Cyanogen Bromide–Dimethylaminopyridine (CAP): A Convenient Source of *Positive Cyanide* for the Synthesis of 2-Cyanoimidazoles

Jeffrey P. Whitten,*[a] James R. McCarthy,[b] Donald P. Matthews[b]

[a] Merrell Dow Research Institute, Indianapolis Center, Indianapolis, IN 46268-0470, USA
[b] Merrell Dow Research Institute, Cincinnati Center, Cincinnati, OH 45215-6300, USA

Dimethylaminopyridine activates cyanogen bromide towards C–C bond formation by forming 1-cyano-4-dimethylaminopyridinium bromide. The latter serves as a convenient reagent for the synthesis of 2-cyanoimidazoles.

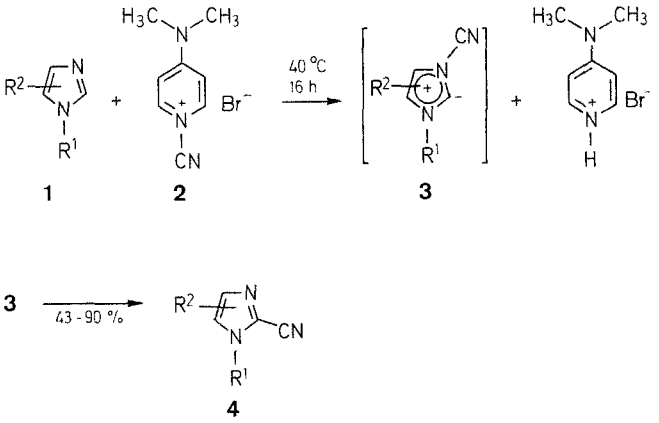
The convenient introduction of the cyano group onto heterocyclic systems is important in many synthetic transformations.[1–9] Recently we reported a one-step synthesis of 2-

cyanoimidazoles **(4)** via *N*-cyanoimidazole ylides utilizing cyanogen chloride.[8] However, cyanogen chloride is an extremely toxic gas, which is not readily available. Thus, we have investigated alternative reagents for the synthesis of 2-cyanoimidazoles.

Cyanogen bromide is a readily available solid, but when reacted with imidazole derivatives predominately yields bromoimidazoles.[10] We wish to report that modification of cyanogen bromide to a cyanogen bromide-dimethylaminopyridine salt, 1-cyano-4-dimethylaminopyridinium bromide **(2)**[11] (CAP), activates cyanogen bromide towards carbon–carbon bond formation and serves as a convenient reagent for the cyanation of imidazoles **1**.

1-Cyano-4-dimethylaminopyridinium bromide **(2)** (CAP), has been reported[11] to cyanate enzymes but surprisingly, this activation of cyanogen bromide towards carbon–carbon bond formation has not been exploited in synthetic organic chemistry. We felt that the conversion of cyanogen bromide to CAP should also serve as a convenient cyanation agent for the ylide reaction with *N*-substituted imidazoles **1**.

Reaction of 2.5 equivalents of CAP **(2)** in dimethylformamide with *N*-substituted imidazoles provided good yields of 2-cyanoimidazoles **4** (Table) via intermediate **3**. The yield of product **4** was dependent on the prompt addition of the *N*-substituted imidazole to freshly formed CAP in dimethylformamide as well as using an excess of the reagent. For example, adding 1-benzylimidazole to 2.5 equivalents of freshly formed CAP provided a 77% yield of **4a**, whereas adding 1-benzylimidazole 0.5 h after CAP formation resulted in a 23% yield of **4a**. Fodor has reported that *N*-cyanoammonium bromides rapidly decompose between −10° and 10 °C.[12] Addition of cyanogen bromide to a mixture of 1-benzylimidazole and dimethylaminopyridine resulted in exclusive formation of 2-bromo-1-benzylimidazole.[10] Thus both prior formation of the reagent CAP and its expedient use are necessary.



The nature of the cyanation catalyst was investigated. As CAP forms a precipitate in dimethylformamide a more soluble form was investigated. Both 4-(4-methyl-1-piperidyl)pyridine, a less powerful alkylating catalyst and 4-(1-pyrrolidinyl)pyridine, a more potent alkylating catalyst than 4-dimethylaminopyridine,[13] form dimethylformamide soluble complexes but gives mixtures of 2-bromo- and 2-cyano-1-benzylimidazoles.

Table. Compounds **4a–h** Prepared

Product	R^1	R^2	Yield (%)	mp (°C) or bp (°C)/mbar[a]	Molecular Formula[b] or Lit. mp (°C)	^{1}H-NMR ($CDCl_3$/TMS)[c] δ, J(Hz)	^{13}C-NMR ($CDCl_3$/TMS)[d] δ
4a	H	$CH_2C_6H_5$	77	51–52	51–52[1]	5.18 (s, 2H); 6.98–7.38 (m, 7H)	51.4; 111.13; 121.8; 123.55; 127.73; 128.96; 129.26; 131.91; 134.32
4b	H	$CH_2OCH_2CH_2Si(CH_3)_3$	64[e]	110–120/0.53	110–120/0.53[1]	0.0 (s, 9H); 0.91 (t, 2H, J = 8.2); 3.55 (t, 2H, J = 8.2); 5.57 (s, 2H); 7.3 (d, 1H, J = 1.5); 7.84 (d, 1H, J = 1.5)	−1.56; 17.52; 67.34; 75.92; 110.63; 121.83; 123.06; 132.08
4c	4-CH_3	$CH_2C_6H_5$	74[f]	51.5–52.5	51.5–52.5[1]	2.22 (s, 3H); 5.21 (s, 2H); 6.82 (s, 1H); 7.22–7.39 (m, 5H)	13.74; 51.3; 111.29; 120.36; 127.72; 128.4; 129.24; 134.52; 142.51
4d	5-CH_3	$CH_2C_6H_5$	74[f]	112–113	113–115[15]	2.18 (s, 3H); 5.26 (s, 2H); 6.81 (s, 1H); 6.99–7.4 (m, 5H)	9.94; 48.86; 111.62; 126.66; 126.69; 128.59; 129.26; 130.37; 132.57; 134.30
4e	H	CH_3	78	65–70/0.53	$C_5H_5N_3$ (107.1)	3.95 (s, 2H); 7.20 (s, 1H); 7.55 (s, 1H)	–
4f	5-Cl	CH_3	43	87–89	90–91[16]	3.80 (s, 3H); 7.03 (s, 1H)	–
4g	4-C_6H_5	$CH_2C_6H_5$	90[e]	95–96	95–96[1]	5.22 (s, 2H); 7.13–7.81 (m, 11H)	51.6; 111.13; 118.79; 121.76; 125.16; 127.78; 128.13; 128.77; 129.05; 129.34; 132.11; 134.16; 144.54
4h	H	2-CH_2-thienyl	72	64–65	$C_9H_7N_3S$ (189.2)	5.42 (s, 2H); 6.86–7.35 (m, 5H)	–

