – 5.87 (m, 1H), 6.96 (s, 1H), 7.27 (s, 1H), 8.03 (t, J = 5.2 Hz, 1H), 9.36 (s, 1H), 9.95 (s, 1H); ^{13}C NMR (DMSO-d_6, 100.6 MHz), δ (ppm), major isomer: 44.4, 45.8, 55.6, 55.8, 89.5, 113.8, 115.3, 121.3, 130.8, 134.8, 148.2, 148.9, 169.2, 181.9 (br).

2-[2-(2-Iodo-4,5-dimethoxyphenyl)acetyl]-N-phenylhydrazinecarboxamide (**14**)

A mixture of 2-(2-iodo-4,5-dimethoxyphenyl)acetohydrazide (**8**, 672 g, 2 mmole) and phenyl isocyanate (238 mg, 2 mmole) in tetrahydrofuran (20 mL) was heated at reflux temperature for 3 h. The cooled reaction mixture was filtered, the solid was washed sequentially with 2-propanol (10 mL) and hexanes (2 × 10 mL), and air-dried to yield colorless crystals (801 mg, 89 %). The analytical sample (mp 214 – 215 °C) was obtained by recrystallization of a small portion of crude material from 96 % ethanol. ^{1}H NMR (DMSO-d_6, 400.1 MHz), δ (ppm): 3.56 (s, 2H), 3.74 (s, 3H), 3.75 (s, 3H), 6.95 (t, J = 7.2 Hz, 1H), 7.09 (s, 1H), 7.25 (t, J = 7.6 Hz, 2H), 7.27 (s, 1H), 7.44 (d, J = 7.6 Hz, 2H), 8.10 (s, 1H), 8.68 (s, 1H), 9.88 (s, 1H); ^{13}C NMR (DMSO-d_6, 100.6 MHz), δ (ppm): 44.3, 55.5, 55.8, 89.2, 113.9, 118.3, 121.4, 121.8, 128.6, 131.0, 139.5, 148.1, 148.9, 155.2, 169.4.

General procedure for the synthesis of triazolethiones

A mixture of thiosemicarbazide (2 mmole) and KOH (200 mg, 3 mmole, 85 % purity) in distilled water (40 mL) was heated at reflux temperature for 3 h, then it was cooled in an ice bath, and treated dropwise with aqueous 10 % acetic acid until pH was 5. The suspension was further stirred at room temperature for 30 min, then the solid was filtered, washed with distilled water (3 × 30 mL), air-dried, and recrystallized from 96 % ethanol.

3-(2-Iodo-5-methoxybenzyl)-4-phenyl-1H-1,2,4-triazole-5(4H)-thione (**15**). Colorless crystals (700 mg, 83 %), mp 228 – 229 °C. ^{1}H NMR (DMSO-d_6, 400.1 MHz), δ (ppm): 3.70 (s, 3H), 3.83 (s, 2H), 6.65 (dd, J = 2.8 and 8.8 Hz, 1H), 6.83 (d, J = 3.2 Hz, 1H), 7.36 – 7.39 (m, 2H), 7.50 – 7.58 (m, 3H), 7.63 (d, *J* = 8.8 Hz, 1H), 13.78 (s, 1H); ^{13}C NMR (DMSO-d_6, 100.6 MHz), δ (ppm): 36.9, 55.2, 89.5, 115.0, 117.0, 128.2, 129.5, 129.6, 133.5, 138.6, 139.5, 150.3, 159.4, 167.8. *Anal.* calcd. for $C_{16}H_{14}IN_3OS$, %: C, 45.40; H, 3.33; N, 9.93. Found, %: C, 45.16; H, 3.60; N, 10.07.

4-Allyl-3-(2-iodo-5-methoxybenzyl)-1H-1,2,4-triazole-5(4H)-thione (**16**). Colorless crystals (675 mg, 87 %), mp 203 – 204 °C. ^{1}H NMR (DMSO-d_6, 400.1 MHz), δ (ppm): 3.72 (s, 3H), 4.05 (s, 2H), 4.65 (d, *J* = 4.8 Hz, 2H), 5.09 (dd, *J* = 0.8 and 17.2 Hz, 1H), 5.21 (dd, *J* = 0.8 and 10.4 Hz, 1H), 5.82 – 5.91 (m, 1H), 6.70 (dd, *J* = 2.8 and 8.4 Hz, 1H), 6.92 (d, *J* = 2.8 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 13.61 (s, 1H); ^{13}C NMR (DMSO-d_6, 100.6 MHz), δ (ppm): 36.3, 44.9, 55.3, 89.8, 115.0, 117.0, 117.7, 131.1, 138.7, 139.6, 150.4, 159.5, 166.8. *Anal.* calcd. for $C_{13}H_{14}IN_3OS$, %: C, 40.32; H, 3.64; N, 10.85. Found, %: C, 40.60; H, 3.59; N, 10.98.

