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Dithiocarbamate and CuO promoted one-pot synthesis of 2-(N-substituted)-aminobenzimidazoles and related heterocycles ☆

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Abstract

A rapid and efficient one-pot method for the synthesis of 2-(N-substituted)-aminobenzimidazoles is described. The reaction is promoted by dithiocarbamate and catalytic CuO. This procedure is general and can be applied to synthesize many potential drug candidates.

2-(N-Substituted)-aminobenzimidazoles are widely used structural motifs in medicinal chemistry as well as in drug discovery and can be found in a number of biologically active molecules.[1] Several compounds from this class have been used as anticancer,[1d] antihistamine[1e] and antiviral agents.[2] Some examples of pharmaceutical interest are shown below (Fig. 1).

Therefore, an efficient practical method for the synthesis of a diverse collection of aminobenzimidazoles would be of great value for drug discovery. Several synthetic methodologies have been reported in the literature for the synthesis of 2-aminobenzimidazoles. Most involve formation of thioureas using isothiocyanates followed by cyclodesulfurization using desulfurizing agents such as mercury(II) oxide,[3] mercury(II) chloride,[4] copper(I) chloride,[5] methyl iodide,[6] tosyl chloride,[7] dicyclohexylcarbodiimide (DCC)[8] and PS-carbodiimide[9] (Fig. 2).

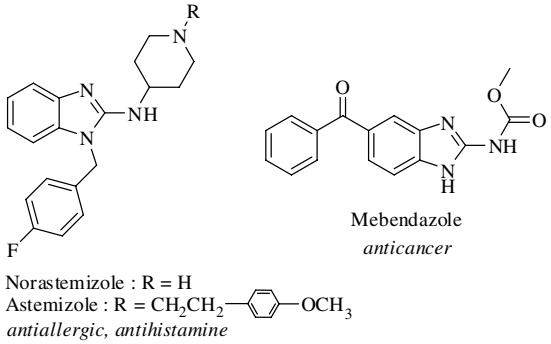

Fig. 1.

Most of the above reagents are either expensive or highly toxic in nature and commonly require cumbersome work-up and purification procedures. Apart from these toxic agents, the synthesis of isothiocyanates requires the use of highly toxic thiophosgene. Moreover, disadvantages with isothiocyanates are that they are unstable if stored for long periods.

We were particularly interested in the synthesis of 2-aminobenzimidazoles via a method suitable for large scale preparations as well as not requiring toxic starting materials and reagents.

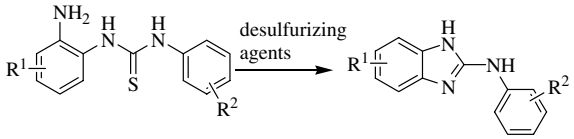

Fig. 2.

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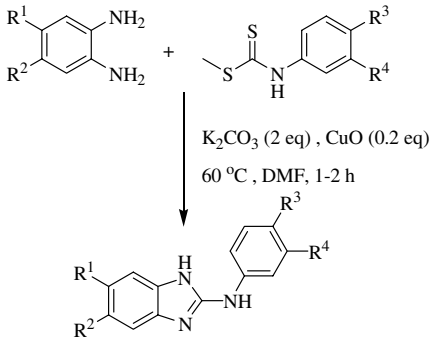
Herein, we report a highly efficient copper(II) oxide mediated one-pot synthesis of 2-aminobenzimidazoles using various substituted diamines and substituted dithiocarbamates. Unlike isothiocyanates, dithiocarbamates are highly stable and easy to handle. They are easy to synthesize in large quantities using readily available substituted anilines.[10] The initial experiments were performed with commercially available *o*-phenylenediamines and methyl-*N*-aryldithiocarbamate using CuO (0.2 equiv)[11] and K_2CO_3 in DMF at 60 °C for 1–2 h. The desired 2-aminobenzimidazole was isolated in good yield.[12] We also investigated this methodology with respect to different diamines and dithiocarbamates (Table 1). Several functionalized 2-aminobenzimidazoles were synthesized from structurally diverse diamines. The reaction gave good yields with both electron-withdrawing groups (entries 11 and 14) and electron-donating groups (entry 6).

