Cascade Reactions

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Double Duty for Cyanogen Bromide in a Cascade Synthesis of Cyanoepoxides**

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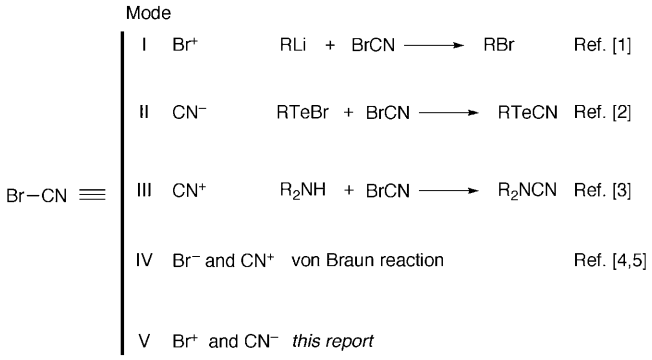
Cyanogen bromide is a versatile reagent used in organic synthesis. Under different conditions, the Br–C bond can be cleaved in a diverse manner (Scheme 1, Modes I–IV). Thus, BrCN was shown to serve as a donor of Br^+ in reactions with strongly nucleophilic organometallic reagents to provide the corresponding vinyl- or arylbromides (Mode I).[1] In the reaction with vinyltellrium bromide, cyanogen bromide acted as an equivalent of a cyanide anion, and converts vinyltellurium bromide into a vinyltellurium cyanide (Mode II).[2] When reacted with primary or secondary amines or alcohols, cyanogen bromide behaves as an equivalent of CN^+, and gives rise to cyanamides or cyanates (Mode III).[3] In the von Braun reaction, BrCN acts as an equivalent of both CN^+ and Br^- by fragmenting tertiary amines into cyanamides and alkylbromides (Mode IV).[4,5] Herein, we report an unprecedented Mode V, in which cyanogen bromide works as an equivalent of Br^+ and CN^- in a one-pot transformation of ketones into cyanoepoxide derivatives (Mode V).

Our research group has recently demonstrated that alkynyl bromides can act as equivalents of both Br^+ and alkynyl anions in a highly efficient, one-pot conversion of ketones into alkynylepoxides.[6] We hypothesized that cyanogen bromide could potentially be involved in a similar transformation as an equivalent of both Br^+ and CN^- (Scheme 2). It was anticipated that a ketone enolate would attack the bromine atom of cyanogen bromide to generate the α-bromoketone **3**. Then nucleophilic addition of the formed cyanide to the ketone to give **4**, would be followed by the formation of a cyanohydrin anion, which upon intramolecular S_N2 reaction would produce the product cyanoepoxide **2**. Thus, cyanogen bromide would act as an equivalent of both Br^+ and CN^- in one cascade transformation.

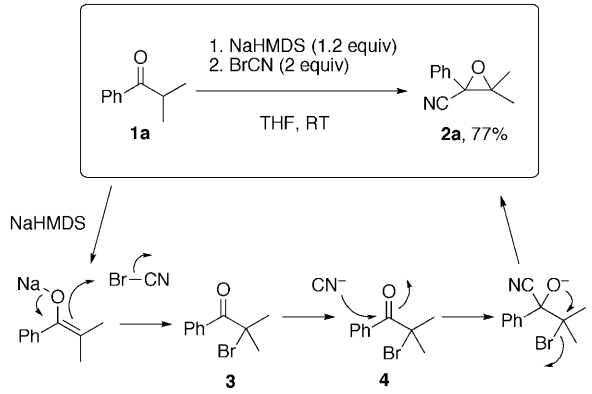


Scheme 1. Diverse reactivity of cyanogen bromide.

To test the above hypothesis, we examined the reaction of isobutyrophenone (**1a**) and cyanogen bromide in the presence of a strong base. It was found that the deprotonation of isobutyrophenone with NaHMDS, and subsequent addition of cyanogen bromide resulted in the formation of cyanoepoxide **2a** in good yield, along with trace amounts of α-bromoketone **3**, and provided support for the proposed path for this transformation.[7]

A brief optimization of the reaction conditions (Table 1) revealed that employment of other ethereal solvents, such as diethyl ether or 1,4-dioxane, did not improve the yield of **2a** (Table 1, entries 2 and 5). Increasing the concentration of the reaction mixture by adding NaHMDS solution to a neat ketone resulted in a better yield, but this result was not reproducible on other ketones (Table 1, entry 3). Changing the solvent to dichloromethane suppressed the reaction (Table 1, entry 4). Finally, employment of DMF has substantially improved the yield with no traces of α-bromoketone **3** being produced (Table 1, entry 6). Switching the base to LiHMDS slightly further improved the yield (Table 1, entry 7). Weak bases, such as triethylamine and cesium carbonate, gave no reaction product (Table 1, entry 8 and 9).