3-(2-Iodo-4,5-dimethoxybenzyl)-4-phenyl-1H-1,2,4-triazole-5(4H)-thione (**18**). Colorless crystals (840 mg, 93 %), mp 215 – 217 °C. ^{1}H NMR (DMSO-d_6, 400.1 MHz), δ (ppm): 3.71 (s, 3H), 3.77 (s, 3H), 3.86 (s, 2H), 6.85 (s, 1H), 7.26 (s, 1H), 7.41 – 7.43 (m, 2H), 7.55 – 7.63 (m, 3H), 13.80 (s, 1H); ^{13}C NMR (DMSO-d_6, 100.6 MHz), δ (ppm): 36.4, 55.5, 55.8, 89.1, 114.1, 121.5, 128.2, 129.4, 129.5, 129.6, 133.5, 148.4, 148.8, 150.5, 167.8. *Anal.* calcd. for $C_{17}H_{16}IN_3O_2S$, %: C, 45.04; H, 3.56; N, 9.27. Found, %: C, 45.19; H, 3.44; N, 9.41.

4-Allyl-3-(2-iodo-4,5-dimethoxybenzyl)-1H-1,2,4-triazole-5(4H)-thione (**19**). Colorless crystals (800 mg, 96 %), mp 183 – 184 °C. ^{1}H NMR (DMSO-d_6, 400.1 MHz), δ (ppm): 3.70 (s, 3H), 3.75 (s, 3H), 4.02 (s, 2H), 4.65 (d, *J* = 5.2 Hz, 1H), 5.08 (dd, *J* = 1.2 and 17.2 Hz, 1H), 5.21 (dd, *J* = 0.8 Hz and 10.2 Hz, 1H), 5.82 – 5.92 (m, 1H), 6.95 (s, 1H), 7.29 (s, 1H), 13.57 (s, 1H); ^{13}C NMR (DMSO-*d*$_6$, 100.6 MHz), δ (ppm): 35.9, 44.9, 55.6, 55.8, 89.4, 114.1, 117.6, 121.6, 129.7, 131.1, 148.5, 149.0, 150.7, 166.8. *Anal.* calcd. for $C_{14}H_{16}IN_3O_2S$, %: C, 40.30; H, 3.86; N, 10.07. Found, %: C, 40.52; H 3.98; N, 10.21.

General procedure for the synthesis of triazolones

A mixture of semicarbazide (1.5 mmole) and KOH (150 mg, 2.25 mmole, 85 % purity) in distilled water (30 mL) and 96 % ethanol (10 mL) was heated at reflux temperature for 3 h, then it was cooled in an ice bath, and treated dropwise with aqueous 10 % acetic acid until pH was 5. The solid was filtered, washed with distilled water (3 × 30 mL), air-dried, and recrystallized from 96 % ethanol.

3-(2-Iodo-5-methoxybenzyl)-4-phenyl-1H-1,2,4-triazol-5(4H)-one (**17**). Colorless crystals (215 mg, 35 %), mp 200 – 201 °C. ^{1}H NMR (DMSO-*d*$_6$, 400.1 MHz), δ (ppm): 3.69 (s, 3H), 3.80 (s, 2H), 6.63 (dd, *J* = 3.2 and 8.8 Hz, 1H), 6.82 (d, *J* =3.2 Hz, 1H), 7.35 – 7.37 (m, 2H), 7.42 – 7.53 (m, 3H), 7.63 (d, *J* = 8.4 Hz, 1H), 11.73 (s, 1H); ^{13}C NMR (DMSO-*d*$_6$, 100.6 MHz), δ (ppm): 37.2, 55.2, 89.5, 114.8, 116.7, 127.4, 128.7, 129.4, 132.7, 138.9, 139.4, 144.9, 154.3, 159.4. *Anal.* calcd. for $C_{16}H_{14}IN_3O_2$, %: C, 47.19; H, 3.47; N, 10.32. Found, %: C, 46.96; H 3.59; N, 10.23.

