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ORIGINAL PAPER

A mild one-pot synthesis of *S*-aryl carbamimidothioates using diazonium salts under catalyst-free condition

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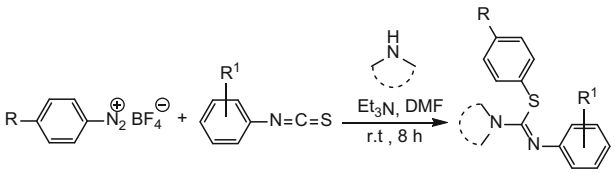
Abstract A simple, new method for the synthesis of *S*-aryl carbamimidothioates is described using aryl diazonium fluoroborates, aryl isothiocyanates, amines, and Et_3N as the base at room temperature.
Graphical Abstract



Keywords Diazonium salt · Carbamimidothioate · Aryl isothiocyanate · Aryl thiourea

Introduction

In recent decades, the development of practical, efficient, and rapid synthetic methodologies for the construction of fascinating molecules from readily available reagents in both organic chemistry and biochemistry has been a key target in modern organic synthesis [1]. To this end, multistep reactions, performed in a one-pot process, such as tandem, domino, and cascade reactions, have attracted much attention in combinatorial chemistry because of assembly efficiency, environmental compatibility, and operational simplicity [2, 3]. In this area, isothiourea compounds have received much attention due to the presence of this moiety in many molecules that are widely used in functional materials and pharmaceuticals [4, 5]. Recently, thiourea derivatives emerged as powerful tools for asymmetric organocatalysis [6]. Therefore, we would like to disclose our recent efforts toward the synthesis of various carbamimidothioate derivatives via catalyst-free tandem reactions of amines with aryl isothiocyanates in the presence of aryl diazonium salts. Usually, the methods employed for the synthesis of carbamimidothioates include copper-catalyzed arylation of thiourea compounds in the presence of diazonium salts [7]. In addition, Kartritzky and co-workers [8, 9] reported formation of *S*-aryl isothiourea by a metathesis exchange reaction between isothioureas and aryl isocyanates. An *S*-aryl carbamimidothioate has been previously formed in a low yield as an unwanted by-product via a reaction involving benzyne as the electrophile [10]. To circumvent these difficulties, the choice of a metal with moderate affinity for aryl diazonium salts or the development of metal-free *S*-arylation would be highly desirable. We herein present a new three-component coupling under mild, economic and efficient conditions that are desirable for this C_{aryl}–S bond formation (Scheme 1).

Results and discussion

We started our studies by exposing aryldiazonium fluoroborates **1** to aryl thiourea, prepared in situ by the reaction of secondary amines **3** with aryl isothiocyanates **2** in DMF under air atmosphere. A facile reaction leading to the exclusive formation of aryl *N*,*N*-dialkyl-*N*′-arylcarbamimidothioates **4** occurred. But these products are not prepared

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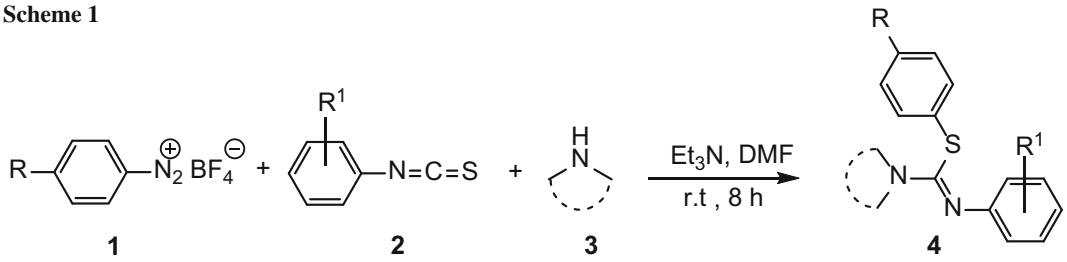
Scheme 1



Product	R	R^1	Amine **3**	Yield /%
4a	NO_2	H	Morpholine	72
4b	OMe	H	Diethylamine	70
4c	H	H	Diethylamine	68
4d	NO_2	H	Diethylamine	67
4e	OMe	H	Morpholine	76
4f	NO_2	4-F	Morpholine	68
4g	NO_2	4-F	Diethylamine	71
4h	Cl	2,4-Cl_2	Morpholine	65

with good total yield by two-step synthesis compared to the one-pot reaction.

