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One-pot and catalyst-free synthesis of thiosemicarbazones via multicomponent coupling reactions

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ABSTRACT

A novel and efficient procedure for the synthesis of thiosemicarbazones has been achieved via a multicomponent and catalyst-free reaction of phenyl or *p*-chlorophenyl isothiocyanate, hydrazine, and aldehydes or ketones. The method afforded 20 thiosemicarbazones in good yields and short reaction time.

Presently, synthetic organic chemists are faced with environmental concerns that demand new procedures and/or procedure improvements where atom economy, minimal waste production, and energy/cost-effective preparations should be prime considerations.[1] In this scenario, multicomponent reactions represent an advanced approach to achieve efficient target and diversity-oriented synthesis.[2]

Thiosemicarbazones and their metal complexes derivatives are an essential structural unit with a wide range of biological and pharmacological properties such as anticancer and antimicrobial activities, Figure 1.[3] Besides, thiosemicarbazones are versatile building blocks in the synthesis of densely substituted heterocycles.[4] Despite of these important characteristics the available synthetic methodologies for this class of thiocompound are stop-and-go approaches involving isolation and purification of each prepared intermediate, which are time, solvent, and energy consuming procedures.[5,6]

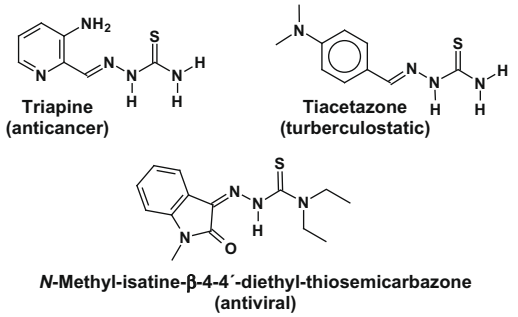

Figure 1. Representative bioactive thiosemicarbazones.

We disclose herein our results concerning the first one-pot, catalyst-free synthesis of thiosemicarbazones via multicomponent coupling reactions of hydrazine, isothiocyanates, and oxo compounds.

The most successful routes to access thiosemicarbazones consist of step-by-step reactions of hydrazine with different

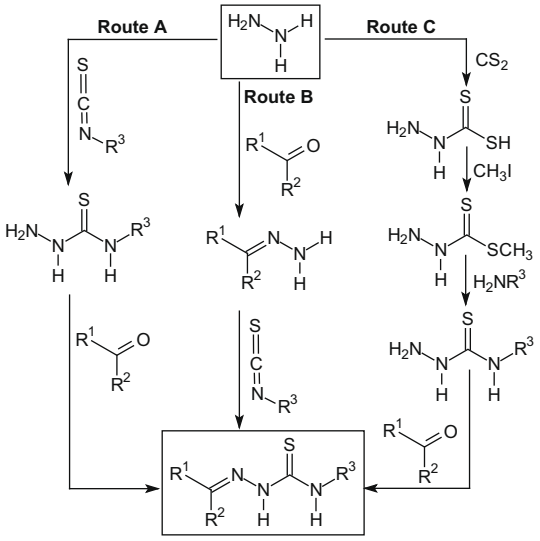

Figure 2. Synthetic routes to thiosemicarbazones.

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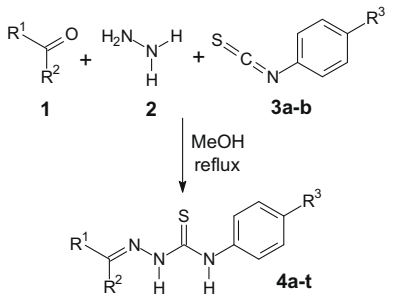
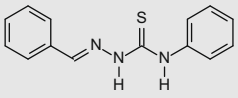
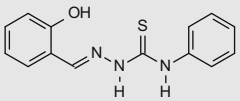
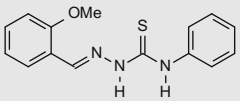
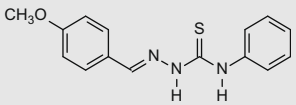
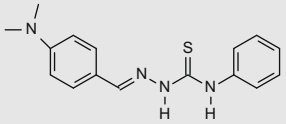
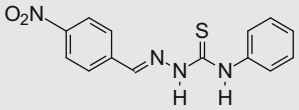
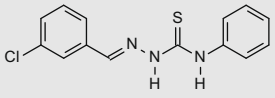
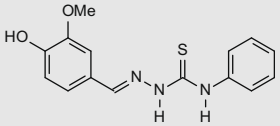
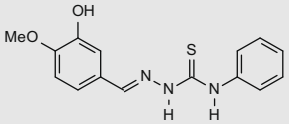
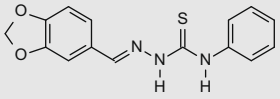


