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A Facile One-Pot Synthesis of Substituted *N*-{[2-(Aminocarbonyl)phenylamino]thioxomethyl}benzamides and 2-Aryl-quinazolin-4(3*H*)-ones[1]

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Abstract—The substituted *N*-{[2-(aminocarbonyl)phenylamino]thioxomethyl}benzamides and 2-arylquinazolin-4(3*H*)-ones are synthesized by the reaction of ammonium thiocyanate and aroyl chlorides with 2-aminobenzamide under solvent-free conditions or under reflux in MeCN.

Keywords: 2-aminobenzamide, aroyl chlorides, ammonium thiocyanate, *N*-{[2-(aminocarbonyl)phenylamino]-thioxomethyl}benzamides, 2-aryl-quinazolin-4(3*H*)-ones

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INTRODUCTION

Many acyl thiourea derivatives are well known in agriculture as fungicidal, antiviral, and regulating agents for plant protection [1–5]. Also, they are commercial insecticides [6] and herbicides [7, 8] and chelating agents in transition metal complexes [9]. The complexes of thiourea derivatives also show a wide range of biological activities [10]. Thioureas and their substituted analogues are epoxy resin curing agents [9] and intermediates in synthesis of *N*-aroyl, *N*′-aryl-thioureas [9, 11, 12].

Quinazolin-4(3*H*)-ones are important precursors for the synthesis of natural and pharmacological compounds, including febrifugine and isofebrifugine [13]. They can also be obtained by the cyclization of anthranilamides with aldehydes and by other similar methods [14–22]. In the study, *N*-{[2-(aminocarbonyl)-phenylamino]thioxomethyl}benzamides and 2-aryl-quinazolin-4(3*H*)-ones were synthesized by the reaction of ammonium thiocyanate and aroyl chlorides with 2-aminobenzamide under solvent-free conditions or under reflux in MeCN.

EXPERIMENTAL

NMR spectra were measured on a Bruker DRX-400 Avance spectrometer (^{1}H NMR at 400 Hz, ^{13}C NMR at 100 Hz) in DMSO-d_6 using TMS as internal standard. Melting points were determined with an Electrothermal 9100 apparatus. Elemental analyses were performed with a Costech ECS 4010 CHNS-O analyzer at the analytical laboratory of the Islamic Azad University, Yazd branch. IR spectra were recorded on a Shimadzu IR-470 spectrometer. Mass spectra were measured on a FINNIGAN-MAT 8430 mass spectrometer (ionization potential 70 eV). The chemicals for this study were purchased from Fluka (Buchs, Switzerland) and used without further purification.

General procedure. In a 50-mL round bottom flask, ammonium thiocyanate (2 mmol) and aroyl chloride **1** (2 mmol) were added, the mixture was heated at about 80°C for 5 min and. then cooled to room temperature. *a*. 2-aminobenzamide 2 (2 mmol) in MeCN (5 mL) was then added and the mixture was refluxed for 30 min. The solvent was removed in vacuum and then the reaction mixture was treated with 20 mL water. The precipitate was filtered off and dried. The residue was then purified by a column chromatography [silica gel (60, 230–400 mesh), hexane–ethyl acetate (3 : 1)]. Fractions containing **3** and **4** were evaporated to obtain pure compounds. Compounds **3c–3e** and **4c–4e** obtained by Method A can be also simply separated by filtration and recrystallized from EtOH.

Method *b*. 2-aminobenzamide 2 (2 mmol) was then added slowly and the mixture was stirred for 3 h at

[1] The text was submitted by the authors in English.

Yield by *N*-{[2-(aminocarbonyl)phenylamino]thioxomethyl}benzamides (**3a–3e**) and 2-aryl-quinazolin-4(3*H*)-ones (**4a–4e**) from the reaction between 2-aminobenzamide and aroyl chlorides in the presence of ammonium thiocyanate (see Scheme 1, methods *a* and *b*)

Comp. no.	Ar	Yield[a], %		mp, °C	
		method *a*	method *b*	found, %	calculated, %
3a	C_6H_5	37	87	180–190	188–190 [23]
3b	3-MeC_6H_4	43	93	193–195	194–195 [23]
3c	4-BrC_6H_4	12	77	213–215	–
3d	3-$NO_2C_6H_4$	6	55	226–228	–
3e	4-$NO_2C_6H_4$	–	34	198–200	–
4a	C_6H_5	46	8	235–237	235–237 [24]
4b	3-MeC_6H_4	44	5	219–221	219–220 [25]
4c	4-BrC_6H_4	73	16	314–315	314–316 [26]
4d	3-$NO_2C_6H_4$	76	36	348–249	351–353 [27]
4e	4-$NO_2C_6H_4$	84	55	360–262	363–364 [27]

[a] Yields refer to the pure isolated products.