The procedure could also be applied to other diamine moieties, providing quinazolines and purine-like products in good yields (Table 2).

In connection with a drug discovery program, we recently required an efficient synthetic protocol into the new class of trisubstituted purines known as Aurora-A Kinase inhibitors.[13] To synthesize this class of compound we applied this methodology (Scheme 1). Thus, condensa-

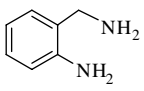
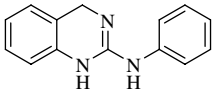
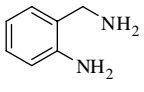
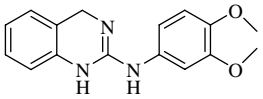
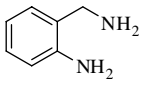
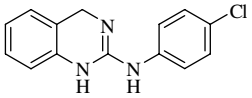
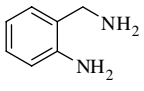
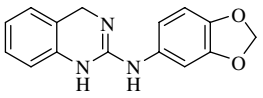
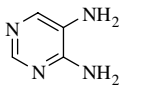
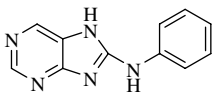
Table 1
Synthesis of 2-aminobenzimidazoles from various diamines and dithiocarbamates



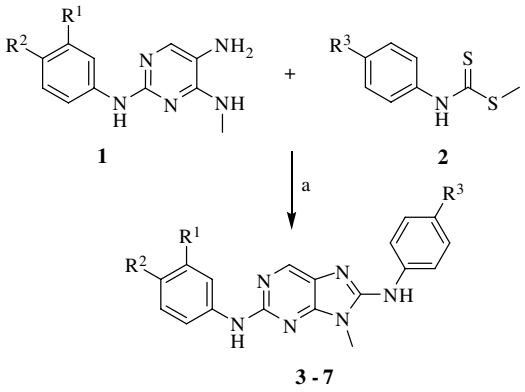
Entry	R^1	R^2	R^3	R^4	Time (h)	Yield[a] (%)
1	CH_3	H	H	H	0.5	78
2	CH_3	H	Cl	H	1	70
3	CH_3	H	OCH_3	OCH_3	0.5	76
4	OCH_3	H	H	H	0.5	80
5	OCH_3	H	Cl	H	0.5	75
6	OCH_3	H	OCH_3	OCH_3	0.5	82
7	F	H	H	H	1	72
8	F	H	Cl	H	1.5	70
9	F	H	OCH_3	OCH_3	0.5	76
10	Cl	Cl	H	H	1.5	70
11	Cl	Cl	Cl	H	1.5	69
12	Cl	Cl	OCH_3	OCH_3	1	70
13	NO_2	H	H	H	1.5	75
14	NO_2	H	Cl	H	1.5	75
15	NO_2	H	OCH_3	OCH_3	1	78

[a] Isolated yields. All the compounds were characterized by IR, ^1H NMR, ^{13}C NMR spectroscopy and mass spectrometry.

Table 2
Cyclization of diamines with various dithiocarbamates

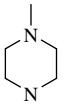
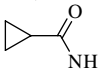
Entry	Reactant	Product	Time (h)	Yield[a] (%)
1			1	92
2			1	85
3			2	82
4			2	80
5			1	80

[a] Isolated yields. All the compounds were characterized by IR, ^1H NMR, ^{13}C NMR spectroscopy and mass spectrometry.



Scheme 1. Reagents and conditions: (a) CuO, K_2CO_3, DMF, 60 °C, 2 h.

Table 3
Trisubstituted purines

Compound	R^1	R^2	R^3	Yield[a] (%)
3		H	Cl	75
4	H	Cl		77
5	H	Cl		74
6	H	NHCOPh		75
7	H			73

[a] Isolated yield.

tion of 2,4,5-trisubstituted pyrimidines **1**[14] with dithiocarbamates **2** in the presence of CuO (0.2 equiv) and K_2CO_3 in DMF at 60 °C for 2 h furnished the desired substituted purines **3**–**7** (Table 3) in good yields.[15]

In conclusion, we have developed an efficient and practical procedure for the synthesis of a wide variety of 2-(N-substituted)-aminobenzimidazoles using a catalytic amount of CuO and nontoxic dithiocarbamate. This procedure can be scaled-up and can be applied to synthesize many potential drug candidates.