Scheme 1.

electrophiles, Figure 2. In the two-step route A, hydrazine reacts with isothiocyanates followed by reaction with appropriate oxo compound such as aldehydes or ketones, whereas in route B the same reagents react in an inverse order of events to provide the required thiosemicarbazone. In the four-step pathway presented in route C, hydrazine reacts with carbon disulfide followed by reaction with methyl iodide affording methyl hydrazinecarbodithioate, and sequential nucleophilic substitution with amines followed by condensation with the appropriate oxo compound affords the thiosemicarbazone, Figure 2. As one can see, routes A–B are degenerated operations[1a] and they present less steps than route C. Thus, we reasoned that they should be appropriate to test a multicomponent synthetic approach to thiosemicarbazones.

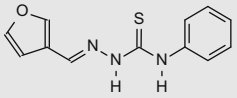
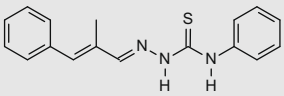
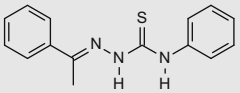
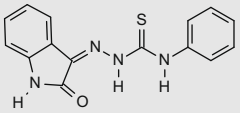
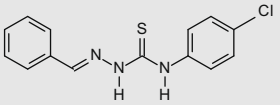
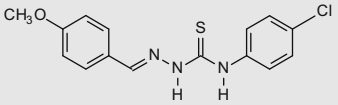
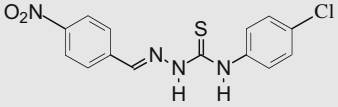
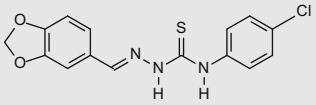
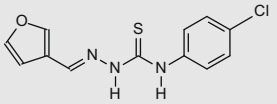
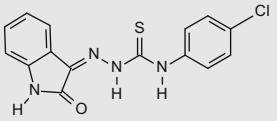
To acquire the best reaction condition two reaction controls were performed at room temperature employing only one pair of each electrophilic and nucleophilic reagent. In the first reaction, benzaldehyde and hydrazine were reacted in methanol, and in the second one phenyl isothiocyanate was reacted with hydrazine.

Table 1
Isolated thiosemicarbazones yields

Entry	Compound	Structure	Time (h)	Yield (%)
1	**4a**		24	87
2	**4b**		24	50
3	**4c**		24	54
4	**4d**		24	51
5	**4e**		24	75
6	**4f**		12	80
7	**4g**		6	71
8	**4h**		24	86
9	**4i**		12	61
10	**4j**		8	98

(*continued on next page*)

Table 1 (*continued*)

Entry	Compound	Structure	Time (h)	Yield (%)
11	**4k**		8	72
12	**4l**		24	52
13	**4m**		24	47
14	**4n**		8	60
15	**4o**		1	66
16	**4p**		3	56
17	**4q**		1	57
18	**4r**		24	65
19	**4s**		3	25
20	**4t**		3	66

Only in the last reaction we observed the consumption of the reagent. However, when both reaction mixtures were heated under reflux all reagents were consumed. These experiments indicated that to the three-multicomponent approach, the reaction must be performed under heating condition. Thus, we initiated our study exploring the possibility of a multicomponent reaction toward thiosemicarbazones by mixing in the same pot 1 equiv of benzaldehyde, phenyl isothiocyanate, and hydrazine in methanol under reflux, according to Scheme 1. In this condition compound **4a** was obtained in good yield (87%).

In search of an environmentally safe solvent, ethanol and isopropanol were investigated. Contrary to our expectation, the three-component reaction showed to be very sensitive to solvent variation, because when these solvents were employed at room temperature or under reflux no formation of thiosemicarbazone **4a** was observed. However, in these experiments phenyl thiosemicarbazide was detected by TLC. The reason to the no formation of the thiosemicarbazone is not entirely understood. A possible explanation to this fact may be the more acid character of methanol in comparison to ethanol and isopropanol (pK_a 15.5, 15.9, and 17.1, respectively[7]). This acid character should be responsible for the carbonyl activation, which is necessary to the attack by the nucleophilic $R–NH_2$ species present in the reaction media in the routes A and B shown in Figure 2.