With the optimized conditions in hand, the generality of this cascade transformation was examined (Table 2). α,α-



Scheme 2. Proposed concept and initial trial. HMDS = 1,1,1,3,3,3-hexamethyldisilazane.

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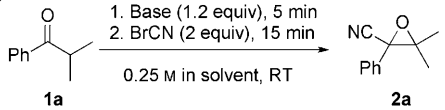
Table 1: Optimization of reaction conditions.



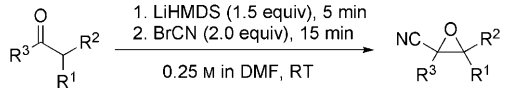
1a **2a**

Entry	Solvent	Base	Yield [%][a]
1	THF	NaHMDS[b]	77 (17% of **3**)
2	Et_2O	NaHMDS	62
3	THF[c]	NaHMDS	88
4	CH_2Cl_2	NaHMDS	N.R.
5	1,4-dioxane	NaHMDS	44
6	DMF	NaHMDS	90
7	**DMF**	**LiHMDS[b]**	**92**
8	DMF	TEA	N.R.
9	DMF	Cs_2CO_3	N.R.

[a] Yield was determined by GC-MS analysis using diphenyl ether as an internal standard. [b] 1 M in THF. [c] A solution of NaHMDS in THF was added to a neat ketone. DMF = *N*,*N*-dimethylformamide, N.R. = no reaction, TEA = triethylamine, THF = tetrahydrofuran.

Disubstituted methyl aryl ketones were found to be suitable substrates for this reaction. Thus, isopropyl, cyclopentyl, and cyclohexyl ketones were efficient in this reaction (**1a–c**). Isopropyl ketones usually provide better yield compared with that of the corresponding cyclopentyl and cyclopentyl counterparts that bear the same aryl group. A relatively lower yield for the latter was probably caused by a competing elimination of HBr during the reaction.[8] Certain groups at the aromatic moiety of ketone, such as methoxy (**1d**) and nitrile (**1e–g**), were tolerated. Cyanoepoxidation of unsymmetrically substituted ketone **1h** produced an almost 1:1 diasteriomeric mixture of cyanoepoxide **2h** in low yield.[9] A slightly better yield of cyanoepoxide was obtained by cyclization of α,α-diphenylacetophenone (Table 2, entry 9). This reaction turned out to be efficient with pyridyl-containing ketones. Thus, 3-pyridinyl ketones **1j–l** (Table 2, entries 10–12) and 2-pyridinyl ketones **1m–o** (Table 2, entries 13–15) were smoothly converted into the corresponding cyanoepoxides **2j–o** in good to excellent yields. Finally, it was found that the propargyl ketone **1p** is a suitable substrate

Table 2: Synthesis of cyanoepoxides.



1a–p **2a–p**

Entry	Substrate **1**	Product **2**	Yield [%][a]	Entry	Substrate **1**	Product **2**	Yield [%][a]
1	**1a**	**2a**	78, 92[b]	9	**1i**	**2i**	52
2	**1b**	**2b**	75	10	**1j**	**2j**	84
3	**1c**	**2c**	66	11	**1k**	**2k**	70
4	**1d**	**2d**	71	12	**1l**	**2l**	80
5	**1e**	**2e**	70	13	**1m**	**2m**	93
6	**1f**	**2f**	70	14	**1n**	**2n**	90
7	**1g**	**2g**	80	15	**1o**	**2o**	78
8	**1h**	**2h**	40	16	**1p**	**2p**	85

[a] Yield of isolated product. [b] Yield determined by GC-MS analysis.

for this reaction and produced the alkynyl cyanoepoxide **2p** in high yield (Table 2, entry 16).[10]

In summary, we have demonstrated that cyanogen bromide can serve an equivalent of both CN^- and Br^+ in a cascade conversion of ketones into cyanoepoxide derivatives. This reaction proceeds through α bromination of a ketone by cyanogen bromide, followed by a nucleophilic addition of the produced cyanide at the ketone and a subsequent replacement of the α bromide by a cyanohydrine anion. This approach provides a convenient and efficient route[11] for the preparation of fully substituted and diverse cyanoepoxide derivatives[12] from easily available ketones.