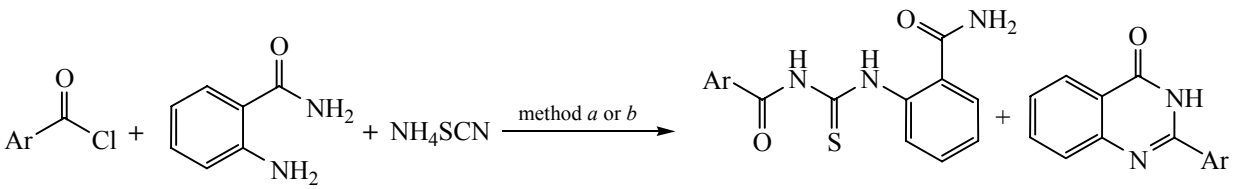
room temperature under solvent-free conditions. Then, the reaction mixture was treated with a 20 mL of water. The following procedure was the same as in method *a*.

General procedure for conversion of 3 to 4 by NaOH. A mixture of compound **3** (2 mmol) and 5 mL of NaOH (10% w/v) was stirred at room temperature for 1 h. The compound was extracted with ethyl acetate (5 × 3 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuum. The crude product was ground to a fine powder with diethyl ether to obtain a pure compound **4** as white solid.

***N*-{[(2-(Aminocarbonyl)phenyl]amino)thioxomethyl}-4-bromobenzamide (3c).** Cream powder, mp 213–215°C. IR spectrum, ν, cm^{-1}: 3480, 3315, 3205, 3045, 1675, 1644, 1609, 1585, 1514, 1475, 1326, 1250, 1147. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.30 t (1H, 7.6 Hz, CH_{arom}), 7.49 t (1H, 7.6 Hz, CH_{arom}), 7.57 s (1H, NH), 7.60 br.d (1H, 7.2 Hz, $1CH_{arom}$), 7.73 d (2H, 8.8 Hz, $2CH_{arom}$), 7.88 d (2H, 8.4 Hz, $2CH_{arom}$), 8.09 s (1H, NH), 8.12 br.d (1H, 8 Hz, CH_{arom}), 11.63 s (1H, NH), 13.08 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 126.2, 126.3, 127.4, 127.5, 128.3, 129.9, 130.3, 131.3, 131.9, 136.9 (carbons of aromatics), 166.9, 169.4 (2C=O), 179.7 (C=S). Found, %: C 47.50; H 3.28; N 11.07, S 8.45. $C_{15}H_{12}BrN_3O_2S$. Calculated, %: C 47.63; H 3.20; N 11.11; S 8.48. *M* 379.

***N*-{([2-(Aminocarbonyl)phenyl]amino)thioxomethyl}-3-nitrobenzamide (3d).** Cream powder, mp 226–228°C. IR spectrum, ν, cm^{-1}: 3465, 3305, 3200, 3060, 1676, 1646, 1608, 1576, 1525, 1499, 1347, 1243, 1144. ^{1}H NMR spectrum, (*J*, Hz): 7.33 t (1H, 7.6 Hz, CH_{arom}), 7.52 t (1H, 7.6 Hz, CH_{arom}), 7.60 s (1H, NH), 7.63 br.d (1H, 8.0 Hz, CH_{arom}), 7.82 t (1H, 8.0 Hz, CH_{arom}), 8.12 s (1H, NH), 8.16 br.d (1H, 7.6 Hz, CH_{arom}), 8.36 d (1H, 7.4, CH_{arom}), 8.47 d (1H, 7.6 Hz, CH_{arom}), 8.76 s (1H, CH_{arom}), 12.00 s (1H, NH), 13.09 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 123.6, 124.2, 126.3, 127.3, 128.4, 129.3, 129.7, 130.4, 131.2, 136.5, 140.2, 148.5 (carbons of aromatics), 165.8, 169.4 (2C=O), 179.6 (C=S). Found, %: C 52.12; H 3.62; N 16.20; S 9.27. $C_{15}H_{12}N_4O_4S$. Calculated, %: C 52.32; H 3.51; N 16.27; S 9.31. *M* 344.

***N*-{([2-(Aminocarbonyl)phenyl]amino)thioxomethyl}-4-nitrobenzamide (3e).** Cream powder, mp 198–200°C. IR spectrum, ν, cm^{-1}: 3520, 3365, 3245, 3055, 1683, 1644, 1609, 1579, 1520, 1482, 1329, 1244, 1139. ^{1}H NMR spectrum, (*J*, Hz): 7.32 t (1H, 7.6 Hz, CH_{arom}), 7.51 t (1H, 7.2 Hz, CH_{arom}), 7.58 s (1H, NH), 7.62 br.d (1H, 8.0 Hz, CH_{arom}), 8.11 s (1H, NH), 8.15 d (2H, 8.8 Hz, $2CH_{arom}$), 8.19 br.d (1H, 7.6 Hz, CH_{arom}), 8.33 d (2H, 8.8 Hz, $2CH_{arom}$), 11.92 s (1H, NH), 13.07 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 123.8, 126.4, 127.3, 128.4, 129.7, 130.4, 130.8, 136.9, 138.6, 150.3 (carbons of aromatics), 166.3, 169.4 (2C=O), 179.5



1 **2** **3** **4**

Fig. 1. The reaction between 2-aminobenzamide and aroyl chlorides in the presence of ammonium. thiocyanate. Method *a*: CH_3CN, teflux; method *b*: solvent-free.

