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Csp^3–N bond formation in aminothiophenes by 1,1-dibromo isocyanide: the unexpected 1,5-binucleophilicity of substrates

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Abstract The *N*-cyclohexylcarbonimidoyl dibromide in situ, generated by cyclohexylisocyanide and bromine in reaction with several deactivated 5-acetyl-4-amino-2-methylsulfanyl-3-carbonitrile, appears as a cyclohexyl transformer to the substrate via Csp^3–N bond formation without using any base or catalyst at room temperature. The present transformation suggests three main innovations. First, regarding the selective monoalkylation of aromatic amines, the performed condition is unprecedented. Second, for the first time in the field of isocyanide-based reactions, isocyanide is applied as an alkyl transformer agent. Third, this is the first example of coupling aminothiophenes with a secondary alkyl group. Interestingly, high yield and selectivity, short reaction time, easy purification accompany this protocol. Through this study, we investigated the electronic effects of substituents linked to acetyl on the efficiency of the reaction. Also, the potential of isocyanide dibromide for the synthesis of cyclic guanidine is evaluated.

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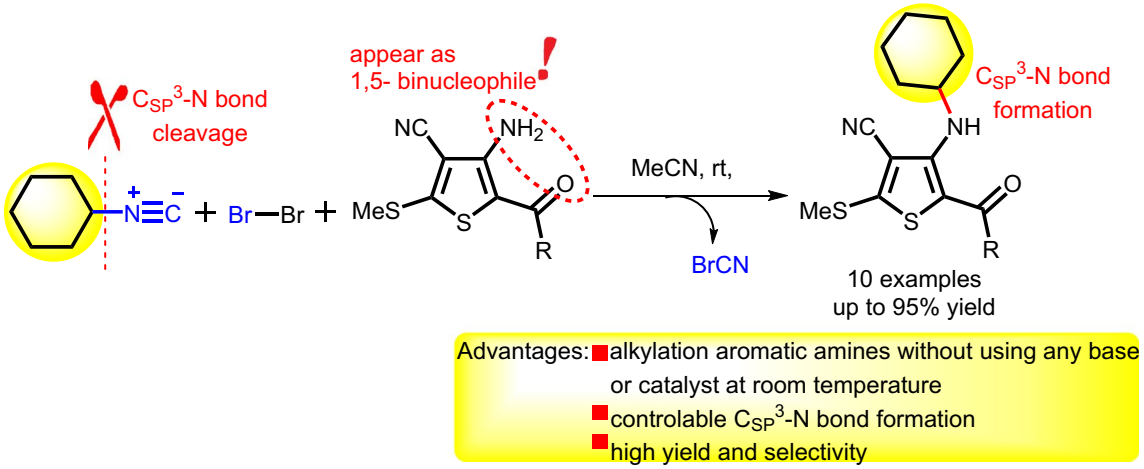
Graphical Abstract An efficient, useful and general procedure for the synthesis of 5-aroyl-4-cyclohexylamino-2-methylsulfanyl-3-thienyl cyanide via one-pot three-component reaction of 5-acetyl-4-amino-2-methylsulfanyl-3-carbonitrile, cyclohexylisocyanide and bromine in acetonitrile at room temperature has been described. The major advantages of this protocol are high yield and selectivity, short reaction time, easy purification.



Keywords Csp^3–N bond formation · Selective monoalkylation · Isocyanide dihalides · Aminothiophene · Tetrasubstituted thiophenes