Acknowledgements

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11. In this reaction protocol, increasing the amount of catalyst loading up to 1 equiv did not show noticeable improvement in product conversion whereas a reduced catalyst loading (0.1 equiv) led to a significant drop in product conversion.
12. *A typical experimental procedure*: To a suspension of 4-methylbenzene-1,2-diamine (0.1 g, 0.819 mmol) (Table 1, entry 1) and methylphenylcarbamodithioate (0.165 g, 0.901 mmol) (entry 1) in 2 ml of DMF were added CuO (0.013 g, 0.163 mmol) and K_2CO_3 (0.226 g, 1.63 mmol). The resulting mixture was heated to 60 °C and kept at this temperature for 30 min. The reaction mixture was then cooled to room temperature and filtered through Celite and washed with ethyl acetate (100 ml). The combined filtrate was washed with brine and water. The organic layer was dried over Na_2SO_4 and concentrated in vacuo and the resulting mixture chromatographed on silica gel (hexane–acetone, 90:10) to yield 5-methyl-*N*-phenyl-1*H*-benzo[*d*]imidazol-2-amine (0.137 g, 78% yield) as a light yellow solid: mp 164–165 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.74 (s, 1H) 9.28 (d, $J = 13.2$ Hz, 1H) 7.73 (d, $J = 8$ Hz, 2H) 7.31–7.27 (m, 2H) 7.21–6.77 (m, 4H) 2.35 (s, 3H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 150.46, 141.04, 140.43, 132.95, 130.59, 128.78, 121.23, 120.43, 116.99, 116.34, 115.54, 21.32; MS (ESI) 224 ($M+H^+$); HPLC = 99.56%.
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14. Compound **1** was synthesized from commercially available 5-nitrouracil. Das, P.; Kirankumar, C.; Iqbal, J., unpublished results.
15. *Experimental procedure and spectral data for compound* **3**: To a suspension of **1** (0.1 g, 0.333 mmol) and methyl 4-chlorophenylcarbamodithioate **2** (0.079 g, 0.364 mmol) in 2 ml of DMF were added CuO (0.005 g, 0.066 mmol) and K_2CO_3 (0.092 g, 0.666 mmol). The resulting mixture was heated to 60 °C and kept at this temperature for 2 h. The reaction mixture was then cooled to room temperature and filtered through Celite and washed with ethyl acetate (100 ml). The combined filtrate was washed with brine and water. The organic layer was dried over Na_2SO_4 and concentrated in vacuo and the resulting mixture chromatographed on silica gel (DCM/MeOH, 97:3) to yield compound **3** (0.108 g, 75% yield). The physical data of the synthesized compounds are reported below.
Compound **3**. Yellow solid; mp 215–217 °C; IR (KBr, cm^{-1}) 2959, 2924, 1672, 1610, 1565, 1494, 1453, 1411; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.67 (s, 2H), 8.42 (s, 1H), 7.93 (d, $J = 8.8$ Hz, 2H), 7.44–7.42 (m, 2H), 7.24–7.17 (m, 3H), 3.78–3.71 (m, 4H), 3.69 (s, 3H), 3.14–3.12 (m, 4H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 154.77, 153.01, 151.43, 149.63, 142.23, 142.16, 139.07, 128.70, 128.42, 126.95, 125.09, 119.79, 109.45, 107.81, 104.95, 66.14, 48.74, 27.60; MS (ESI) 436 ($M+H^+$); HRMS calcd for $C_{22}H_{23}N_7OCl$ [$M+H^+$] 436.1653, found: 436.1645.
Compound **4.** Brown solid; mp 268–270 °C; IR (KBr, cm^{-1}) 3255, 2961, 2803, 1606, 1553, 1537; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.41 (s, 1H), 8.95 (s, 1H), 8.3 (s, 1H), 7.89 (d, $J = 8.8$ Hz, 2H), 7.74 (d, $J = 9.2$ Hz, 2H), 7.29 (d, $J = 8.8$ Hz, 2H), 6.96 (d, $J = 8.8$ Hz, 2H), 3.76–3.73 (m, 4H), 3.65 (s, 3H), 3.17–3.05 (m, 4H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 153.87, 153.46, 150.84, 146.39, 140.84, 140.58, 132.29, 128.11, 127.84, 123.28, 119.91, 119.01, 115.62, 66.12, 49.16, 27.57; MS (ESI) 436 ($M+H^+$); HRMS calcd for $C_{22}H_{23}N_7OCl$ [$M+H^+$] 436.1653, found: 436.1638.
Compound **5.** Pink solid; mp 191–193 °C; IR (KBr, cm^{-1}) 3259, 3046, 2802, 1606, 1557, 1514, 1490; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.43 (s, 1H), 8.93 (s, 1H), 8.32 (s, 1H), 7.89 (d, $J = 8.8$ Hz, 2H), 7.71 (d, $J = 9.2$ Hz, 2H), 7.29 (d, $J = 8.8$ Hz, 2H), 6.95 (d, $J = 8.8$ Hz, 2H), 3.65 (s, 3H), 3.09 (m, 4H), 2.50 (s, 3H), 2.49–2.44 (m, 4H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 153.87, 153.48, 150.89,146.42, 140.80, 140.60, 131.97, 128.12, 127.89, 123.30, 119.97, 119.03, 115.84, 54.65, 48.76, 45.72, 27.57; MS (ESI) 449 ($M+H^+$); HRMS calcd for $C_{23}H_{26}N_8Cl$ [$M+H^+$] 449.1969, found: 449.1953.
Compound **6.** Brown solid; mp 319–320 °C; IR (KBr, cm^{-1}) 3335, 2927, 2857, 1603, 1568, 1524, 1436, 1409, 1323; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.08 (s, 1H), 9.22 (s, 1H), 8.29 (s, 1H), 8.31 (s, 1H), 7.96 (d, $J = 6.8$ Hz, 2H), 7.81 (d, $J = 9.2$ Hz, 2H), 7.74 (d, $J = 9.2$ Hz, 2H),

