ORGANIC LETTERS

2006
Vol. 8, No. 26
5979−5982

Efficient Addition Reaction of Bromonitromethane to Aldehydes Catalyzed by NaI: A New Route to 1-Bromo-1-nitroalkan-2-ols under Very Mild Conditions

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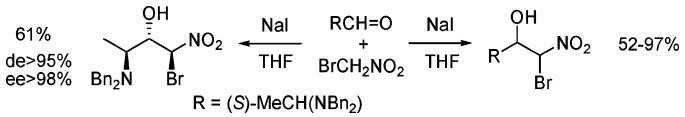
Received October 5, 2006

ABSTRACT



A catalytic NaI-mediated novel synthesis of 1-bromo-1-nitroalkan-2-ols was carried out by reaction of bromonitromethane with a variety of aldehydes, under very mild conditions. When the reaction was performed with chiral *N*,*N*-dibenzyl alaninal, the corresponding enantiopure (1*S*,2*S*,3*S*)-3-dibenzylamino-1-bromo-1-nitrobutan-2-ol was obtained with good stereoselectivity. The structure of this enantiopure bromohydrin was established by X-ray analysis.

1-Bromo-1-nitroalkan-2-ols present important practical applications. These compounds are used in the manufacturing of photographic[1] and ink-based materials.[2] Some of them also present biocide[3] and antimicrobial activity[4] inhibiting the growth of a broad range of organisms including species of *Pseudomonas*.[5]

Given these applications, several patents in connection with the preparation of 1-bromo-1-nitroalkan-2-ols have been registered.[6] These registered syntheses are carried out by reaction of 1-nitroalkan-2-ols with bromine,[6] which sometimes can produce the undesirable double bromination, affording 1,1-dibromo-1-nitroalkanols as byproducts. In addition, these 1-bromo-1-nitroalkan-2-ols are prepared as a 1:1 mixture of diastereoisomers.

In contrast to the relatively important number of patents, only one paper describing the synthesis of 1-bromo-1-nitroalkan-2-ols, by treatment of the sodium nitronate product derived from the corresponding nitroaldol adduct with bromine in diethyl ether, has previously been published.[5] In

(1) (a) Satake, M.; Maekawa, Y.; Shishido, T. (Fuji Photo Film Co., Ltd., Japan), Japanese Patent Application JP 01100532 A2, 1989; *Chem. Abstr.* **1990**, *112*, 108414. (b) Hirabayashi, S. (Konishiroku Photo Industry Co., Ltd., Japan), Japanese Patent Application JP 07140620 A2, 1995; *Chem. Abstr.* **1995**, *123*, 241899. (c) Marui, T. (Konica Co., Japan), Japanese Patent Application JP 03120531 A2, 1991; *Chem. Abstr.* **1991**, *115*, 266714. (d) Sakata, H.; Nagashima, T.; Arai, T. (Konica Co., Japan), Japanese Patent Application JP 03038634 A2, 1991; *Chem. Abstr.* **1991**, *115*, 243848.

(2) Mine, K.; Kobayashi, Y.; Kawaguchi, Y.; Aoki, S. (Konishiroku Photo Industry Co., Ltd., Japan), Japanese Patent Application JP 61055173 A2, 1986; *Chem. Abstr.* **1986**, *105*, 99202.

(3) (a) Elsmore, R.; Guthrie, W. G.; Parr, J. A. *Spec. Chem. Mag.* **1987**, *7*, 166−176. (b) Yamada, T. (Konishiroku Photo Industry Co., Ltd., Japan), Japanese Patent Application JP 08134371 A2, 1996; *Chem. Abstr.* **1996**, *125*, 208284. (c) Kanesho Co., Ltd., Japanese Patent Application JP 60048903 A2, 1985; *Chem. Abstr.* **1985**, *103*, 49761.

(4) Clark, N. G.; Croshaw, B.; Spooner, D. F. (Boots Pure Drug Co., Ltd.), English Patent Application GB 1057131, 1967; *Chem. Abstr.* **1967**, *66*, 104675.

(5) Clark, N. G.; Croshaw, B.; Leggetter, B. E.; Spooner, D. F. *J. Med. Chem.* **1974**, *17*, 977−981.

