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A one-pot method for the synthesis of 2-aminobenzimidazoles and related heterocycles

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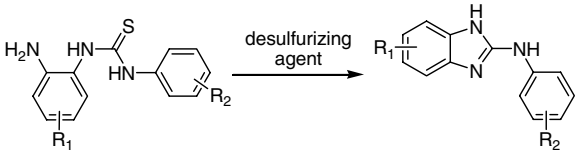
Abstract—A rapid and efficient one-pot method for the synthesis of 2-aminobenzimidazoles and related heterocycles is described. The reaction is mediated by a polymer-supported carbodiimide, which simplifies product isolation. The scope and limitations of this method are described.

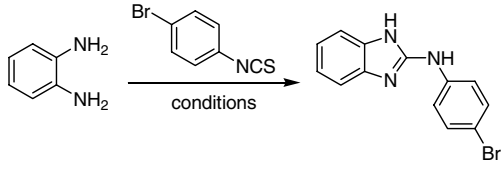
The aminobenzimidazole is an important structural motif in medicinal chemistry and can be found in a number of biologically active molecules.[1] A popular approach to this heterocycle involves the cyclodesulfurization of a pre-formed thiourea (Eq. 1). Reported desulfurization agents include mercury (II) oxide,[2] mercury (II) chloride,[3] copper (I) chloride,[4] methyl iodide,[5] tosyl chloride,[6] and dicyclohexylcarbodiimide.[7]



(1)

We recognized that this process could be considerably simplified by the development of a one-pot procedure involving the combination of a diamine, isothiocyanate, and desulfurizing agent, thereby avoiding the isolation of the intermediate thiourea (Eq. 2). To this end, methods reported for the cyclodesulfurization of thioureas were studied in a one-pot process (Table 1). Metal-mediated reactions[8] proved to be significantly less effective in a one-pot approach (entries 1 and 2), while carbodiimide reagents, DCC and EDC (entries 3 and 4), provided better yields.[9]

Table 1. Application of reported cyclodesulfurization conditions in a one-pot process



(2)

Entry	Reagent	Conditions	Yield (%)
1	HgO, S (cat.)	EtOH, reflux	53
2	CuCl	4:1 PhMe/ACN, reflux	35
3	DCC	THF, 70 °C	68
4	EDC	THF, 70 °C	63

While the carbodiimide conditions were acceptable, we wished to avoid the time-consuming removal of carbodiimide byproducts from the reaction. A number of reports have highlighted the procedural improvements offered by polymer-supported (PS) carbodiimide,[10] and we found this reagent to be quite effective in promoting the desired transformation (Table 2, Eq. 2). THF proved to be the optimal solvent (entry 4), with toluene, DMF, and DCE requiring longer reaction times. The amount of PS-carbodiimide necessary to effect cyclodesulfurization was also studied (entries 4–7) and 2 equiv of PS-carbodiimide (entry 5) proved to be optimal. The reaction proceeded at ambient temperature (entry 8), but required an extended reaction time. Under optimized conditions (entry 5), the desired benzimidazole was isolated in 86% yield.[11]

Keywords: Aminobenzimidazole; Cyclodesulfurization; Polymer-supported carbodiimide.
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Table 2. Optimization of conditions for PS-carbodiimide-mediated cyclodesulfurization Eq. 2

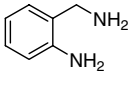
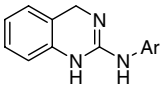
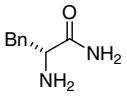
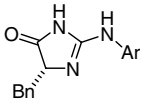
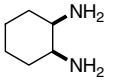
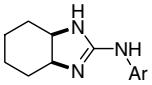
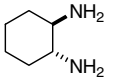
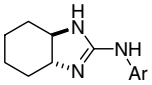
Entry	Solvent	Temp. (°C)	Equiv	Time (h)[a]	Yield[b] (%)
1	PhMe	70	3	2.5	79
2	DMF	70	3	4	98
3	DCE[c]	70	3	6	72
4	THF	70	3	2	97
5	THF	70	2	2	99 (86)[d]
6	THF	70	1	48	94
7	THF	70	0	—	—
8	THF	20	2	24	98

[a] Time until thiourea was consumed (monitored by TLC).
[b] Measured by HPLC with naphthalene as internal standard.
[c] 1,2-Dicholoroethane.
[d] Isolated yield.