The products were characterized by spectroscopic analysis. The ^{1}H NMR spectrum of **4a** showed signals for the morpholine ring at $\delta = 3.67$ ppm, and signals at 6.67–8.03 ppm for phenyl and 4-nitrophenyl moiety. The ^{13}C resonance signals of the two OCH_2CH_2N groups were seen at $\delta = 48.5$ and 66.4 ppm, whereas the imine signal was seen at 150.2 ppm. The structure of **4a** was established unambiguously by an X-ray crystallography (Fig. 1).

On the basis of nucleophilic reaction of sulfur atom with diazonium salts [11], it is reasonable to assume that aryl thiourea **5** results from the first addition of cyclic and open chain amine **3** to aryl isothiocyanate **2**. Then, the aryldiazonium fluoroborate **1** is attacked by the aryl thiourea ion **6** to form products **4**, through N_2 elimination (Scheme 2).

In summary, we have uncovered a novel and simple synthesis of *N*,*N*-dialkyl-*N*′-arylcarbamimidothioate derivatives by reaction of amines, aryl isothiocyanates with aryl diazonium salts under catalyst-free conditions. This reaction will be useful for the conversion of aryl thiourea to aryl carbamimidothioate.

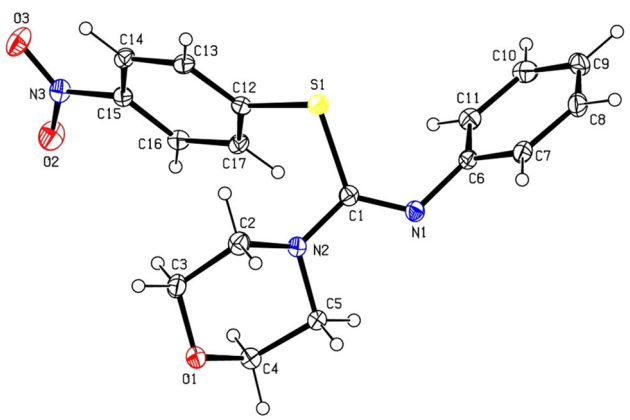


Fig. 1 Structure of product **4a**

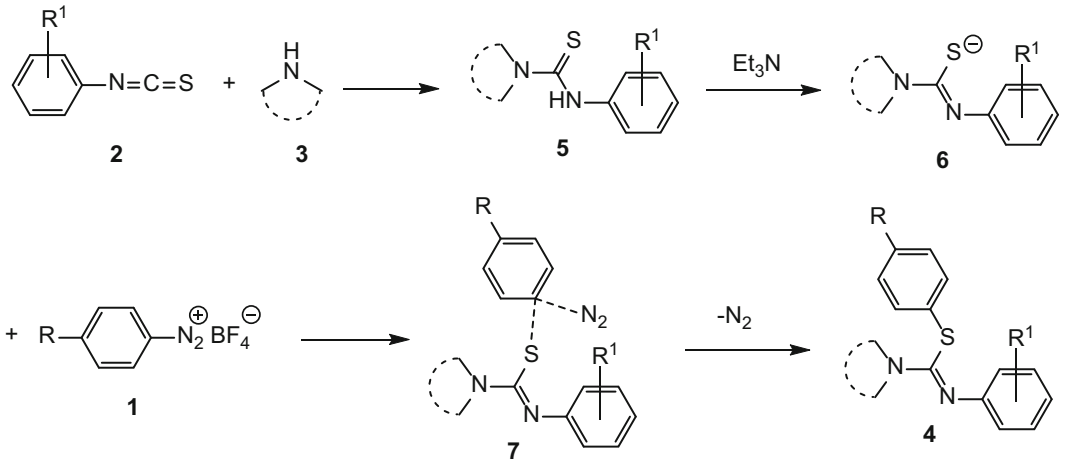
Experimental

An Electrothermal-9100 apparatus was used for melting points. The data of IR, NMR, elemental analysis, and mass spectra were recorded by Shimadzu-IR-460 spectrometer, Bruker DRX-400, Vario EL III CHNOS, and Finnigan-MAT-8430EI-MS, respectively.

General procedure for the synthesis of ***4***

Aryl isothiocyanate **2** (2.2 mmol) and amine **3** (2 mmol) in 6 cm^3 DMF were reacted for 20 min at room temperature. Then, Et_3N (2 mmol) and aryl diazonium fluoroborate **3** (2.2 mmol) were added and the reaction was allowed to stir for 8 h at this temperature. The mixture was poured into 8 cm^3 H_2O, extracted twice with 10 cm^3 AcOEt, dried ($MgSO_4$), and the solvent was evaporated. The reaction mixture was purified by silica gel column chromatography

Scheme 2



using 30 % ethyl acetate in hexane as eluent to give product **4**.