Introduction

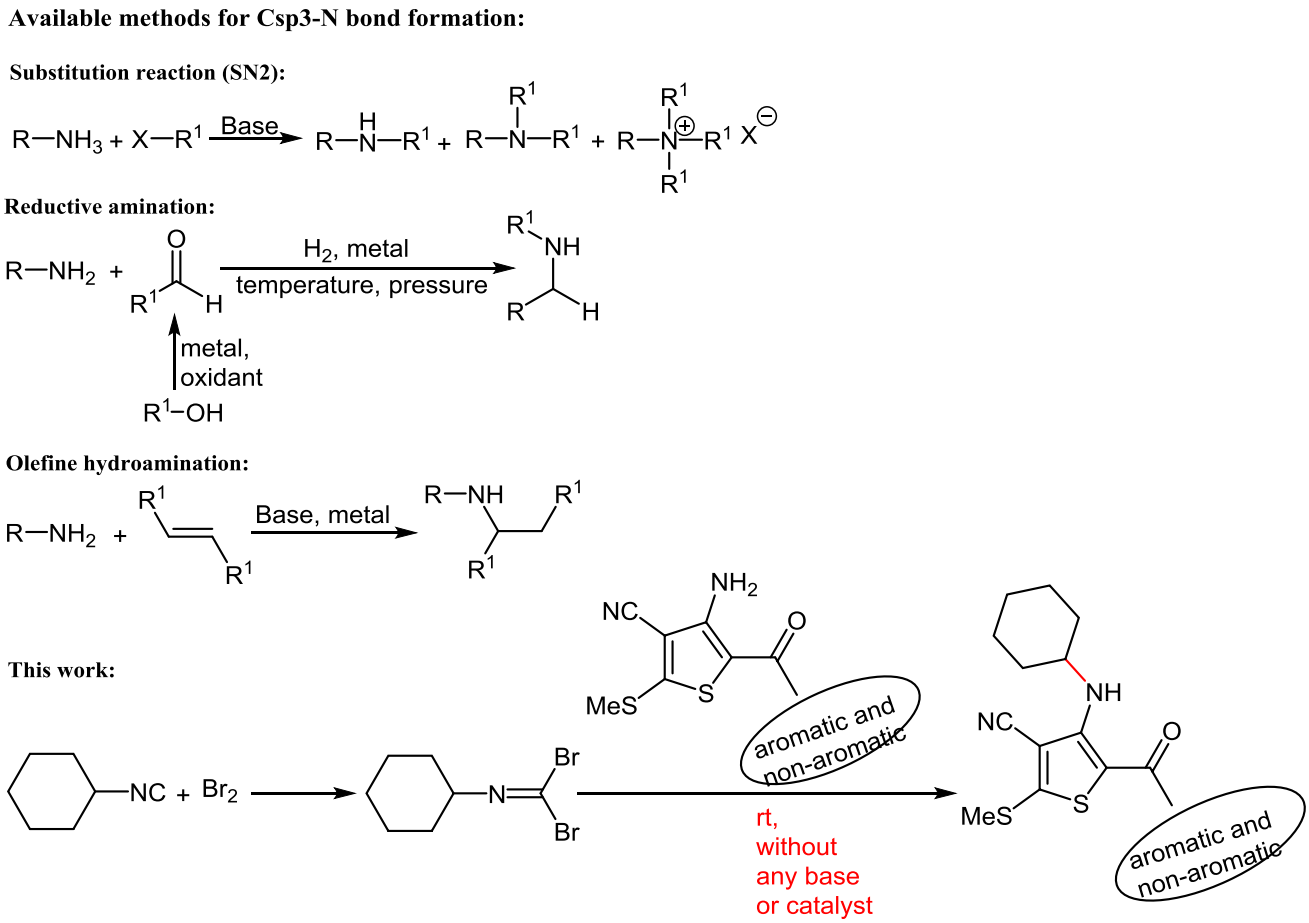
Nitrogen-containing structures, omnipresent in natural products, pharmaceuticals and functional polymers/materials, are among the most valuable classes of compounds [1, 2]. The development of efficient methodologies for C–N bond formation is a central challenge in organic chemistry [3–10]. In this regard, the development of synthetic approaches for selective mono-*N*-alkylation has been the focus of research studies for many decades. The widely used substitution reaction (SN_2) for Csp^3–N monoalkylation through direct addition of nucleophile to electrophilic reagents, such as alkyl halide, often fails due to competitive consecutive overalkylation processes, even if the single equivalent of electrophile is used (Scheme 1) [11, 12]. Other available methods for Csp^3–N monoalkylation include reductive amination [13, 14], olefin hydroamination [15, 16], alkylation by alkyl halides equivalents, such as dialkyl sulfates or sulfonates [17–19], and alkylation by alcohols (Scheme 1) [20–26].

Thiophenes, as one of the most fundamental sulfur-containing heterocycles, are of particular interest from the point of view of both medicinal and synthetic chemists due to their utility as versatile intermediates in organic synthesis [27, 28]. A review of the literature reveals a lack of enough studies on direct *N*-alkylation of aminothiophene [29, 30]. Accordingly, Hoischen and co-workers demonstrated that *N*-methylation of 5-acetyl-4-amino-2-methylsulfanyl-3-carbonitrile substantially increases their microbicides and herbicides effect. However, the reported approaches for *N*-alkylation of aminothiophenes are limited to alkylation with only active alkyl halides such as methyl iodide and ethyl iodide. There is no report for direct Csp^3–N bond formation with a secondary alkyl group, to the best of our knowledge.

Generally, beside difficulties in controlling the selective monoalkylation and harsh reaction condition, the presence of one of the elements, including a base catalyst (for aromatic amines), metal catalyst or heat, has been reported in all documented procedures for Csp^3–N monoalkylation. Therefore, inventing a protocol that lacks these three necessary obligations would be of high interest.

In this account, and in continuation of our efforts to develop facile access to polysubstituted thiophene derivatives [31, 32], we have now established a selective Csp^3–N monoalkylation for tetrasubstituted thiophenes including 5-acetyl-4-amino-2-methylsulfanyl-3-carbonitrile, without using any base or catalyst at room temperature.

This is achieved via a one-pot reaction of cyclohexylisocyanide, bromine and the thiophene derivatives. This transformation needs to be considered from several perspectives. The corresponding aminothiophene, due to deactivation effect of electron-withdrawing groups in the ortho-position, is considered as an unreactive substrate. Nevertheless, in reaction with the in situ generated *N*-cyclohexylcarbonimidoyl dibromide, aminothiophene performs an unusual



Scheme 1 Comparison between Csp^3–N bond formation methods and this work, substituting cyclohexyl on aromatic amine

function as a 1,5-binucleophile (N and O) partner through two consecutive Csp^2–N and Csp^2–O substitution reactions, under absolutely inert condition. In another view, under the performed condition of this protocol, cyclohexylisocyanide appears as cyclohexyl transformer to amine moiety via Csp^3–N bond cleavage. To the best of our knowledge, this is a novel event in the field of isocyanide chemistry. More importantly, this study represents the first selective monoalkylation of a secondary alkyl in aminothiophenes as a representative of aromatic amines that marks the important feature of this transformation under unique conditions of free base and free catalyst at room temperature.