Experimental Section

Ketone (0.5 mmol) was added to an oven dried conical vial, equipped with a magnetic stirring bar and a screw cap, and the atmosphere was replaced by argon. Then dry DMF was added and the mixture was stirred until the ketone was completely dissolved. LiHMDS (1M in THF, 0.75 mL) was subsequently added to the DMF solution and the mixture was stirred for 5 min. Then a solution of BrCN (10M in THF) was added drop wise to the mixture and the reaction mixture was stirred for another 15 min. The mixture was quenched with water (10 mL) and the product was extracted with ethyl acetate or diethyl ether. The organic extract was dried over sodium sulfate and solvent was removed in vacuo. The residue was purified by a column chromatography on silica gel using hexanes/ethyl acetate (1:1) as an eluent to give the final product.

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[1] For reaction of cyanogen bromide with aryllithium reagents, see: a) L. A. Paquette, F. Pierre, C. E. Cottrell, *J. Am. Chem. Soc.* **1987**, *109*, 5731; b) L. A. Paquette, K. S. Learn, J. L. Romine, H. S. Lin, *J. Am. Chem. Soc.* **1988**, *110*, 879; c) J. A. Miller, W. Leong, G. Zweifel, *J. Org. Chem.* **1988**, *53*, 1839; d) C. Jaramillo, J. C. Carretero, J. de Diego, M. del Prado, C. Hamdouchi, J. L. Roldán, C. Sánchez-Martinez, *Tetrahedron Lett.* **2002**, *43*, 9051; e) Y. Kobayashi, A. Fukuda, T. Kimachi, M. Ju-ichi, Y. Takemoto, *Tetrahedron Lett.* **2004**, *45*, 677; f) A. Casoni, G. Celentano, F. Clerici, A. Contini, M. L. Gelmi, G. Mazzeo, S. Pellegrino, C. Rosini, *Tetrahedron: Asymmetry* **2009**, *20*, 2247.

[2] T. G. Back, B. P. Dyck, M. Parvez, *J. Org. Chem.* **1995**, *60*, 4657.

[3] For preparation of cyanamide from cyanogen bromide, see: a) W. J. Ross, R. G. Harrison, M. R. J. Jolley, M. C. Neville, A. Todd, J. P. Verge, W. Dawson, W. J. F. Sweatman, *J. Med. Chem.* **1979**, *22*, 412; b) R. J. Sundberg, B. C. Pearce, *J. Org. Chem.* **1985**, *50*, 425; c) K. Futaki, S. Tosa, *Chem. Pharm. Bull.* **1986**, *8*, 908; d) A. Padwa, M. A. Brodney, B. Liu, K. Satake, T. Wu, *J. Org. Chem.* **1999**, *64*, 3595; e) B. B. Snider, S. M. O'Hare, *Tetrahedron Lett.* **2001**, *42*, 2455; f) F. M. Rivas, A. J. Giessert, S. T. Diver, *J. Org. Chem.* **2002**, *67*, 1708; g) M. P. Price, W. Guida, T. Jackson, J. Nydick, P. Gladstone, J. Juarez, F. Doñate, R. Ternansky, *Bioorg. Med. Chem.* **2003**, *13*, 107; h) M. Amir, K. Shikha, *Eur. J. Med. Chem.* **2004**, *39*, 535; i) R. K. Grover, A. P. Kesarwani, G. K. Srivastava, B. Kundu, R. Roy, *Tetrahedron* **2005**, *61*, 5011; j) Y. Cheng, Q. Zhu, Q. S. Li, O. Meth-Cohn, *J. Org. Chem.* **2005**, *70*, 4840; k) D. G. Barrett, D. N. Deaton, A. M. Hassell, R. B. McFadyen, A. B. Miller, L. R. Miller, J. A. Payne, L. M. Shewchuk, J. Willard, L. L. Wright, *Bioorg. Med. Chem.* **2005**, *5*, 3039; l) K. Starcevic, I. Caleta, D. Cincic, B. Kaitner, M. Kralj, K. Ester, G. M. Karminski-Zamola, *Heterocycles* **2006**, *68*, 2285; m) L. Hwang, C. Tus, J. Wang, *J. Heterocycl. Chem.* **2006**, *43*, 889; n) U. Köhn, M. Klopfleisch, H. Görls, E. Anders, *Tetrahedron: Asymmetry* **2006**, *17*, 811; o) M. Hasegawa, N. Nishigaki, Y. Washio, K. Kano, P. A. Harris, H. Sato, I. Mori, R. I. West, M. Shibahara, H. Toyoda, L. Wang, R. T. Nolte, J. M. Veal, M. Cheung, *J. Med. Chem.* **2007**, *50*, 4453; p) O. García Mancheño, C. Bolm, *Org. Lett.* **2007**, *9*, 2951; q) S. Nag, A. Mishra, S. Batra, *Tetrahedron* **2008**, *64*, 10162; r) M. Saitoh, J. Kunitomo, E. Kimura, H. Iwashita, Y. Uno, T. Onishi, N. Uchiyama, T. Kawamoto, T. Tanaka, C. D. Mol, *J. Med. Chem.* **2009**, *52*, 6270.