4-Nitrophenyl N-phenylmorpholine-4-carbimidothioate (**4a**, $C_{17}H_{17}N_3O_3S$)
Colorless powder; yield 72 %; m.p.: 120 °C; IR (KBr): $\overline{\nu} = 2926, 1610, 1564, 1495, 1321, 1210, 950, 731\ cm^{-1}$; ^1H NMR (400.1 MHz, $CDCl_3$): $\delta = 3.67$ (br, 8H), 6.67–6.71 (m, 2H), 6.92–6.98 (m, 1H), 7.10–7.16 (m, 2H), 7.30 (d, $^3J = 9.0$ Hz, 2H), 8.03 (d, $^3J = 9.0$ Hz, 2H) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 48.5, 66.4, 122.2, 123.6, 128.2, 129.5, 143.1, 145.8, 147.7, 149.8, 150.2$ ppm; EI-MS: $m/z = 343$ (M^+, 15), 155 (56), 109 (64), 77 (100). Crystallographic data for this compound have been deposited at the Cambridge Crystallographic Data Centre as CCDC-1013351.

4-Methoxyphenyl-N,N-diethyl-N′-phenylcarbamimidothioate (**4b**, $C_{18}H_{22}N_2OS$)
Brown oil; yield 70 %; IR (KBr): $\overline{\nu} = 2910, 1574, 1468, 1415, 1249, 1106, 837\ cm^{-1}$; ^1H NMR (400.1 MHz, $CDCl_3$): $\delta = 1.08$ (t, $^3J = 6.8$ Hz, 6H), 3.49 (q, $^3J = 6.8$ Hz, 4H), 3.68 (s, 3H), 6.56–6.58 (m, 2H), 6.60 (d, $^3J = 8.8$ Hz, 2H), 6.78 (t, $^3J = 7.6$ Hz, 1H), 6.92 (d, $^3J = 8.8$ Hz, 2H), 6.99–7.02 (m, 2H) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 13.5, 44.2, 55.3, 114.3, 121.4, 122.0, 123.5, 128.1, 133.3, 150.6, 152.5, 158.9$ ppm; EI-MS: $m/z = 314$ (M^+, 20), 140 (50), 109 (75), 77 (100).

Phenyl-N,N-diethyl-N′-phenylcarbamimidothioate (**4c**, $C_{17}H_{20}N_2S$)
Brown oil; yield 68 %; IR (KBr): $\overline{\nu} = 2908, 1588, 1523, 1431, 1265, 1121, 963\ cm^{-1}$; ^1H NMR (400.1 MHz, $CDCl_3$): $\delta = 1.08$ (t, $^3J = 7.2$ Hz, 6H), 3.49 (q, $^3J = 7.2$ Hz, 4H), 6.58–6.60 (m, 2H), 6.77–6.80 (m, 1H), 6.98–7.00 (m, 2H), 7.05 (br, 5H) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 13.4, 44.1, 121.7, 122.1, 126.5, 128.1, 128.7, 130.5, 131.0, 133.5, 150.6$ ppm; EI-MS: $m/z = 284$ (M^+, 25), 109 (65), 77 (100).

4-Nitrophenyl-N,N-diethyl-N′-phenylcarbamimidothioate (**4d**, $C_{17}H_{19}N_3O_2S$)
Colorless powder; yield 67 %; m.p.: 75 °C; IR (KBr): $\overline{\nu} = 2918, 1586, 1531, 1489, 1423, 1350, 1208, 1121, 934\ cm^{-1}$; ^1H NMR (400.1 MHz, $CDCl_3$): $\delta = 1.26$ (t, $^3J = 6.8$ Hz, 6H), 3.63 (q, $^3J = 6.8$ Hz, 4H), 6.66 (d, $^3J = 7.6$ Hz, 2H), 6.88 (t, $^3J = 7.2$ Hz, 1H), 7.07 (t, $^3J = 8.0$ Hz, 2H), 7.24 (d, $^3J = 8.8$ Hz, 2H), 7.99 (d, $^3J = 8.8$ Hz, 2H) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 13.7, 44.6, 122.2, 123.6, 126.4, 128.2, 129.5, 143.1, 145.8, 147.7, 149.8$ ppm; EI-MS: $m/z = 329$ (M^+, 15), 155 (68), 109 (70), 77 (100).