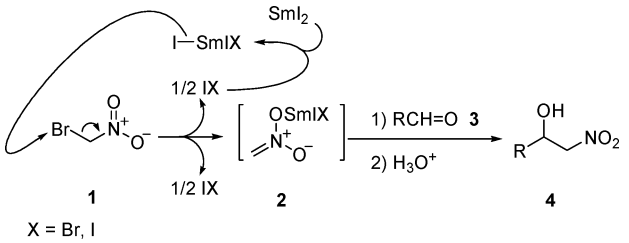
(6) (a) Wuest, W.; Eskuchen, R.; Esser, H. (Henkel K.-G.a.A., Fed. Rep. Ger.), German Patent Application DE 3814773 A1, 1989; *Chem. Abstr.* **1990**, *112*, 234796. (b) Mir Soler, J. (Coprima, S. A., Spain), Spanish Patent Application ES 453224 A1, 1977; *Chem. Abstr.* **1978**, *89*, 59652. (c) Wessendorf, R. (Henkel und Cie. G.m.b.H.), German Patent Application DE 1954173 A, 1971; *Chem. Abstr.* **1971**, *75*, 19690.

10.1021/ol062451f CCC: $33.50
Published on Web 12/01/2006

this paper, the described 1-bromo-1-nitroalkan-2-ols were obtained in low to moderate yields (52−70%). So, alternative procedures for an efficient preparation of 1-bromo-1-nitroalkan-2-ols, avoiding the use of toxic bromine would be of great interest.

Very recently, we have described the synthesis of 1-nitroalkan-2-ols by reaction of bromonitromethane with various aldehydes in the presence of samarium diiodide or samarium triiodide.[7] This transformation took place with substoichiometric amounts of SmI_2 or SmI_3, and the aldol reaction was promoted by the iodide released by the SmI_3 (traces of SmI_3 are always present in the THF solutions of samarium diiodide). So, the released iodide could attack the bromine atom of bromonitromethane **1** generating IBr and promoting the addition of the nitronate anion **2** to the corresponding aldehyde **3**, to give 1-nitroalkan-2-ols **4** (Scheme 1).

Scheme 1. Synthesis of 1-Nitroalkan-2-ols **4**



These previous results prompted us to test the possibility of performing the synthesis of 1-nitroalkan-2-ols mediated by other cheaper iodide sources, such as sodium iodide. Therefore, in this communication, we describe the results obtained from the addition reaction of bromonitromethane **1** to various aldehydes **3** promoted by sodium iodide. In this case, 1-bromo-1-nitroalkan-2-ols **5** were obtained instead of the expected 1-nitroalkan-2-ols **4**. This reaction takes place under very mild reaction conditions in nearly quantitative yields. A mechanism, different from that proposed in the samarium-promoted process (Scheme 1),[7] is tentatively proposed to explain this transformation. The previous results of the chiral version of this transformation, performed on *N*,*N*-dibenzyl alaninal, are also described. The absolute configuration (1*S*,2*S*,3*S*) of the obtained enantiopure 3-dibenzylamino-1-bromo-1-nitrobutan-2-ol has been established by X-ray analysis (Figure 1).

The initial attempts to obtain compounds **5** were performed using 1.5 equiv of sodium iodide. After studying the reaction conditions, it can be established that this aldol reaction can also be performed with catalytic amounts of sodium iodide. When the reaction was performed in the absence of NaI, no reaction took place and the starting materials were recovered unchanged.

So, when solutions of a variety of aldehydes **3** (1.0 equiv) in THF and 1.0 equiv of bromonitromethane **1** were treated with 0.15 equiv of sodium iodide at room temperature for 3 h, 1-bromo-1-nitroalkan-2-ols **5** were obtained in high yields (Scheme 2 and Table 1).

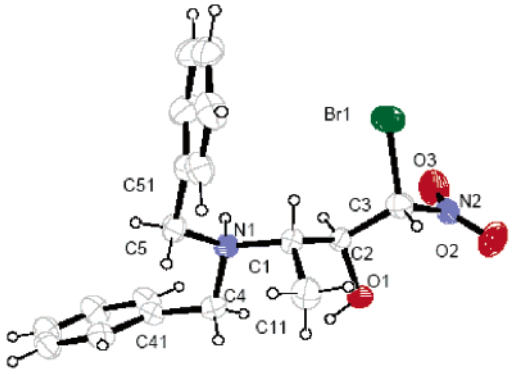
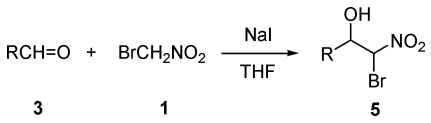


Figure 1. X-ray structure of compound **9**.