3-(2-Iodo-4,5-dimethoxybenzyl)-4-phenyl-1H-1,2,4-triazol-5(4H)-one (**20**). Colorless crystals (290 mg, 44 %), mp 236 – 238 °C. ^{1}H NMR (DMSO-*d*$_6$, 400.1 MHz), δ (ppm): 3.65 (s, 3H), 3.71 (s, 3H), 3.78 (s, 2H), 6.78 (s, 1H), 7.20 (s, 1H), 7.3 – 47.37 (m, 2H), 7.45 – 7.53 (m, 3H), 11.70 (s, 1H); ^{13}C NMR (DMSO-*d*$_6$, 100.6 MHz), δ (ppm): 36.8, 55.5, 55.8, 89.1, 113.9, 121.5, 127.4, 128.6, 129.4, 129.9, 132.8, 145.2, 148.2, 148.7, 154.3. *Anal.* calcd. for $C_{17}H_{16}IN_3O_3$, %: C, 46.70; H, 3.69; N, 9.61. Found, %: C, 46.47; H 3.78; N, 9.49.

General procedure for the aminomethylation of triazolethiones

A mixture of triazolethione (1 mmole), aqueous 36 % formaldehyde (167 mg, 2 mmole) and morpholine (174 mg, 2 mmole) in 96 % ethanol (15 mL) was stirred at room temperature for 2 h, and then it was heated at reflux temperature for another hour. The mixture was kept at room temperature for 5 h, the solid that separated was filtered, washed with 96 % ethanol (10 mL), air-dried, and recrystallized from 96 % ethanol.

3-(2-Iodo-5-methoxybenzyl)-1-(morpholinomethyl)-4-phenyl-1H-1,2,4-triazole-5(4H)-thione (**21**). Colorless crystals (380 mg, 73 %), mp 136 – 137 °C. ^{1}H NMR (DMSO-d_6, 400.1 MHz), δ (ppm): 2.69 (t, J = 4.4 Hz, 4H), 3.55 (t, J = 4.4 Hz, 4H), 3.70 (s, 3H), 3.90 (s, 2H), 5.04 (s, 2H), 6.64 (dd, J = 3.2 and 8.8 Hz, 1H), 6.82 (d, J = 3.2 Hz, 1H), 7.36 – 7.39 (m, 2H), 7.52 – 7.56 (m, 3H), 7.64 (d, J = 8.8 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100.6 MHz), δ (ppm): 36.6, 50.2, 66.1, 68.5, 89.3, 115.2, 116.6, 128.2, 129.5, 129.7, 133.9, 138.4, 139.6, 149.0, 159.4, 168.8. *Anal.* calcd. for $C_{21}H_{23}IN_4O_2S$, %: C, 48.28; H, 4.44; N, 10.72. Found, %: C, 48.45; H 4.59; N, 10.58.

4-Allyl-3-(2-iodo-5-methoxybenzyl)-1-(morpholinomethyl)-1H-1,2,4-triazole-5(4H)-thione (**22**). Colorless crystals (320 mg, 66 %), mp 116 – 117 °C. ^{1}H NMR (DMSO-d_6, 400.1 MHz), δ (ppm): 2.60 (t, J = 4.6 Hz, 4H), 3.51 (t, J = 4.6 Hz, 4H), 3.72 (s, 3H), 4.12 (s, 2H), 4.70 (d, J = 5.2 Hz, 2H), 4.98 (s, 2H), 5.05 (dd, J = 1.2 and 17.2 Hz, 1H), 5.19 (dd, J = 1.2 and 10.4 Hz, 1H), 5.82 – 5.90 (m, 1H), 6.70 (dd, J = 3.2 and 8.8 Hz, 1H), 6.93 (d, J = 3.2 Hz, 1H), 7.74 (d, J = 8.8 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100.6 MHz), δ (ppm): 36.0, 46.0, 50.1, 55.2, 66.0, 68.3, 89.7, 115.3, 116.6, 117.5, 130.8, 138.4, 139.7, 149.3, 159.5, 167.9. *Anal.* calcd. for $C_{18}H_{23}IN_4O_2S$, %: C 44.45; H, 4.77; N, 11.52. Found, %: C, 44.63; H 4.88; N, 11.33.