Experimental section

Melting points were measured on an Electrothermal 9100 apparatus. IR spectra were recorded as KBr pellets on a Nicolet FT-IR 100 spectrometer. ^{1}H NMR (300and) and ^{13}C NMR (100 MHz) spectra were obtained using Bruker DRX-300 AVANCE. All NMR spectra at room temperature were recorded in DMSO-d_6. Chemical shifts are reported in parts per million (δ) downfield from an internal tetramethylsilane reference. Coupling constants (*J* values) are reported in hertz (Hz), and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Elemental analyses for C, H and N were performed using a Heraeus CHN–O–Rapid analyzer. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 20 or 70 eV. Due to very low solubility of the products **3h**, no ^{13}C NMR data were obtained for these products.

General experimental procedure for the synthesis of cyclohexylaminothiophene (3) To a well-stirred solution of cyclohexylisocyanide (1.0 equiv) in acetonitrile (1.0 mL) were successively added bromine (1.0 equiv) and, after 5 min at room temperature, aminothiophene (1 equiv). After completion of reaction (checked by TLC analysis), the reaction mixture filtered to give crude product, which was further washed by acetonitrile to give the pure adducts **3a–k**.

5-Benzoyl-4-cyclohexylamino-2-methylsulfanyl-3-thienyl cyanide (3a) Yellow powder; mp 166–167 °C; 0.34 g,

yield 95%. IR (KBr): 3413 (NH), 2226 (CN), 1628 (C=O), 1595, 1537 and 1509 (Ar). ^{1}H NMR (300 MHz, DMSO-d_6): 1.04–1.87 (10H, m, 5CH_2), 2.67 (3H, s, SMe), 2.91–2.95 (1H, m, CH–N), 7.48–7.60 (3H, m, CH_{para} and 2CH_{meta} of ph), 7.67 (2H, d, $^3J_{HH}$ = 7.2 Hz, CH of ph), 7.92 (1H, brs, NH). ^{13}C NMR (75 MHz, DMSO): 17.1, 24.1, 25.1, 30.5, 30.6, 49.6, 97.0, 106.5, 112.9, 127.5, 129.2, 131.8, 140.4, 156.8, 163.3, 185.9. (EI, 70 eV): 357 (M^{+1}, 76), 274 (79), 258 (32), 249 (1), 227 (10), 197 (58), 176 (2), 169 (20), 154 (16), 142 (53), 121 (25), 105 (92), 94 (26), 84 (24), 77 (100). Anal. Calcd. for $C_{19}H_{20}N_2OS_2$ (356.50): C, 64.01; H, 5.65; N, 7.86; Found C, 63.99; H, 5.67; N, 7.88.

5-(4-Chlorobenzoyl)-4-cyclohexylamino-2-methylsulfanyl-3-thienyl cyanide (3b) Yellow powder; m.p 190–191 °C; 0.32 g, yield 83%. IR (KBr): 3406, 3301 (NH_2), 2218 (CN), 1597 (C=O), 1490, 1398 (Ar). ^{1}H NMR (300 MHz, DMSO-d_6): 1.08–1.88 (10H, m, 5CH_2), 2.68 (3H, s, SMe), 2.95–2.97 (1H, m, CH–N), 7.57 (2H, d, $^3J_{HH}$ = 8.1 Hz, 2CH of Ar), 7.70 (2H, d, $^3J_{HH}$ = 8.1 Hz, 2CH of Ar), 7.87 (1H, brs, NH). ^{13}C NMR (75 MHz, DMSO): 17.1, 24.2, 25.1, 30.6, 30.7, 49.6, 97.1, 106.2, 112.8, 129.3, 129.5, 136.6, 139.1, 157.0, 163.7, 184.5. (EI, 70 eV): 391 (M^{+1}, 80), 307 (63), 292 (6), 273 (2), 258 (2), 244 (6), 197 (10), 183 (1), 169 (8), 154 (8), 139 (86), 121 (6), 111 (100), 94 (12), 84 (11), 75 (36). Anal. Calcd. for $C_{19}H_{19}ClN_2OS_2$ (390.94): C, 58.37; H, 4.90; N, 7.17; Found C, 50.34; H, 4.91; N, 7.16.

4-Cyclohexylamino-2-methylsulfanyl-5-(4-nitrobenzoyl)-3-thienyl cyanide (3c) Pale yellow powder; m.p 218–219 °C; 0.341 g, yield 85%. IR (KBr): 3423 (NH), 2216 (CN), 1648 (C=O), 1593 (Ar), 1518, 1325 (NO_2). ^{1}H NMR (300 MHz, DMSO-d_6): 1.08–1.89 (10H, m, 5CH_2), 2.68 (3H, s, SMe), 2.95–2.97 (1H, m, CH–N), 7.84 (1H, brs, NH), 7.93 (2H, d, $^3J_{HH}$ = 8.4 Hz, 2CH of Ar), 8.34 (2H, d, $^3J_{HH}$ = 8.4 Hz, 2CH of Ar). ^{13}C NMR (75 MHz, DMSO): 17.1, 24.1, 25.1, 30.6, 30.7, 49.6, 96.9, 106.2, 112.7, 124.4, 129.0, 145.8, 149.2, 157.4, 164.7, 183.7. (EI, 70 eV): 401 (M^+, 100), 319 (16), 304 (1), 272 (14), 258 (3), 226 (2), 197 (24), 165 (78), 155 (18), 151 (40), 146 (45), 137 (78), 120 (80), 104 (46), 92 (50), 84 (49), 76 (45). Anal. Calcd for $C_{19}H_{19}N_3O_3S_2$ (401.49): C, 56.84; H, 4.77; N, 10.47; Found C, 56.89; H, 4.75; N, 10.44.