(C=S). Found, %: C 52.22; H 3.59; N 16.25, S 9.27. $C_{15}H_{12}N_4O_4S$. Calculated, %: C 52.32; H 3.51; N 16.27; S 9.31. *M* 344.

RESULTS AND DISCUSSION

The reaction of aroyl chlorides **1** and 2-aminobenzamide **2** in the presence of ammonium thiocyanate gives products **3** and **4** under solvent-free conditions or under reflux in MeCN (Fig 1).

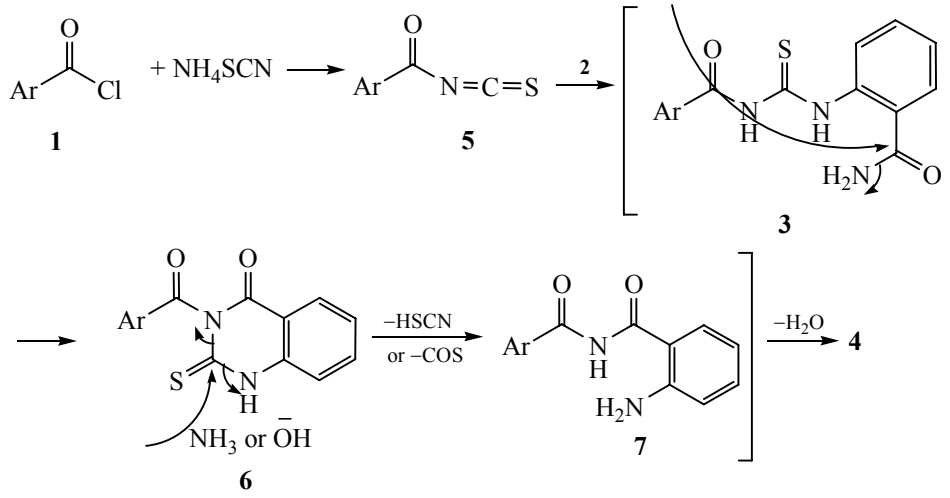
The results are listed in the table.

Compounds **3a, 3b, 4a–4e** are known and their structures were deduced from the comparison of melting points and spectral data with authentic samples [20].

Compounds **3c–3e** are new and their structures were deduced by the elemental and spectral analyses. For example, the mass spectrum of the compound 4a has a molecular ion peak at *m/z* = 222. The ^{1}H NMR spectrum of this compound in DMSO has a single signal at δ = 12.59 ppm that disappears after addition of a few drops of D_2O. This signal is attributed to the NH proton. Multiplets between 7.50 and 8.23 ppm are due to aromatic protons. The ^{13}C NMR spectrum of compound **4a** shows 12 signals, in agreement with the proposed structure. The IR spectrum of compound **4a** also supports the suggested structure. The mass spectrum of compound **3c** has a molecular ion peak at *m/z* = 379. The ^{1}H NMR spectrum of the compound **3c** in DMSO exhibits four single signals at 7.57, 8.09, 11.63, and 13.08 ppm, which disappear after addition of a few drops of D_2O. These signals are attributed to NH protons. Multiplets between 7.30 and 8.12 ppm are due to aromatic protons. The ^{13}C NMR spectrum of the compound 3c shows 13 signals, in agreement with the proposed structure. The suggested structure of this compound is also supported by the IR spectrum.

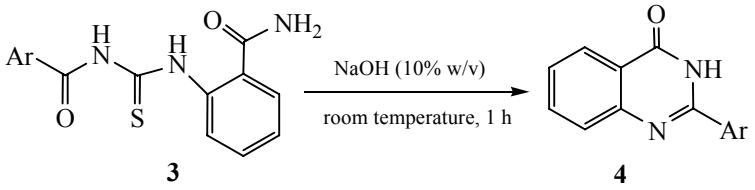
A tentative mechanism of this transformation is proposed in Fig. 2.

Probably, aroyl chloride **1** easily reacts with ammonium thiocyanate to form aroyl thiocyanate **5**, then a compound **3** is generated in the presence of 2-aminobenzamide **2** and is converted to a compound **4** by elimination of HSCN and H_2O.



1 **5** **3** **6** **7**

Fig. 2. The suggested mechanism for the formation of compounds **3** and **4**.



3 **4**

Fig. 3. The compounds **3** are converted to compounds **4** in the presence of NaOH.

In some experiments, we found that compounds **3** are converted to compounds **4** in the presence of triethylamine (Fig. 3).

In conclusion, we have developed a straightforward protocol for the synthesis of acyl thiourea derivatives and quinazoline-4(3*H*)-ones under solvent-free conditions or under reflux in MeCN. This procedure has several advantages, including clean reactions and lower reaction time.

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