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Synthesis of 2-(Alkylamino)benzimidazoles

James J. Perkins, Amy E. Zartman, and Robert S. Meissner*

Department of Medicinal Chemistry, Merck Research Laboratories, West Point, PA 19486

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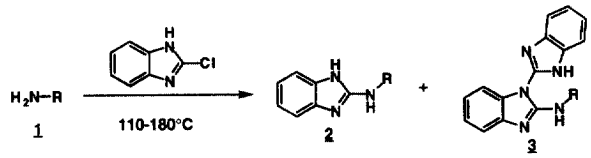
Abstract: A general and highly convenient procedure for the synthesis of 2-(alkylamino)benzimidazoles has been developed and a variety of analogs have been efficiently prepared. Included is a dipeptide mimetic in which the guanidine group of an arginine residue has been replaced with a 2-aminobenzimidazole.

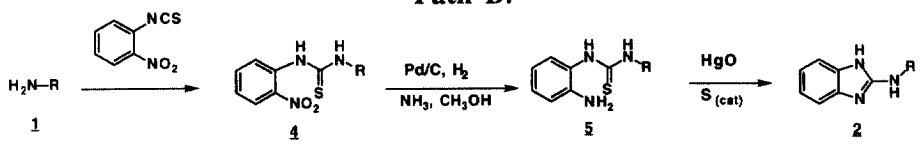
2-(Alkylamino)benzimidazoles (2-ABIs, **2**) are a well-known aminoheterocycle,[1] and are found in a variety of biologically active agents, most notably antihistamines.[2] There is considerable synthetic methodology reported for the synthesis of unsubstituted 2-aminobenzimidazoles, but the pathways described for the preparation of 2-alkylamino derivatives are limited.[2,3] Previous to our work, the two most widely employed methods for the synthesis of 2-ABIs were Path A and Path B, described below. In our hands, both routes had synthetic shortcomings.

Path A:



Path A required the amination of 2-chlorobenzimidazole with an alkylamine at elevated temperatures. When applied to amines containing moderately reactive remote functional groups, such as esters, these forcing conditions provided poor yields of **2**. Major by-products included amino-bis(benzimidazoles) **3** and condensates resulting from the reaction of the esters with reagent and product amines.

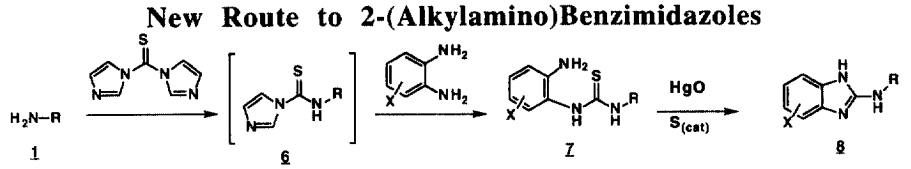
Path B:



For Path B, the hydrogenation step gave poor yields of the aniline **5**, with significant overreduction of the thiourea. In addition, the ammonia/methanol solvent used to minimize overreduction proved incompatible with remote ester functionality.

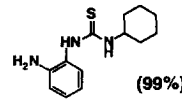
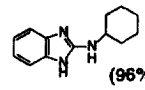
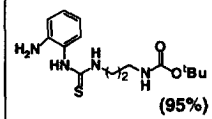
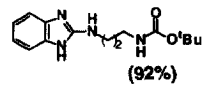
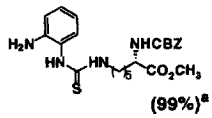
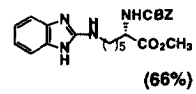
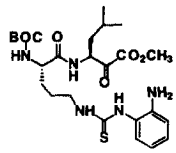
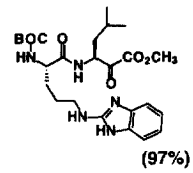
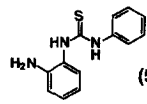
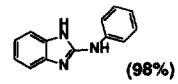
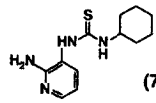
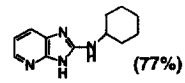
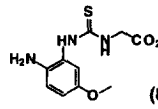
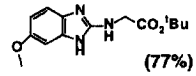
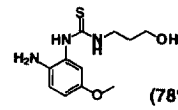
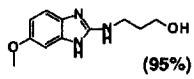
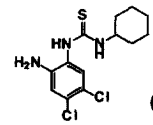
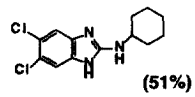
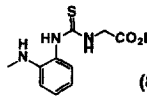
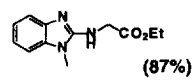
With these difficulties in mind, we have developed a mild, general, and efficient route to 2-ABIs, described in the following scheme.

