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Spotlight 126

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

Cyanogen Bromide (CNBr)

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Introduction

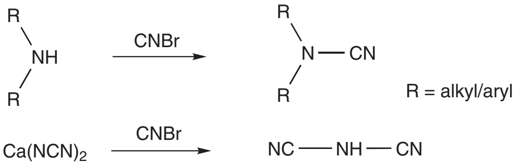
Cyanamides are versatile synthons that can be transformed into many biologically active compounds such as ureas, thioureas, selenoureas, guanidines, hydroxyguanidines, creatine, and a large number of heterocyclic compounds. Cyanogen bromide is a very useful and extensively used reagent for the synthesis of cyanamides. It is a colorless or white crystalline solid that decomposes in the presence of moisture and has a very small liquid range (mp 50–53 °C, bp 61–62 °C). It is cheap and can be obtained commercially, or it can be synthesized by the reaction of sodium cyanide with bromine in aqueous medium.[1] *Caution! It is highly toxic. Reactions should be carried out in a well-ventilated hood.*

$\mathrm{Br{-}C{\equiv}N}$

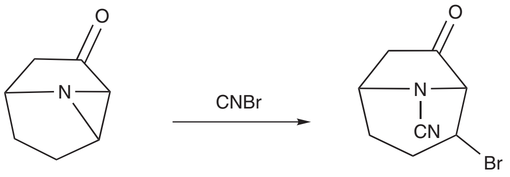
CNBr produces electrophilic cyanide. Therefore, it is attacked by nucleophiles such as amines, alcohols and thiols. Organic chemists are fully utilizing this property of the reagent. CNBr has also been applied in molecular biology to digest some proteins, and as a coupling agent for phosphoramidate or pyrophosphate internucleotide bonds in DNA duplexes.

Abstracts

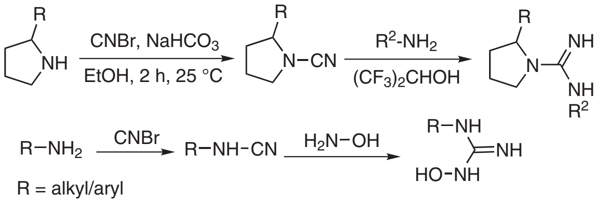
(A) *In the synthesis of cyanamides and dicyanamides:* Primary and secondary amines react with CNBr to give mono- and dialkylcyanamides.[2] Dicyanamides can be synthesized by the reaction of CNBr with calcium cyanamide.[3]



(B) *For the dealkylation of tertiary amines (von Braun reaction):* This involves the reaction of tertiary amines with CNBr to yield disubstituted cyanamides and an alkyl bromide.[4a] The bromodealkylation reaction has also been used to cleave the ring system of aziridine compounds.[4b]



(C) *In the synthesis of guanidines and hydroxyguanidines:* These potential bioactive compounds can be synthesized with the help CNBr. First, CNBr reacts with primary and secondary amines to give their respective cyanamides. The cyanamides further react with amines[5] and hydroxylamine[6] to give the desired end products in good yield.



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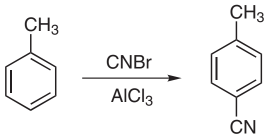
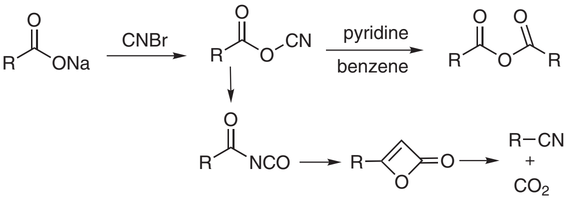
(D) *For cyanation at aromatic rings:* CNBr is a very useful reagent for the preparation of aryl nitriles. It condenses with toluene in the presence of $AlCl_3$ to give *p*-toluonitrile.[7]



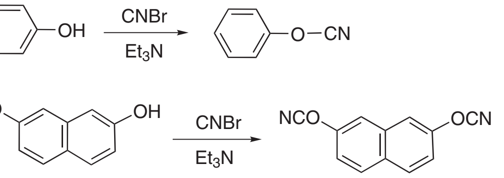
(E) *In the synthesis of α,β-alkynic nitriles*: The reaction of metalated alkynides with CNBr to furnish α,β-alkynic nitriles is a classic method for the preparation of these compounds. With CNBr in Et_2O–MeCN at 35 °C, copper(I) phenylacetylenide produces phenylpropynenitrile in 60% yield.[8]

$$\mathrm{Ph{-}C{\equiv}C{-}Cu} \xrightarrow{\mathrm{CNBr}} \mathrm{Ph{-}C{\equiv}C{-}CN}$$