7.65 (d, $J = 9.2$ Hz, 2H), 7.57 (m, 3H), 6.96 (d, $J = 8.8$ Hz, 2H), 3.76 (m, 4H), 3.66 (s, 3H), 3.07 (m, 4H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 164.98, 154.38, 153.50, 150.62, 146.35, 141.09, 137.73, 135.17, 132.42, 131.89, 131.23, 128.27, 127.49, 120.97, 119.89, 117.79, 115.65, 66.14, 49.20, 27.56; MS (ESI) 521 ($M+H^+$); HRMS calcd for $C_{29}H_{29}N_8O_2$ [$M+H^+$] 521.2413, found: 521.2413.

Compound **7.** White solid; mp 300–302 °C; IR (KBr, cm^{-1}) 3314, 3094, 2962, 2847, 1664, 1613, 1588, 1522, 1437, 1409, 1315; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.07 (s, 1H), 9.03 (d, $J = 12.8$ Hz, 2H), 8.29 (s, 1H), 7.79 (d, $J = 9.2$ Hz, 2H), 7.69 (d, $J = 8.8$ Hz, 2H), 7.55 (d, $J = 8.8$ Hz, 2H), 6.89 (d, $J = 9.2$ Hz, 2H), 3.75 (m, 4H), 3.64 (s, 3H), 3.30 (m, 4H), 1.78 (m, 1H), 0.80 (m, 4H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 171.11, 154.87, 153.41, 149.98, 145.29, 141.55, 134.30, 133.65, 126.95, 119.53, 119.16, 118.75, 115.80, 66.18, 49.55, 27.53, 14.38, 6.88; MS (ESI) 485 ($M+H^+$); HRMS calcd for $C_{26}H_{29}N_8O_2$ [$M+H^+$] 485.2413, found: 485.2425.