[a] Bath temperature of Kugelrohr distillation.
[b] Satisfactory microanalyses obtained: C ± 0.27, H ± 0.21, N ± 0.24.
[c] Recorded on a Varian EM-360 spectrometer.
[d] Recorded on a Varian XL-300 spectrometer.
[e] Based upon recovered starting material.
[f] Starting material was a mixture of 4- and 5-CH_3 substituted indole. The product mixture was separted by flash chromatography into **4c** and **4d**. The yield denotes combined yield.

The yield of 2-cyanoimidazoles **4** using CAP are similar to those using cyanogen chloride, even though only 2.5 equivalents of CAP were used compared to 5 equivalents of cyanogen chloride. With the 2-(trimethylsilyl)ethoxymethyl (SEM) protected imidazole **1b**[8] partial deprotection by reaction of a CAP with the SEM group was observed. Compounds **4c** and **4d** were easily separated by flash chromatography to give the 4- and the 5-isomers.

Thus, 1-cyano-4-dimethylaminopyridinum bromide (CAP) activates cyanogen bromide towards cyanation and provides a new carbon–carbon bond forming reagent. CAP is a convenient cyanogen chloride replacement and it should find additional application in synthetic organic chemistry as a source of *positive cyanide*.

1-Benzyl-2-cyanoimidazole (4a); Typical Procedure:
Under nitrogen, a solution of 4-dimethylaminopyridine (6.1 g, 0.05 mol) in DMF (100 mL) is cooled to 10 °C and cyanogen bromide (5.3 g, 0.05 mol) added. The reaction exotherms to 20 °C and a pale yellow precipitate of CAP forms. The mixture is then allowed to cool to 10 °C (ca. 5 min), and 1-benzylimidazole (**1a**;[15] 3.2 g, 0.02 mol) is added. The mixture is stirred at 40 °C for 16 h and then quenched by pouring into 0.1 M aq. $NaHCO_3$ solution (600 mL), and extracted with EtOAc (3 × 200 mL). The combined EtOAc extract is dried (Na_2SO_4), and concentrated to give 4.1 g of crude product. Flash chromatography (400 g silica gel/EtOAc) gives **4a**; yield: 2.83 g (77%); mp 51–52 °C (cyclohexane).

Received: 31 July 1987; revised: 13 January 1988

(1) McCarthy, J.R., Matthews, D.P., Whitten, J.P. *Tetrahedron Lett.* **1985**, 6273.
(2) Barltrop, J.A., Day, A.C., Mack, A.G., Shahrisa, A., Wakamatsu, S. *J. Chem. Soc. Chem. Commun.* **1981**, 604.
(3) Kimoto, H., Cohen, L.A. *J. Org. Chem.* **1980**, *45*, 3831.
(4) Kimoto, H., Cohen, L.A. *J. Org. Chem.* **1979**, *44*, 2902.
(5) Abramovitch, R.A., Cue, B.W. *J. Am. Chem. Soc.* **1976**, *98*, 1478.
(6) Oledenhof, C., Cornelisse, J. *Recl. Trav. Chim. Pays-Bas* **1978**, *97*, 35.
(7) Whitten, J.P., Matthews, D.P., McCarthy, J.R. *J. Org. Chem.* **1986**, *51*, 3228.
(8) Whitten, J.P., Matthews, D.P., McCarthy, J.R. *J. Org. Chem.* **1986**, *51*, 1891.
(9) Whitten, J.P., Wagner, E.R., Matthews, D.P., McCarthy, J.R., unpublished work.
(10) Langenbeck, W. *J. Prakt. Chem.* **1928**, *119*, 77.
(11) Waselman, M., Guibe-Jampel, E., Raoult, A., Busse, W.D. *J. Chem. Soc. Chem. Commun.* **1976**, 21.
(12) Fodor, G., Abidi, S., Carpenter, T.C. *J. Org. Chem.* **1974**, *39*, 1507.
(13) Scriven, E.F.V. *Chem. Soc. Rev.* **1983**, *12*, 129.
(14) All starting materials are commercially available except **2b** and **2h**, which are prepared by literature methods as in Refs. 7 and 1, respectively.
(15) Ferguson, I.Y., Schofield, K. *J. Chem. Soc. Perkin Trans 1* **1975**, 275.
(16) Del Corona, L., Massaroli, G.G., Signorelli, G., Musa, G. *Bull. Soc. Ital. Farm. Osp.* **1971**, *110*, 645.