[4] For selected samples of Zincke aldehyde formation involving cyanogen bromide, see: a) T. Zincke, G. Heuser, W. Möller, *Justus Liebigs Ann. Chem.* **1904**, *333*, 296; b) A. M. Kearney, C. D. Vanderwal, *Angew. Chem.* **2006**, *118*, 7967; *Angew. Chem. Int. Ed.* **2006**, *45*, 7803.

[5] For von Braun reactions, see: a) W. König, *J. Prakt. Chem.* **1904**, *69*, 105; b) J. von Braun, K. Heider, E. Müller, *Ber. Dtsch. Chem. Ges.* **1918**, *51*, 273; c) R. C. Elderfield, H. A. Hagema, *J. Org. Chem.* **1949**, *14*, 605; d) R. C. Elderfield, M. Green, *J. Org. Chem.* **1952**, *17*, 431; e) S. Chambert, F. Thomasson, J. Décout, *J. Org. Chem.* **2002**, *67*, 1898; f) R. Leung-Toung, T. F. Tam, Y. Zhao, C. D. Simpson, W. Li, D. Desilets, K. Karimian, *J. Org. Chem.* **2005**, *70*, 6230; g) W. S. McCall, T. A. Grillo, D. L. Comins, *J. Org. Chem.* **2008**, *73*, 9744; h) R. L. Giles, R. A. Nkansah, R. E. Looper, *J. Org. Chem.* **2010**, *75*, 261; i) Y. Hayashi, T. Kumamoto, M. Kawahata, K. Yamaguchi, T. Ishikawa, *Tetrahedron* **2010**, *66*, 3836.

[6] A. Trofimov, N. Chernyak, V. Gevorgyan, *J. Am. Chem. Soc.* **2008**, *130*, 13538.

[7] In the test experiment, the commercially available α-bromoketone **3**, upon treatment with NaCN, was quantitatively converted into cyanoepoxide **2a**. For formation of epoxides via an addition/substitution process of nucleophiles with α-halo ketones, see: a) J. Hummeen, H. Wynberg, *Tetrahedron Lett.* **1978**, *19*, 1089; b) G. A. Russell, F. Ros, *J. Am. Chem. Soc.* **1985**, *107*, 2506.

[8] A certain amount of cyclopentenyl and cyclohexenyl phenones was observed by GC-MS analysis of the crude reaction mixtures.

[9] Cyanoepoxidation of ketone **1h** produced an inseparable mixture of diastereomers **2h**. See the Supporting Information for details.

[10] Fully aliphatic ketones appeared to be unstable under these reaction conditions.

[11] For selected examples on the preparation of cyanoepoxides, see: a) M.-X. Wang, G. Deng, D.-X. Wang, Q.-Y. Zheng, *J. Org. Chem.* **2005**, *70*, 2439; b) N. F. Badham, W. L. Mendelson, A. Allen, A. M. Diederich, D. S. Eggleston, J. J. Filan, A. J. Freyer, A. J. Killmer, C. J. Kowalski, L. Liu, V. J. Novack, F. G. Vogt, K. S. Webb, J. Yang, *J. Org. Chem.* **2002**, *67*, 5440; c) K. A. Bhatia, K. J. Eash, N. M. Leonard, M. C. Oswald, R. S. Mohan, *Tetrahedron Lett.* **2001**, *42*, 8129; d) A. E. Lurain, A. Maestri, A. R. Kelly, P. J. Carroll, P. J. Walsh, *J. Am. Chem. Soc.* **2004**, *126*, 13608; see also: e) V. K. Aggarwal, D. M. Badine, V. A. Moorthie in *Aziridines and Epoxides in Organic Synthesis* (Ed.: A. K. Yudin), Wiley-VCH, Weinheim, **2006**, pp. 1.

[12] For selected examples on using fully substituted cyanoepoxides in synthesis, see: a) D. M. Rathod, S. Rengaraju, M. M. Gharpure, N. M. Patel, M. M. Deoahar (Alembic Limited, India), EP1249447 (A1), **2002**; b) M. Aiai, M. Baudy-Floch, A. Robert, P. Le Grel, *Synthesis* **1996**, 403; c) R. Deghenghi, R. Gaudry, *Can. J. Chem.* **1961**, *39*, 1553; d) G. Stork, W. S. Worrall, J. J. Pappas, *J. Am. Chem. Soc.* **1960**, *82*, 4315.