(F) *For the preparation of nitriles and anhydrides from carboxylic acids:* CNBr is known to convert carboxylic acids to nitriles at higher temperature under sealed-tube conditions. The reaction involves the intermediacy of a carboxylic cyanic anhydride. In anhydrous benzene, the carboxylic cyanic anhydride may be trapped and, in the presence of pyridine, symmetrical anhydrides may be produced in yields of 78–95%.[9]



(G) *In the synthesis of cyanates or dicyanates:* Phenol and 2,7-dihydroxynaphthalene react with CNBr in the presence of Et_3N to give phenyl cyanate[10a] and 2,7-dihydroxynaphthalene dicyanate,[10b] respectively. Both are important precursors for many useful synthetic organic compounds.



(H) *As a cleaving agent:* von Braun found that a dialkyl thioether is cleaved by CNBr, at a somewhat elevated temperature (60–70 °C, sealed tube), to an alkyl thiocyanate and an alkyl bromide.[11] More recently, this reaction has been used for the selective cleavage of methionine peptides[12] and other peptides.[13]

$$C_2H_5SCH_3 \xrightarrow{\mathrm{CNBr}} C_2H_5SCN + CH_3Br$$

$$C_3H_7SC_2H_5 \xrightarrow{\mathrm{CNBr}} C_3H_7SCN + C_2H_5Br$$

References

(1) Hartmann, W. W.; Dreger, E. E. *Org. Synth. Coll. Vol. 2*; John Wiley & Sons: London, **1943**, 150.
(2) (a) Podesva, C. P.; Tarlton, E. J.; McKay, A. P. *Can. J. Chem.* **1962**, *40*, 1403. (b) Deaton, D. N.; Hassell, A. M.; McFadyen, R. B.; Miller, A. B.; Miller, L. R.; Shewchuk, L. M.; Tavares, F. X.; Willard, D. H.; Wright, L. L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1815.
(3) Rosowsky, A.; Modest, E. J. *J. Heterocycl. Chem.* **1966**, *3*, 387.
(4) (a) Hageman, H. A. *The von Braun Reactions,* In *Organic Reactions*, Vol. 7; Blatt, A. H.; Cope, A. C.; McGrew, F. C.; Niemann, C.; Snyder, A., Eds.; Wiley: New York, **1953**, 198. (b) Furuya, S.; Okamoto, T. *Heterocycles* **1988**, *27*, 2609.
(5) Snider, B. B.; O'Hare, S. M. *Tetrahedron Lett.* **2001**, *42*, 2455.
(6) Cai, T.; Xian, M.; Wang, P. G. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1507.
(7) Scholl, R.; Kacer, F. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 322.
(8) Companon, P.-L.; Gros, B. *Synthesis* **1976**, 448.
(9) Ho, J.-L.; Wong, C. M. *Synth. Commun.* **1973**, *3*, 63.
(10) (a) Martin, D.; Bauer, M. *Org. Synth. Coll. Vol. 7*; John Wiley & Sons: London, **1990**, 435. (b) Yan, H.; Chen, S.; Qi, G. *Polymer* **2003**, *44*, 7861.
(11) von Braun, J.; Engelbertz, P. *Ber. Dtsch. Chem. Ges.* **1923**, *56*, 1573.
(12) (a) Gross, E.; Witkop, B. *J. Am. Chem. Soc.* **1961**, *83*, 1510. (b) Gross, E.; Witkop, B. *J. Biol. Chem.* **1962**, *237*, 1856. (c) Stadtmana, E. R.; Van Remmen, H.; Richardson, A.; Wahr, N. B.; Levine, R. L. *Biochim. Biophys. Acta* **2005**, *1703*, 135.
(13) Zhong, H.; Marcus, S. L.; Li, L. *J. Am. Soc. Mass Spectrom.* **2005**, *16*, 471.