With the optimal condition in hand, we extended the reaction to other oxo compounds, and results are indicated in Table 1. A representative spectrum of monosubstituted (entries 1–7) and disubstituted (entries 8–10) aldehydes afforded thiosemicarbazones from modest to excellent isolated yields. Therein, the method was adequate to multigram preparation also, and compound **4b** was synthesized in 52% yield (8g) employing 60 mmol of each reagent, a yield comparable to the 2 mmol scale preparation (entry 2). The method is also useful for heteroaromatic and α,β-unsaturated aldehydes (entries 11 and 12, respectively), and to some aromatic ketones (entries 13 and 14). However, when cyclohexanone was reacted a complex mixture was formed. To understand the scope and limitation of this

multicomponent reaction, the method was extended to benzoyl and butyl isothiocyanate, but we could not isolate the desired thiosemicarbazones. However, the method was successfully applied to *p*-chloro-phenyl isothiocyanate (Table 1, entries 15–20).

In conclusion, this study shows for the first time that three-component coupling reaction involving aryl isothiocyanates, hydrazine, and oxo compounds can be conveniently employed as a direct, catalyst-free synthetic route to a broad spectrum of thiosemicarbazones. Since the experimental conditions[8] are extremely simple, inexpensive, and very mild, we hope that this approach would be useful in the context of synthesis of molecular library for pharmacological applications. Besides, because thiosemicarbazone itself can participate in multicomponent reactions[9] we are investigating the application of the conditions here described in more complex situations, and additional studies of our research group will be described in due time.

Acknowledgments

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8. *General synthetic procedure*: 2 mmol of hydrazine, 2 mmol isothiocyanate, and 2 mmol of aldehyde or ketone in 10 mL of MeOH were heated under reflux at the indicated time in Table 1. After this time, the reaction was treated as indicated in each case. For **4a**–**p** the solid was decanted and triturated with cold methanol; **4s** was recrystallized from acetonitrile; **4q,r,t** were purified from silica-gel column chromatography (hexane/ethyl acetate 7:3; dichloromethane; and hexane/ethyl acetate 6:4, respectively). Spectral data for new compound: **4i** brown solid, mp 165.5–166.7 °C (recrystallized from ethanol). IR (KBr): 3306, 3135, 1547, 1513, 1261, 1206 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 11.73 (s, 1H), 9.81 (s, 1H), 7.97 (s, 1H), 7.57 (dd, 2H, *J* 7.2 Hz, *J* 1.5 Hz), 7.44–7.16 (m, 6H), 6.83 (s, 1H), 2.20 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6): δ 176.0, 148.9, 139.4, 137.6, 136.7, 134.7, 129.7, 128.8, 128.4, 128.1, 125.8, 125.5, 13.2 ppm; **4j** greenish solid, mp 179.4–180.2 °C (recrystallized from ethanol), IR (KBr): 3305, 3132, 1552, 1501, 1251, 1194 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 11.69 (s, 1H), 10.07 (s, 1H), 8.06 (s, 1H), 7.82 (d, 1H, *J* 1.2 Hz), 7.55 (d, 2H, *J* 7.8 Hz), 7.40–7.31 (m, 4H), 7.22–7.02 (m, 2H), 6.94 (d, 1H, *J* 7.8 Hz), 6.11 (s, 1H), 6.07 (s, 1H) (*E*–*Z* mixture 2:1) ppm; ^{13}C NMR (DMSO-d_6): δ 175.7, 149.0, 148.0, 142.6, 139.0, 128.5, 128.1, 127.9, 126.0, 125.2, 124.2, 108.1, 105.5, 101.4 ppm; **4l** brown solid, mp 184.7–186.5 °C (recrystallized from ethanol), IR (KBr): 3326, 3144, 1550, 1507, 1273, 1204 cm^{-1}; ^1H NMR(300 MHz, DMSO-d_6): δ 11.63 (s, 1H), 9.97 (s, 1H), 9.04 (s, 1H), 8.03 (s, 1H), 7.58 (d, 2H, *J* 7.8 Hz), 7.41 (d, 1H, *J* 2.1 Hz), 7.35 (t, 2H, *J* 7.5 Hz), 7.21–7.16 (m, 2H), 6.95 (d, 1H, *J* 8.4 Hz), 3.81 (s, 3H) ppm;. ^{13}C NMR (DMSO-d_6): δ 175.4, 149.7, 146.6, 143.3, 139.0, 127.9, 126.8, 125.4, 125.0, 120.6, 113.3, 111.6, 55.6 ppm.
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