3-(2-Iodo-4,5-dimethoxybenzyl)-1-(morpholinomethyl)-4-phenyl-1H-1,2,4-triazole-5(4H)-thione (**23**).

Colorless crystals (445 mg, 81 %), mp 156 – 157 °C. ^{1}H NMR (DMSO-d_6, 400.1 MHz), δ (ppm): 2.71 (t, J = 4.4 Hz, 4H), 3.55 (t, J = 4.4 Hz, 4H), 3.66 (s, 3H), 3.72 (s, 3H), 3.88 (s, 2H), 5.06 (s, 2H), 6.77 (s, 1H), 7.21 (s, 1H), 7.33 – 7.36 (m, 2H), 7.53 – 7.56 (m, 3H); ^{13}C NMR (DMSO-d_6, 100.6 MHz), δ (ppm): 36.1, 50.2, 55.4, 55.8, 66.0, 68.4, 88.8, 113.6, 121.5, 128.2, 129.3, 129.4, 129.6, 133.9, 148.4, 148.8, 149.2, 168.9. *Anal.* calcd. for $C_{22}H_{25}IN_4O_3S$, %: C 47.83; H, 4.56; N, 10.14. Found, %: C, 48.04; H 4.68; N, 10.02.

4-Allyl-3-(2-iodo-4,5-dimethoxybenzyl)-1-(morpholinomethyl)-1H-1,2,4-triazole-5(4H)-thione (**24**). Colorless crystals (310 mg, 60 %), mp 161 – 162 °C. ^{1}H NMR (DMSO-d_6, 400.1 MHz), δ (ppm): 2.61 (t, J = 4.4 Hz, 4H), 3.51 (t, J = 4.4 Hz, 4H), 3.69 (s, 3H), 3.76 (s, 3H), 4.09 (s, 2H), 4.68 (d, J = 5.2 Hz, 2H), 4.99 (s, 2H), 5.03 (dd, J = 0.8 and 17.2 Hz, 1H), 5.19 (dd, J = 0.8 and 10.4 Hz, 1H), 5.81 – 5.90 (m, 1H), 6.92 (s, 1H), 7.31 (s, 1H); ^{13}C NMR (DMSO-d_6, 100.6 MHz), δ (ppm): 35.5, 45.9, 50.2, 55.5, 55.8, 66.0, 68.3, 89.3, 113.6, 117.4, 121.5, 129.4, 130.9, 148.5, 149.0, 149.6, 167.9. *Anal.* calcd. for $C_{19}H_{25}IN_4O_3S$, %: C, 44.19; H, 4.88; N, 10.85. Found, %: C, 44.40; H 4.70; N, 10.70.

Conclusions

The successful synthesis of four iodine-substituted triazolethiones and two iodine-containing triazolones through a five-step reaction sequence has been reported in this study. In the first step, iodination of two arylacetic acids having electron – rich aromatic rings underwent in facile manner using *N*-iodosuccinimide. Esterification of these acids and subsequent hydrazinolysis afforded the corresponding hydrazides with very good yields. Reaction of these hydrazides with isothiocyanates led to *N,N'*-disubstituted thiosemicarbazides, for which the presence of conformers or tautomers in deuterated DMSO (but not in $CDCl_3$) could be observed by NMR. The yields of related *N,N′*-disubstituted semicarbazides resulted from the reaction of hydrazides with phenyl isocyanate where significantly lower, and no conformers or tautomers could be evidenced for these compounds by NMR. Ring closure of the intermediate (thio)semicarbazides under strong basic conditions produced 1,2,4-triazole derivatives, for which the aminomethylation at *N*-1 was examined in the case of triazolethiones. All of these novel iodine-containing triazoles could find applications in medicinal chemistry as potential biologically active substances or as radiographic contrast agents, whereas the presence of iodine in their structure could make these compounds attractive as intermediates that allow easy access to structurally diverse biaryl- or (heteroaryl-aryl)-substituted triazolethiones *via* Pd(0)-catalyzed organic reactions.

Conflicts of interest

The authors declare no conflicts of interest regarding this manuscript.

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