4-Cyclohexylamino-2-methylsulfanyl-5-(3-nitrobenzoyl)-3-thienyl cyanide (3d) Yellow powder; m.p 224–225 °C; 0.325 g, yield 81%. IR (KBr): 3411 (NH), 2223 (CN), 1650 (C=O), 1601 and 1496 (Ar), 1530 and 1496 (NO_2). ^{1}H NMR (300 MHz, DMSO-d_6): 1.09–1.89 (10H, m, 5CH_2), 2.68 (3H, s, SMe), 3.01–3.03 (1H, m, CH–N), 7.82 (1H, t, $^3J_{HH}$ = 7.5 Hz, CH of Ar), 7.85 (H, brs, NH), 8.14 (1H, d, $^3J_{HH}$ = 7.5 Hz, CH of Ar), 8.38 (1H, d, $^3J_{HH}$ = 7.5 Hz, CH of Ar), 8.41 (1H, s, CH of Ar). ^{13}C NMR (75 MHz, DMSO): 17.2, 24.1, 25.1, 30.7, 49.6, 97.0, 106.0, 112.7, 122.4, 126.2, 131.1, 133.8, 141.5, 148.2, 157.4, 164.4, 183.0. (EI, 70 eV): 401 (M^+, 77), 319 (35), 304 (1), 272 (12), 258 (5), 244 (15), 229 (2), 197 (74), 185 (1), 169 (20), 154 (20), 151 (68), 142 (71), 127 (21), 116 (34), 104 (46), 94 (73), 83 (55), 76 (100). Anal. Calcd. for $C_{19}H_{19}N_3O_3S_2$ (401.50): C, 56.84; H, 4.77; N, 10.47; Found C, 56.87; H, 4.77; N, 10.48.

4-Cyclohexylamino-5-(4-methoxybenzoyl)-2-methylsulfanyl-3-thienyl cyanide (3e) Orange powder; m.p 177–178 °C; 0.305 g, yield 79%. IR (KBr): 3420 (NH), 2224 (CN), 1629 (C=O), 1602 and 1492 (Ar), 1275 (C–O). ^{1}H NMR (300 MHz, DMSO-d_6): 1.08–1.88 (10H, m, 5CH_2), 2.69 (3H, s, SMe), 2.95 (1H, m, CH–N), 3.82 (3H, s, OMe), 8.04 (2H, d, $^3J_{HH}$ = 8.1 Hz, 2CH of Ar), 7.7 (2H, d, $^3J_{HH}$ = 8.4 Hz, 2CH of Ar), 7.86 (1H, brs, NH). ^{13}C NMR (75 MHz, DMSO): 17.1, 24.1, 25.1, 30.6, 30.7, 49.7, 55.9, 97.2, 106.4, 113.1, 114.3, 129.8, 132.8, 156.6, 162.2, 162.4, 185.0. (EI, 70 eV): 386 (M^+, 100), 304 (73), 289 (27), 274 (6), 261 (9), 244 (7), 229 (1), 217 (2), 197 (18), 185 (5), 170 (6), 154 (6), 144 (23), 135 (56), 121 (8), 107 (39), 92 (63), 83 (47), 77 (80). Anal. Calcd. for $C_{20}H_{22}N_2O_2S_2$ (386.52): C, 62.15; H, 5.74; N, 7.25; Found C, 62.18; H, 5.72; N, 7.26.

5-Acetyl-4-cyclohexylamino-2-methylsulfanyl-3-thienyl cyanide (3f) White powder; m.p 140–141 °C; 0.235 g, yield 80%. IR (KBr): 3444 (NH), 2225 (CN), 1682 (C=O). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.10–1.90 (10H, m, 5CH_2), 2.09 (3H, s, COMe), 2.95–2.97 (1H, m, CH–N), 3.08 (3H, s, SMe), 7.95 (1H, brs, NH). ^{13}C NMR (75 MHz, DMSO) δ 17.7 (SMe), 24.2, 25.5, 30.7 (CH_2), 32.8 (COMe), 49.7 (CH–N), 99.9 (C–CN), 111.8 (CN), 125.6 (C^5), 150.5 (C^2), 156.7 (C^4), 182.3 (C=O). (EI, 70 eV): 295 (M^{+1}, 100), 212 (67), 197 (95), 183 (12), 169 (63), 155 (50), 142 (80), 125 (20), 111 (17), 94 (35), 84 (50), 72 (37). Anal. Calcd. for $C_{14}H_{18}N_2OS_2$ (294.43): C, 57.11; H, 6.16; N, 9.51; Found C, 57.12; H, 6.18; N, 9.49.