Scheme 2. Synthesis of 1-Bromo-1-nitroalkan-2-ols **5**



In general, crude reaction products were obtained in high purity, after filtration through a pad of celite and further solvent removal under vacuum. So, it is noteworthy that no column chromatography purification was necessary to obtain compounds **5** with high purity (Table 1, entries 1−6 and 8), except for product **5g** (Table 1, entry 7) where distillation was required to remove the unreacted benzaldehyde **3g**.

Table 1. Synthesis of 1-Bromo-1-nitroalkan-2-ols **5**

entry	**5**	R	yield (%)[a]
1	**5a**	n-C_7H_{15}	90
2	**5b**	Cy	97
3	**5c**	i-Bu	90
4	**5d**	s-Bu	92
5	**5e**	C_9H_{17}[b]	63
6	**5f**	$PhCH_2$	99
7	**5g**	Ph	52
8	**5h**	(*E*)-CH_3CH=CH	91

[a] Yield of the corresponding isolated products **5** based on aldehydes **3**. [b] Me_2C=$CH(CH_2)_2CH(Me)CH_2$.

This transformation is general, and as shown in Table 1, the reaction can be performed with linear, branched, cyclic, aromatic, and conjugated aldehydes. However, the reaction did not work with highly hindered aldehydes such as pivaldehyde or ketones.

To the best of our knowledge, this is the first example in which NaI is catalytically utilized to promote a nitroaldol-

(7) Concellón, J. M.; Rodríguez-Solla, H.; Concellón, C. *J. Org. Chem.* **2006**, *71*, 7919−7922.

type reaction. This synthesis fulfills standards to define it as an atom-economical procedure.[8]

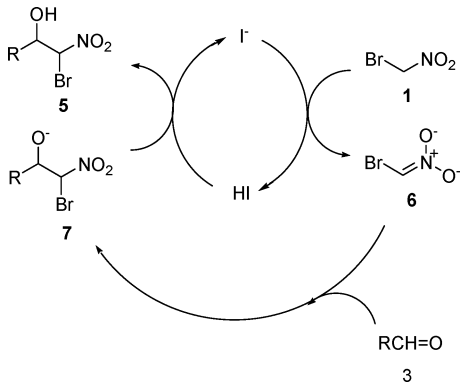
Compounds **5** were isolated as a mixture of diastereoisomers in approximately a 1:1 ratio, determined by ^{1}H and ^{13}C NMR analyses of the crude reaction products. These stereochemical results were similar to those previously reported in the literature.[5,6]

As expected, the reaction also took place when another iodide source was used. So, when the reaction was performed with KI instead of NaI, compound **5a** was also obtained in comparable yield (91%). In this case, longer reaction times were however required (18 h), probably due to the lower solubility of KI in THF.

Similarly, the reaction can also be performed using tetrabutylammonium iodide as a source of iodide. Thus, compound **5a** has also been obtained in high yield (89%); however, the main drawback in the utilization of $(Bu_4N)^+ I^-$ when compared with NaI is that a purification by column chromatography was necessary to eliminate completely the ammonium salt and to isolate 1-bromo-1-nitroalkan-2-ols **5** in a pure form.

Mechanistically, a possible explanation of this transformation could be based on the high acidity of bromonitromethane **1**. Although the iodide is a very weak base in an aqueous medium, in THF it could be sufficiently strong to abstract the proton from bromonitromethane. Thus, the abstraction of a proton of bromonitromethane could generate a bromonitronate intermediate **6** that could react with the aldehyde **3** to afford the alcoholate **7** which after protonolysis would generate the corresponding bromonitroalcohol **5** and the iodide anion that would continue the process (Scheme 3).

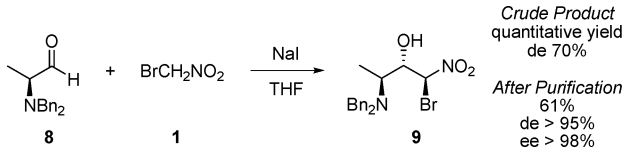
Scheme 3. Mechanistic Proposal



The different behavior of the iodide atoms depending on their cationic partner (Sm^{+2} or Sm^{+3} vs Na^+) could be rationalized considering the ionic (NaI) or covalent (SmI_2 or SmI_3) character of these species. So, iodide from NaI could be completely dissociated and could abstract acidic hydrogens, whereas iodide from SmI_2 or SmI_3 would be partially bonded to the samarium center decreasing the basic properties of these iodide ions.