A variety of functionalized 2-aminobenzimidazoles can be prepared from structurally diverse diamines (Table 3). The reaction tolerated both electron withdrawing groups (entries 3–6) and electron donating groups (entries 7 and 8), although in the case of nitro-substituted diamines (entries 3 and 4) extended reaction times were necessary. The reaction was also successful with heterocyclic diamines (entries 12 and 13). N^1-Substituted benzimidazoles could also be obtained (entries 14 and 15), but *N*-methyl phenylenediamine proved to be a difficult substrate, requiring high temperature and extended reaction time to achieve full conversion of the intermediate thiourea. Aminobenzoxazole was obtained from 2-aminophenol in reasonable yield (entry 16). In contrast, 2-aminothiophenol provided the aminobenzthiazole product in low yield under the standard conditions (entry 17). We subsequently found that aminobenzthiazole could be produced in good yield in the absence of PS-carbodiimide.[12] This result appears to be unique to 2-aminothiophenol; 2-aminophenol and *o*-phenylenediamine do not produce cyclized products under the reaction conditions in the absence of PS-carbodiimide.[13]

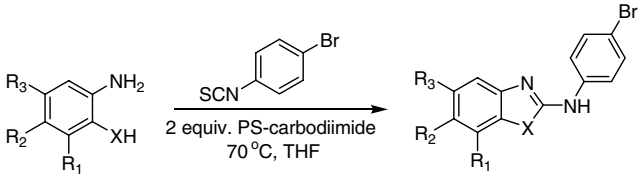
The procedure could also be extended beyond phenylene diamines (Table 4) to other diamine motifs, providing

Table 4. Cyclization of other diamines[a]

Entry	Reactant	Product[b]	Time (h)	Yield (%)
1			24	44
2			24	62[c]
3			18	49
4			6	63

[a] Reaction conditions: 2 equiv PS-carbodiimide, THF, 70 °C.
[b] Ar = 4-bromophenyl.
[c] Product is 99.8% ee as determined by chiral HPLC: ChiralPak AD-H, 5–40% isopropanol/heptane, 1 mL/min, T_R (major) = 12.0 min, T_R (minor) = 9.7 min.

Table 3. Diamine scope

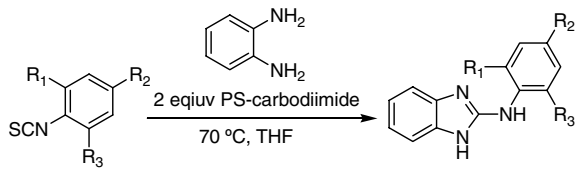


(3)

Entry	R_1	R_2	R_3	X	Time (h)	Yield (%)
1	H	H	H	NH	2	86
2	Me	Me	H	NH	2	62
3	NO_2	H	H	NH	48	62
4	H	NO_2	H	NH	48	63
5	H	CF_3	H	NH	3	72
6	H	CN	H	NH	3	57
7	H	OMe	H	NH	2	71
8	H	4-Me-Piperazine	H	NH	3	61
9	H	Br	H	NH	2	80
10	H	F	F	NH	7	67
11	H	Cl	Cl	NH	3	66
12		2,3-Diaminopyridine		NH	4	83
13		3,4-Diaminopyridine		NH	4	82
14[a]	H	H	H	NMe	36	75
15	H	H	H	NPh	3	66
16	H	H	H	O	3	63[b]
17	H	H	H	S	4	38 (75)[c]

[a] 100 °C, sealed tube.
[b] 4 equiv PS-carbodiimide.
[c] 0 equiv PS-carbodiimide.