Ethyl 2-(4-cyano-3-cyclohexylamino-5-methylsulfanyl-2-thienyl)-2-oxoacetate (3g) Pale green; m.p 193–194 °C; 0.271 g, yield 77%. IR (KBr): 3381 (NH), 2220 (CN), 1720, 1602 (C=O). ^{1}H NMR (300 MHz, DMSO-d_6): 1.05–1.88 (10H, m, 5CH_2), 1.30 (3H, t, $^3J_{HH}$ = 6.6 Hz, OCH_2CH_3), 2.77 (3H, s, SMe), 2.91–2.95 (1H, m, CH–N), 4.30 (2H, q, $^3J_{HH}$ = 6.9 Hz, OCH_2CH_3), 8.33 (1H, brs, NH). ^{13}C NMR (75 MHz, DMSO): 14.3, 16.6, 24.2, 25.1, 30.7, 49.6, 62.8, 95.1, 104.3, 112.7, 159.9, 162.7, 168.7, 170.4. (EI, 70 eV): 352 (M^+, 100), 270 (74), 244 (8), 197 (66), 183 (6), 169 (46), 155 (26), 142 (90), 107 (15), 94 (33), 84 (53), 72 (30). Anal. Calcd. for $C_{16}H_{20}N_2O_3S_2$ (352.46): C, 54.52; H, 5.72; N, 7.95; Found C, 54.53; H, 5.74; N, 7.98.

Methyl 3-(4-cyano-3-cyclohexylamino-5-methylsulfanyl-2-thienyl)-3-oxopropanoate (3h) Pink powder; m.p 297–298 °C; 0.282 g, yield 80%. IR (KBr): 3338 (NH), 2234 (CN), 1639 (CO_2Me), 1609 (C=O). ^{1}H NMR (300 MHz, DMSO-d_6):1.08–1.88 (10H, m, $5CH_2$), 2.72 (3H, s, SMe), 2.95–2.97 (1H, m, CH–N), 3.85 (2H, s, CH_2CO_2Me), 4.05 (3H, s, CH_2CO_2Me), 7.84 (1H, brs, NH). (EI, 70 eV): 352 (M^+, 88), 270 (30), 238 (50), 223 (4), 212 (5), 197 (100), 183 (9), 170 (55), 155 (13), 142 (43), 130 (16), 123 (20), 116 (23), 109 (27), 102 (57), 94 (17), 84 (48), 72 (24). Anal. Calcd. for $C_{16}H_{20}N_2O_3S_2$ (352.46): C, 54.52; H, 5.72; N, 7.95; Found C, 54.51; H, 5.73; N, 7.93.

Methyl 4-cyano-3-cyclohexylamino-5-methylsulfanyl-2-thiophenecarboxylate (3i) White powder; m.p 199–200 °C; 0.261 g, yield 84%. IR (KBr): 3410 (NH), 2218 (CN), 1669 (CO_2Me), 1313 and 1199 (C–O). ^{1}H NMR (300 MHz, DMSO-d_6): 1.09–1.88 (10H, m, $5CH_2$), 2.70 (3H, s, SMe), 2.95–2.97 (1H, m, CH–N), 3.73 (2H, s, OMe), 7.84 (1H, brs, NH). ^{13}C NMR (75 MHz, DMSO): 17.1, 24.2, 25.0, 30.7, 30.8, 49.7, 51.9, 96.5, 98.5, 113.1, 154.5, 160.4, 162.7 (. (EI, 70 eV):311 (M^{+1}, 100), 228 (81), 213 (4), 197 (90), 185 (18), 170 (27), 154 (9), 142 (36), 125 (7), 109 (25), 98 (29), 84 (31). Anal. Calcd. for $C_{14}H_{18}N_2O_2S_2$ (310.43): C, 54.17; H, 5.84; N, 9.02; Found C, 54.17; H, 5.81; N, 9.03.

Ethyl 4-cyano-3-cyclohexylamino-5-methylsulfanyl-2-thiophenecarboxylate (3k) White powder; m.p 205–207 °C; 0.282 g, yield 87%. IR (KBr): 3213 (NH), 2216 (CN), 1693 (C=O), 1276 (C–O). ^{1}H NMR (300 MHz, DMSO-d_6): 1.08–1.88 (10H, m, $5CH_2$ and OCH_2CH_3), 1.28 (3H, t, $^3J_{HH}$ = 7.2 Hz, OCH_2CH_3), 2.68 (3H, s, SMe), 3.59 (1H, m, CH–N), 4.31 (2H, q, $^3J_{HH}$ = 7.2 Hz, OCH_2CH_3), 9.03 (1H, brs, NH). ^{13}C NMR (75 MHz, DMSO): 14.6, 18.3, 24.5, 25.1, 31.3, 51.9, 61.9, 106.7, 112.6, 115.4, 150.5, 156.1, 160.5. (EI, 70 eV): 324(M^+, 78), 270 (100), 197 (52), 170 (32), 155 (27), 142 (12), 125 (14), 117 (23), 109 (63), 94 (45), 84 (38).Anal. Calcd. for $C_{15}H_{20}N_2O_2S_2$ (324.45): C, 55.53; H, 6.21; N, 8.63; Found C, 55.52; H, 6.21; N, 8.60.