New Route to 2-(Alkylamino)Benzimidazoles



PII: S0040-4039(98)02592-1

Table: 2-(Alkylamino)benzimidazoles Prepared

Entry	Thiourea (Yield)	Aminobenzimidazole (Yield)	HRMS Data	pK_a
1	 (99%)	 (96%)	$C_{13}H_{17}N_3$: M+H: 216.1513 Found: 216.1495	7.93
2	 (95%)	 (92%)	$C_{15}H_{22}N_4O_2$: M+H: 291.1815 Found: 291.1832	7.46
3	 (99%)[a]	 (66%)	$C_{22}H_{26}N_4O_4$: M+H: 411.2027 Found: 411.2019	7.22
4	 (78%)	 (97%)	$C_{24}H_{37}N_5O_5$: M+H: 476.2867 Found: 476.2897	7.34
5	 (50%)	 (98%)	$C_{13}H_{11}N_3$: M+H: 210.1026 Found: 210.1031	6.42
6	 (79%)[a,b]	 (77%)	$C_{12}H_{16}N_4$: M+H: 217.1448 Found: 217.1457	6.47
7	 (89%)[b]	 (77%)	$C_{14}H_{19}N_3O_3$: M+H: 278.1499 Found: 278.1497	6.60
8	 (78%)[b]	 (95%)	$C_{11}H_{15}N_3O_2$: M+H: 222.1237 Found: 222.1242	7.42
9	 (84%)[a]	 (51%)	$C_{13}H_{15}N_3Cl_2$: M+H: 284.0716 Found: 284.0711	6.20
10	 (81%)	 (87%)	$C_{12}H_{15}N_3O_2$: M+H: 234.1237 Found: 234.1251	6.34

a. Yields of thioureas not fully purified. The yields of 2-ABIs are for analytically pure material.

b. Unassigned regioisomer or mixture of regioisomers.

The acylation of the alkylamine **1** with thiocarbonyldiimidazole is followed by the addition of an excess of the 1,2-phenylenediamine, promoting formation of the unsymmetric thiourea **7**. The use of hydrochloride salts of the alkylamine or phenylenediamine is well accommodated, by using an excess of imidazole to neutralize the HCl. Cyclodesulfurization can then be effected by treatment with mercury(II)oxide in refluxing ethanol.[2a,4] Simple filtration is often sufficient to produce high purity 2-ABIs, with silica gel chromatography sometimes warranted.

The table illustrates that a wide variety of alkylamines and phenylenediamines are compatible with this sequence, producing 2-ABIs in excellent yields. Some synthetic comments can be made: 1) The complete purification of the intermediate thiourea is not necessary; the submission of impure material to the cyclodesulfurization is acceptable. 2) Alcohol, ester, amide, and carbamate functionalities are fully compatible with the reaction sequence. 3) Aniline can be used in place of an alkylamine, but the efficiency of the thiourea formation is reduced.

The modular nature of this sequence allows for the incorporation of a variety of substituted 1,2-phenylene diamines and alkylamines, which leads to 2-ABIs of varying basicity. The pK_a's of the 2-ABIs prepared range from 7.93 to 6.20.[5]

Noteworthy is the synthesis of the Arg-Leu dipeptide mimetic of entry 4. This compound was efficiently prepared from BOC-Orn-Leu-OMe via the standard protocol, installing an arginine analog in the sequence. Replacement of the arginine guanidine with 2-aminobenzimidazole results in a side chain that has a reduced pK_a and an aryl group which offers additional potential interactions.