Table 5. Isothiocyanate scope



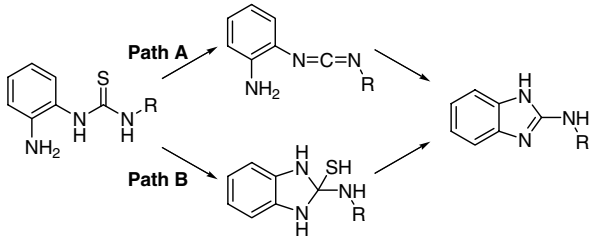
(4)

Entry	R_1	R_2	R_3	Time (h)	Yield (%)
1	H	Br	H	2	86
2	H	H	H	4	85
3	H	OMe	H	4	64
4	H	CN	H	3	75
5	H	NO_2	H	2	66
6	H	COMe	H	3	71
7	Me	H	H	5	86
8	Me	H	Me	24	54
9	Cl	H	Cl	2	88
10	1-Naphthylisothiocyanate			4	75
11	Benzyl isothiocyanate			22	68
12	Ethyl 2-isothiocyanatoacetate			16	63
13	Benzoyl isothiocyanate			3	73

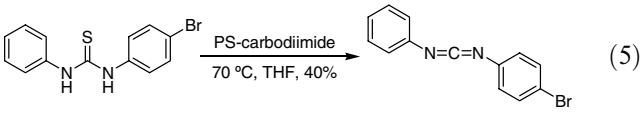
quinazoline, imidazolinone, and hexahydrobenzimidazole products in modest yields. It is notable that the cyclization of phenylalanine amide to aminoimidazolinone (entry 2) proceeds with no detectable racemization.

A variety of N^{α}-substituted aminobenzimidazoles could be synthesized from diverse isothiocyanates (Table 5). Electron donating (entry 3) and electron withdrawing groups (entries 4–6) were well tolerated in the para position. A single *ortho*-methyl substituent was well tolerated (entry 7), but 2,6-dimethylisothiocyanate required an extended reaction time and provided only a modest yield of the desired product (entry 8). In contrast, 2,6-dichloroisothiocyanate (entry 9) was rapidly converted to the aminobenzimidazole in excellent yield. It is notable that alkyl as well as acyl isothiocyanates were also successful (entries 11–13).

Two mechanistic pathways to the product could be operating (Scheme 1). Pathway **A** involves an initial desulfurization of the thiourea to give a carbodiimide, which cyclizes to the aminobenzimidazole.[7] Pathway **B** involves initial cyclization of the thiourea to a tetrahedral thiol intermediate, which is desulfurized to give the aminobenzimidazole. The finding that PS-carbodiimide can transform a diarylthiourea into a carbodiimide (Eq. 5) suggests that pathway **A** is possible, but does not rule out pathway **B**.[14]



Scheme 1. Possible mechanisms for benzimidazole formation.



(5)

A rapid and efficient one-pot method for the synthesis of 2-aminobenzimidazoles and related heterocycles has been developed. The reaction is mediated by a polymer-supported carbodiimide reagent, which simplifies product isolation. This procedure is successful with a wide range of structurally diverse diamine and isothiocyanate substrates, and does not require the isolation of the intermediate thiourea. The related benzoxazole and benzthiazole heterocycles can be produced under these conditions, but it was found that the cyclization of 2-aminothiophenol proceeds best in the absence of the desulfurizing agent. It was also shown that PS-carbodiimide is capable of transforming a diaryl thiourea to the corresponding carbodiimide under the reaction conditions, suggesting that carbodiimides may be intermediates in the reaction.

Acknowledgements

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11. Typical experimental procedure: A mixture of 4-bromophenylisothiocyanate (0.107 g, 0.50 mmol), 1,2-phenylenediamine (0.054 g, 0.50 mmol) and PS-carbodiimide (Argonaut Technologies, 1.3 mmol/g, 0.769 g, 1.0 mmol) was suspended in 10 mL anhydrous THF. The reaction vessel was sealed and heated to 70 °C with stirring. After 2 h, the vessel was cooled to an ambient temperature and filtered. The residue was washed with MeOH (3×10 mL). The filtrate was concentrated and the resulting solid was suspended in CH_2Cl_2, held at 0 °C for 1 h, and filtered to give *N*-(4-bromophenyl)-1*H*-benzo[*d*]imidazol-2-amine (0.124 g, 86% yield) as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.16 (s, 1H) 9.70 (s, 1H) 7.77 (d, $J = 8.8$ Hz, 2H) 7.47 (d, $J = 8.8$ Hz, 2H) 7.27–7.36 (m, 2H) 7.00 (dd, $J = 5.9$, 3.1 Hz, 2H) ppm. MS: $m/z =$ 288, 290 $(M+1)^+$.
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