Experimental procedure for the synthesis of bicyclic guanidine (9) After implementation of the required conditions for the synthesis *N*-cyclohexylcarbonimidoyl dibromide **1a**, 1,4,5,6-tetrahydro-2-pyrimidinylhydrazine **8** was added to the mixture and reaction stirred for 5 min in room temperature. The formed precipitate was filtered and further washed by acetonitrile to give pure adduct (**9**).

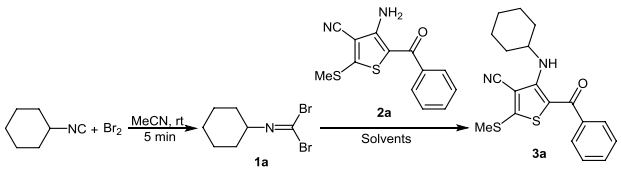
***N*^{3}-cyclohexyl-1,2,3,5,6,7-hexahydro[1, 2, 4] triazolo[4,3-*a*]pyrimidin-3-iminehydrobromide (9)** Pale yellow powder; m.p 188–189 °C; 0.223 g, yield 74%. IR (KBr): 3223 and 3280 (NH). ^{1}H NMR (300 MHz, DMSO-d_6): 1.04–2.00 (12H, m, $6CH_2$), 2.95–2.98 (1H, m, CH–N), 3.38–3.43 (2H, m, CH_2N=C), 4.04 (2H, m, CH_2N–C), 7.93–7.94 (1H, brs, NH), 8.47 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO): 19.36, 24.16, 25.00, 30.66, 30.71, 38.60, 42.10, 140.10, 148.10. (EI, 70 eV): 222 (M^{+1}, 100), 179 (56), 165 (44), 138 (23), 124 (36), 97 (57), 85(42), 83 (72), 56 (43). Anal. Calcd. for $C_{11}H_{20}N_5Br$ (302.21): C, 59.70; H, 9.90; N, 31.65; Found C, 59.71; H, 9.91; N, 31.65.

Results and discussion

The cyclohexylisocyanide was chosen as a model input for starting material. When treated with 1 equivalent of bromine in acetonitrile at room temperature, the cyclohexylisocyanide was totally transformed to the *N*-cyclohexyldibromomethanimine **1a** [33]. Also, tetrasubstituted thiophenes **2** were prepared according to our recently reported approach from cyclic thiourea, ketene dithioacetal and corresponding primary and secondary α-haloketones [31]. The result of the reaction of **1a** with **2a** as a model reaction is given in Table 1.

Similar to the most derivatives of 1,1-dihalogeno isocyanides, **1a** is highly hygroscopic matter and is not stable enough to be stored for long [34]. El Kaim and co-workers

Table 1 Screening studies of the addition of **1a** to **2a**



Entry	Solvent	Time (s)	Yield[a] (%)
1	MeCN	30	95
2[b]	CH_2Cl_2	70	91
3[b]	$CHCl_3$	50	89
4[b]	Toluene	240	90
5[b]	THF	130	86
6[b]	DMF	30	92
7[b]	DMSO	–	91
8[b]	MeOH	260	74
9[b]	EtOH	310	67
10[c]	MeCN	30	95

Reaction performed with 1 mmol of **1a** and 1 mmol of **2a** in 3 mL of solvent at 25 °C and the required time for the completion of the reactions obtained by checking TLC in every 10 s

[a]Isolated yield

[b]Reaction conditions: one pot, after implementing the condition for synthesis **1a**, MeCN was evaporated and interchange of the solvents evaluated

[c]Dry solvent, under inert atmosphere

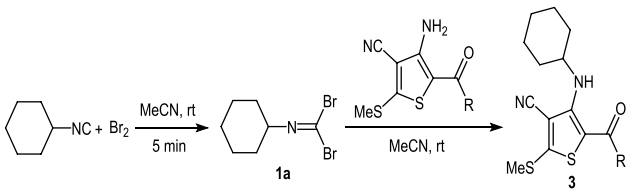
efficiently synthesized 1,1-dibromo isocyanides in acetonitrile [33]. Considering the above-mentioned limiting factors, we envisioned that the whole sequence could be performed in the same pot with an intermediate change of solvent. Thus, we performed the addition of **2a** to the in situ generated 1,1-dibromo isocyanide **1a** in acetonitrile (Table 1, entry 1) that readily led to the monosubstitution of cyclohexyl on the corresponding aromatic amine in 95% yield, in about half of a minute. In the next trial, the resulting mixture from the first step (synthesis of **1a**) was evaporated and diluted with a range of solvents for the evaluation of the efficiency of the second step (addition **2a** to **1a**) (Table 1, entries 2–9). According to our experiments, using aprotic solvents afforded high yield 86–91% (entries 2–7), but the reaction time for toluene increased to 4 min. In the case of protic solvents such as MeOH and EtOH (entries 8 and 9), the overall yield decreased to 74 and 67%, respectively. Also, trying the reaction under inert atmosphere did not affect the reaction efficiency (entry 10). Therefore, the one-pot strategy without changing solvent approved as an ideal condition (Table 1, entry 1).