4-Methoxyphenyl N-phenylmorpholine-4-carbimidothioate (**4e**, $C_{18}H_{20}N_2O_2S$)
Brown oil; yield 76 %; IR (KBr): $\overline{\nu} = 2901, 1578, 1468, 1412, 1263, 1165, 1021, 823, 741\ cm^{-1}$; ^1H NMR (400.1 MHz, $CDCl_3$): $\delta = 3.54$ (br, 4H), 3.59 (br, 4H), 3.79 (s, 3H), 6.75–6.78 (m, 4H), 7.00 (br, 1H), 7.14 (d, $^3J = 7.2$ Hz, 2H), 7.21 (d, $^3J = 7.2$ Hz, 2H) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 48.5, 55.3, 66.4, 114.6, 121.8, 122.6, 123.2, 128.4, 133.6, 150.0, 155.1, 159.2$ ppm; EI-MS: $m/z = 328$ (M^+, 10), 140 (61), 109 (70), 77 (100).

4-Nitrophenyl N-(4-fluorophenyl)morpholine-4-carbimidothioate (**4f**, $C_{17}H_{16}FN_3O_3S$)
Colorless powder; yield 68 %; m.p.: 111 °C; IR (KBr): $\overline{\nu} = 2914, 1613, 1579, 1523, 1441, 1325, 1281, 1213, 1121, 931, 841, 720\ cm^{-1}$; ^1H NMR (400.1 MHz, $CDCl_3$): $\delta = 3.68$ (br, 8H), 6.64–6.67 (m, 2H), 6.81–6.86 (m, 2H),

7.30 (d, $^3J = 8.4$ Hz, 2H), 8.06 (d, $^3J = 8.4$ Hz, 2H) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 48.3$, 66.4, 115.1 (d, $^2J_{CF} = 19.9$ Hz), 122.9 (d, $^3J_{CF} = 7.1$ Hz), 123.9, 129.9, 142.1, 145.4, 146.2, 150.7, 158.5 (d, $^1J_{CF} = 216.1$ Hz) ppm; EI-MS: $m/z = 361$ (M^+, 25), 317 (40), 155 (63), 110 (53), 109 (70), 77 (100).

4-Nitrophenyl-N,N-diethyl-N′-(4-fluorophenyl)carbamimidothioate (**4g**, $C_{17}H_{18}FN_3O_2S$)
Colorless powder; yield 71 %; m.p.: 102 °C; IR (KBr): $\overline{\nu} = 2908$, 1618, 1586, 1545, 1414, 1343, 1241, 1161, 895, 758 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$): $\delta = 1.25$ (t, $^3J = 6.8$ Hz, 6H), 3.62 (q, $^3J = 6.8$ Hz, 4H), 6.63–6.67 (m, 2H), 6.80–6.85 (m, 2H), 7.30 (d, $^3J = 8.4$ Hz, 2H), 8.05 (d, $^3J = 8.4$ Hz, 2H) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 13.7$, 44.5, 115.1 (d, $^2J_{CF} = 19.9$ Hz), 122.9 (d, $^3J_{CF} = 7.1$ Hz), 123.9, 129.9, 142.1, 145.4, 146.2, 152.8, 158.5 (d, $^1J_{CF} = 216.3$ Hz) ppm; EI-MS: $m/z = 347$ (M^+, 13), 317 (48), 155 (60), 110 (46), 109 (80), 77 (100).

4-Chlorophenyl N-(2,4-dichlorophenyl)morpholine-4-carbimidothioate (**4h**, $C_{17}H_{15}Cl_3N_2OS$)
Brown oil; yield 65 %; IR (KBr): $\overline{\nu} = 2914$, 1578, 1523, 1461, 1243, 1130, 1043, 976, 695 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$): $\delta = 3.61$–3.63 (m, 4H), 3.67–3.69 (m, 4H), 6.70 (d, $^3J = 8.4$ Hz, 1H), 7.05–7.08 (m, 1H), 7.15–7.23 (m, 4H), 7.26–7.28 (m, 1H) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 48.5$, 66.4, 124.0, 126.9, 127.2, 128.0, 128.9, 129.2, 130.0, 132.7, 133.9, 145.5, 155.0 ppm; EI-MS: $m/z = 401$ (M^+, 20), 109 (65), 92 (50), 86 (45), 77 (100).

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