The first application of this method to obtain enantiopure 3-amino-1-bromo-1-nitroalkan-2-ols[9] was carried out by using chiral *N*,*N*-dibenzyl alaninal **7**. Hence, crude 3-amino-1-bromo-1-nitrobutan-2-ol **9** was obtained in quantitative yield and with good diastereoisomeric excess (de 70%) (Scheme 4).

Scheme 4. Synthesis of Enantiopure (1*S*,2*S*,3*S*)-3-Amino-1-bromo-1-nitrobutan-2-ol **9**



The stereoselectivity of the reaction was determined by ^{1}H NMR spectroscopy (300 MHz) on the crude product **9**. It is noteworthy that in the synthesis of **9** two new stereogenic centers were generated with good stereoselectivity (70% de). In addition, after conventional column chromatography, pure compound **9** was obtained with de > 95%.

The structure of compound **9** was unambiguously established by single-crystal X-ray diffraction.[10]

The absolute configuration of compound **9** was in accordance with the addition of the bromonitronate anion to alaninal **8** under a nonchelation control mechanism. This fact is in agreement with other previously reported additions of nucleophiles to *N*,*N*-dibenzyl α-aminoaldehydes.[11]

The enantiomeric purity of compound **9** was determined by chiral HPLC chromatography, showing an enantiomeric excess (ee) >98%. Racemic mixtures of **9** were prepared from racemic alaninal **8** to exclude the possibility of coelution of both enantiomers in HPLC.[12]

In conclusion, we have described a novel reaction of bromonitromethane with a variety of aldehydes under very mild conditions, promoted by catalytic amounts of NaI to afford 1-bromo-1-nitroalkan-2-ols and with 100% atom economy. When chiral *N*,*N*-dibenzyl alaninal was utilized as the starting material, the enantiopure (1*S*,2*S*,3*S*)-3-amino-1-bromo-1-nitrobutan-2-ol was obtained after column chromatography purification.

(8) For a discussion on atom economy, see: (a) Trost, B. M. *Science* **1991**, *254*, 1471−1477. (b) Trost, B. M. *Angew. Chem., Int. Ed.* **1995**, *34*, 259−281.

(9) Preparation of chiral 3-amino-1-bromo-1-nitroalkan-2-ols **9** has not been reported to date. For the syntheses of the related 3-amino-1-nitroalkan-2-ols from chiral aminoaldehydes, see: (a) Sohtome, Y.; Takemura, N.; Iguchi, T.; Hashimoto, Y.; Nagasawa, K. *Synlett* **2006**, 144−146. (b) Klein, G.; Pandiaraju, S.; Reiser, O. *Tetrahedron Lett.* **2002**, *43*, 7503−7506. (c) Ma, D.; Pan, Q.; Han, F. *Tetrahedron Lett.* **2002**, *43*, 9401−9403. (d) Misumi, Y.; Matsumoto, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 1031−1033. (e) Corey, E. J.; Zhang, F. -Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 1931−1934. (f) Hanessian, S.; Devasthale, P. V. *Tetrahedron Lett.* **1996**, *37*, 987−990. (g) Sasai, H.; Kim, W.-S.; Suzuki, T.; Shibasaki, M. *Tetrahedron Lett.* **1994**, *35*, 6123−6126 and ref 7.

(10) CCDC 610565 contains the supplementary crystallographic data for the bromohydrate derivative of compound **9**. These data can be obtained free of charge via: www.ccdc.cam.ac.uk/conts/retrieving.html (or the Cambridge Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

(11) (a) Reetz, M. T. *Chem. Rev.* **1999**, *99*, 1121−1162. (b) Reetz, M. T. *Angew. Chem., Int. Ed.* **1991**, *30*, 1531−1546.

(12) Chiral HPLC analysis for **9** shows an ee > 98 %: Chiracel-OD, UV detector 210 nm, 0.5 mL/min, 98:2 hexane/*i*-PrOH, t_R 21.2 min; racemic mixture, t_R 21.2 and 26.0 min.

The generality and synthetic applications of this reaction and the studies directed toward fully delineating the factors involved in these transformations are currently under investigation within our laboratory.

Acknowledgment. We thank the Ministerio de Educación y Ciencia (CTQ2004-1191/BQU) for financial support. J.M.C. thanks Carmen Fernández-Flórez for her time. H.R.S. and C.C. thank the Ministerio de Educación y Ciencia for a Ramón y Cajal Contract (Fondo Social Europeo) and a predoctoral FPI fellowship, respectively. Our thanks to Euan C. Goddard for his revision of the English.

Supporting Information Available: General procedure, spectroscopic data, and copies of ^{13}C NMR spectra for compounds **5** and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL062451F