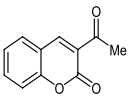
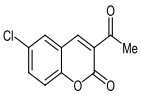
Next, having obtained the optimal conditions, in order to investigate the combinatorial potential of the described protocol, we were interested to see whether this protocol could be extended to other 1,1-dibromo isocyanides **1** and tetrasubstituted thiophenes **2**. First, the scope of the process with a diverse range of 5-acetyl-4-amino-2-methylsulfanyl-3-carbonitrile, decorating aromatic and non-aromatic pendent groups linked to ketone (position 5) on thiophene nucleus in reaction with **1a** was examined (Table 2). It was observed that the reactions were sensitive to the electronic nature of the substituents of the ketone substrates.

The results show that the reaction of **1a** with thiophene derivatives **2** bearing electron-withdrawing groups on phenyl ring gave a better yield in a shorter time in comparison with the ones with electron-donating groups (Table 2, entries 1–5). Additionally, the reactions with non-aromatic motifs afforded good to high yield (Table 2, entries 6–10) similar to their aromatic counterparts, but for R = CO_2Et and CH_2CO_2Me the reactions were completed in longer reaction time (entries 7 and 8). Interestingly, the novel thiophene structures containing chromene backbone that synthesized based on our recently published approach [31] did not take part in this reaction even in the prolonged reaction time and reflux condition (entries 11 and 12). This implies the pivotal role of electronic effects in the accomplishment of the reaction (Scheme 2).

The molecular structures of all the compounds (**3**) were deduced from their elemental analyses and IR, mass, ^{1}H NMR and ^{13}C NMR spectra. Although we did not succeed to analyze the structures by X-ray crystallography, the primary comparison between starting material (thiophene)

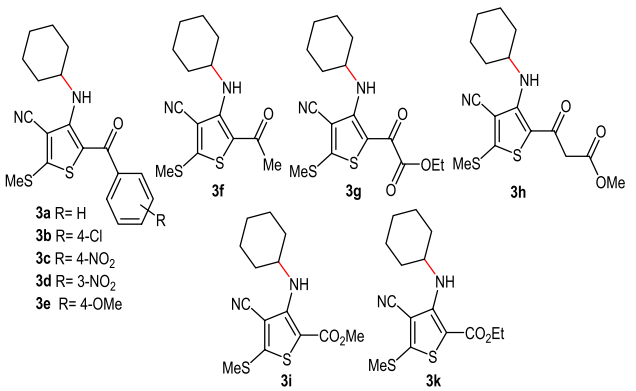
Table 2 One-pot tandem reaction of **1a** with tetrasubstituted thiophenes



Entry	R	Time	Product	Yield[a] (%)
1	Ph	30 s	**3a**	95
2	4-ClC_6H_4	30 s	**3b**	83
3	4-$NO_2C_6H_4$	50 s	**3c**	85
4	3-$NO_2C_6H_4$	2 min	**3d**	81
5	4-$MeOC_6H_4$	4 min	**3e**	79
6	Me	3 min	**3f**	80
7	CO_2Et	1 h	**3g**	77
8	CH_2CO_2Me	3 h	**3h**	80
9	OMe	1 min	**3i**	84
10	OEt	1 min	**3k**	87
11			No reaction	–
12			No reaction	–

Reaction conditions: one pot, 1a (1 mmol), 2 (1 mmol), 3 mL of MeCN, 25 °C

[a]Isolated yield



Scheme 2 Afforded adducts **3**

and final adduct demonstrated the absence of isonitrile (N=C) group in ^{13}C NMR (see supporting information).

Unfortunately, further experiments in order to extend the generality of this protocol based on using *N*-benzylcarbonimidoyl dibromide **1b** did not result in the desired adduct under the applied conditions for the synthesis of **3a–k**,

thus limiting the diversity of the protocol to some extent (Scheme 3).

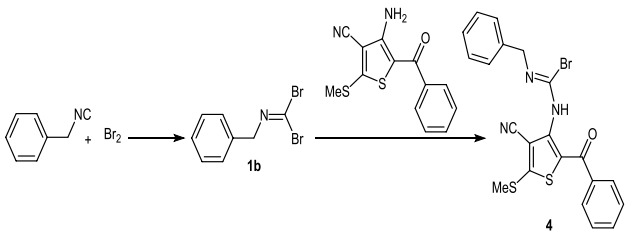
On the basis of the above results, a possible mechanism for the formation of **3a–k** is illustrated in Scheme 4. It is believed that the in situ generated *N*-cyclohexylcarbonimidoyl dibromide **1a** undergoes two consecutive substitution reactions from N and O nucleophilic sites of thiophene, resulting in intermediate **5** with oxazine center. This electron-rich core that presents in three tautomeric forms bears ring opening to afford **6**. Subsequent 1,3-cyclohexyl shift on nitrogen, following a nucleophilic attack of the excluded bromide ion to **7**, discards cyanide that leads to produce the final adduct.

To investigate the behavior of *N*-cyclohexylcarbonimidoyl dibromide **1a** with an alternative bidentate nucleophile, we studied the treatment of **1a** with 1,4,5,6-tetrahydro-2-pyrimidinylhydrazine **8** as 1,4-binucleophile representative (Scheme 5). According to our observation, unlike 3-aminothiophene **2**, the guanidium-like substrate underwent two substitution reactions to produce bicyclic guanidine **9** without further ring opening and cyclohexyl migration.