In conclusion, a novel, efficient, and general procedure for the synthesis of 2-(alkylamino)benzimidazoles has been developed. This mild procedure allows access to a variety of substituted derivatives with sensitive remote functionality. The pK_a's of the derivatives prepared depended on the nature of the substitution on both the aryl and alkylamino groups

SAMPLE EXPERIMENTAL PROCEDURE

To a stirred solution of 1,1'-thiocarbonyldiimidazole (2.7 g, 15.2 mmol), imidazole (206 mg, 3.03 mmol) and CH_3CN (40 ml) at 0°C was added cyclohexylamine (1.15 ml, 10.1 mmol) dissolved in CH_3CN (10 ml) dropwise over 10 minutes. After 10 minutes, the cooling bath was removed. After 3.0 hours, 1,2-phenylenediamine (2.2 g, 20.2 mmol) was added and the reaction was heated to 50°C for 3.0 hours and then stirred at ambient temperature for 16 hours. Following evaporative removal of the solvent, the residue was chromatographed (silica gel, 80:14:5:1 to 60:28:10:2 hexanes/$CHCl_3$/EtOAc/MeOH) to give the thiourea (2.5 g, 99%) as a white solid. TLC R_f = 0.70 (silica gel, 70:25:5 $CHCl_3$/EtOAc/MeOH). ^1H NMR (300 MHz, CD_3OD) δ 7.09 (m, 1H), 6.98 (dd, J=1.5, 8 Hz, 1H), 6.84 (dd, J=1, 8 Hz, 1H), 6.70 (td, J=2, 8 Hz, 1H), 4.19 (s, 1H), 1.92 (m, 2H), 1.63 (m, 3H), 1.31 (m, 2H), 1.13 (m, 3H). HRMS calcd for $C_{13}H_{19}N_3S$: M+H= 250.1372. Found: 250.1374.

A mixture of thiourea (400 mg, 1.60 mmol), HgO (696 mg, 3.20 mmol), sulfur (10 mg, 0.32 mmol) and EtOH (20 mL) was combined and then heated to reflux for 2.0 hours. The cooled reaction mixture was filtered through a celite pad. Following evaporative removal of the solvent, the residue was chromatographed (silica gel, 70:25:5 $CHCl_3$ /EtOAc/MeOH) to give the 2-(cyclohexylamino)benzimidazole (330 mg, 96%) as a white solid. TLC R_f = 0.15 (silica gel, 70:25:5 $CHCl_3$/ EtOAc/ MeOH). ^1H NMR (300 MHz,

$CDCl_3$) δ 7.28 (m, 2H), 7.04 (m, 2H), 4.80 (s, 1H), 3.69 (s, 1H), 2.07 (m, 2H), 1.68 (m, 2H), 1.57 (m, 1H), 1.24 (m, 5H). HRMS calcd for $C_{13}H_{17}N_3$: M+H= 216.1513. Found: 216.1495.

ACKNOWLEDGEMENTS

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1. a) Rastogi, R.; Sharm, S. *Synthesis* **1983**, 861. b) Simonov, A. M.; Anisimova, V. A. *Chem. Heterocycl. Compd.* **1979**, *15*, 705.
2. a) Janssens, F.; Torremans, J.; Janssen, M.; Stokbroekx, R.; Luyckx, M.; Janssen, P. A. J. *J. Med. Chem.* **1985**, *28*, 1925. b) Povstyanoi, M. V.; Kruglenko, V. P.; Fedosenko, E. N.; Klyuev, N. A. *Khim. Geterotsikl. Sodein.* **1990**, *8*, 1065.
3. a) Stedman, R. J. *U.S. Patent* 3455948 **1969**; *C.A.* **71**, 81369 **1969**. b) Chow, A. W. *U.S. Patent* 3468888 **1969**; *C.A.* **72**, 3489 **1970**. c) Kifter, D.; Levy, C. R. *Acad. Sci. Paris Ser. C* **1968**, *267*, 1730.
4. Other reagents, such as MeI or sodium dithionate can be used: a) Ojha, V.; Singh, J.; Bhakuni, D. S.; Singh, S. N.; Fatma, N.; Chatterjee, R. K. *Indian J. Chem. Sect. B 32* **1993**, *3*, 394. b) Omar, M. E.; Mohsen, A. *Synthesis* **1974**, 41. c) Bera, T.; Belsare, D. P. *Indian J. Chem. Sect. B 31* **1992**, *6*, 370.
5. The pKa's were measured on a Sirius Model PCA-101 pKa titrator.