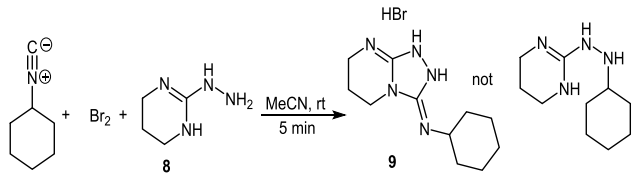
Due to the lack of using any base or promoter, the synthesis of bicyclic guanidines based on this approach is of high importance. Because the presence of all or at least one either a base catalyst, a metal catalyst or heat is found in most of the documented approaches for the synthesis of cyclic guanidines [35].

Conclusions

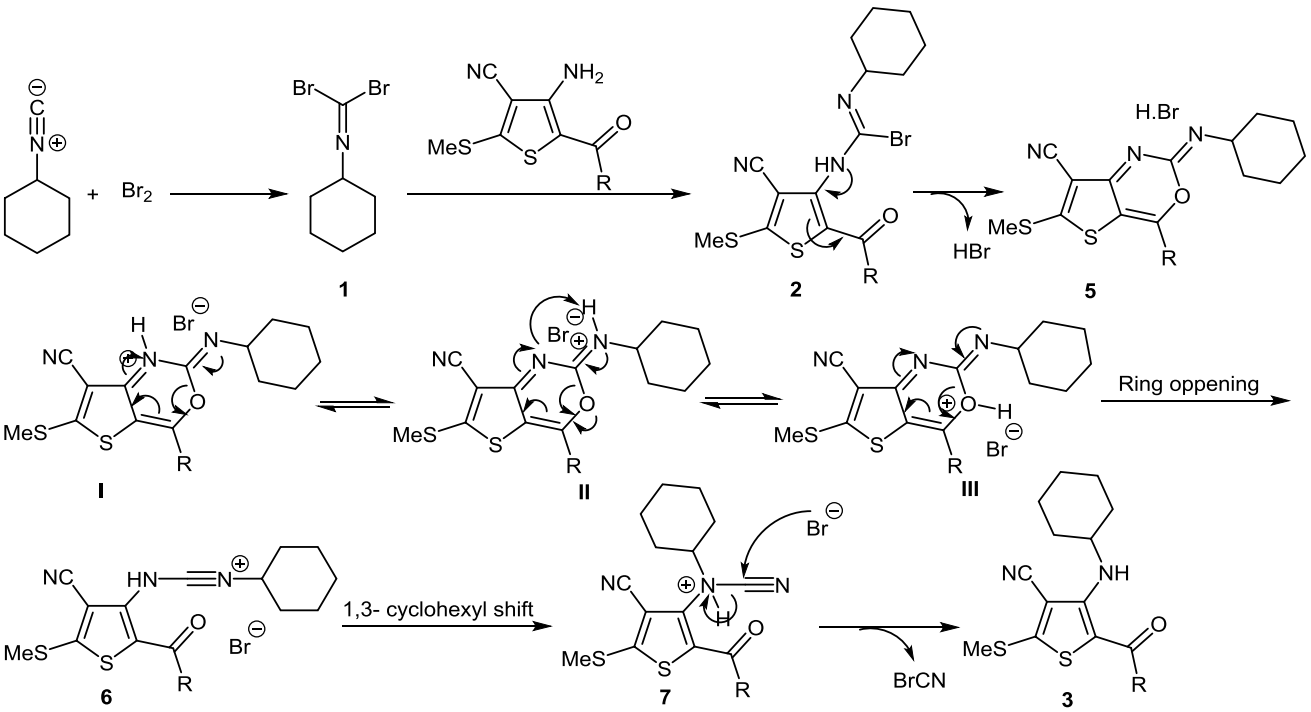
During the recent decades, the chemistry of isocyanide dihalides [36] has been masked by the prominent names of Ugi and Passirini couplings [37–43] in isocyanide-based multicomponent reactions (IMCRs). Herein, we demonstrated the successful marriage of *N*-cyclohexylcarbonimidoyl



Scheme 3 Examination of the interaction of **1b** with **2a**



Scheme 5 Synthesis of bicyclic guanidine **9**



Scheme 4 Mechanistic rationalization for the formation of **3**

dibromide **1a** with biologically valuable tetrasubstituted thiophenes **2**, leading to an unpredictable and selective monosubstitution of cyclohexyl on amine moiety without using any base or promoter at room temperature. Gratefully, the present transformation spontaneously installs Csp^3–N bond through two consecutive substitution reactions (N and O)/ring opening/1,3-cyclohexyl shift on nitrogen domino sequence. The performed condition of the reaction is unprecedented in the field of alkylation of aromatic amines. Additionally, using isocyanide as an alkyl transfer agent through Csp^3–N bond cleavage is a novel event in the field of isocyanide chemistry. The other remarkable features of this reaction are quick and trivial to run, high yield, and the reaction is compatible with the one-pot process. Although the procedure included limitations in terms of extending the scope of the reaction to *N*-benzylcarbonimidoyl dibromide **1b**, the isocyanide dihalide **1a** introduced as the promising substrate for the synthesis of cyclic guanidines.

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