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Formate ester synthesis via reaction of 2-bromoethylamines with dimethylformamide

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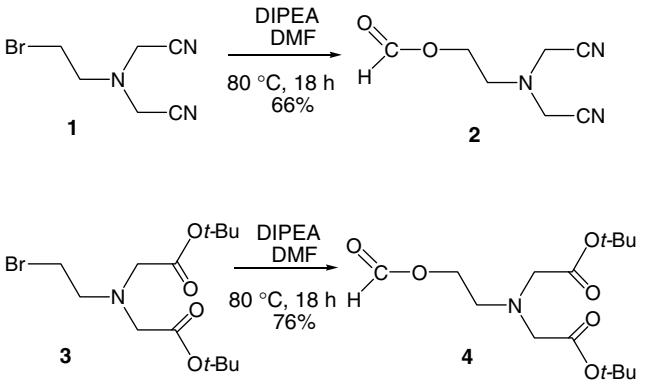
Abstract

2-Bromoethylamines are converted to the corresponding formate esters in the presence of DMF. Both primary and secondary bromides are smoothly transformed to the esters in satisfactory yields. The reaction mechanism involves the formation of an aziridinium ion, which upon reaction with DMF forms a Vilsmeier-type intermediate that is further hydrolyzed to the corresponding formates. Participation of the β-amino group appears to control not only the regioselectivity but also the stereoselectivity of the reaction. Application of the reaction conditions to chiral substrates indicated that non-rearranged products are formed with retention of configuration at the reacting center.

Keywords: 2-Bromoethylamines; Formate esters; Aziridinium ion; Vilsmeier-intermediate

As a part of an ongoing project aimed at the synthesis of zinc chelating sensors,[1] we attempted the alkylation of aromatic amines with 2-[(2-bromoethyl)(cyanomethyl)amino]-acetonitrile (**1**) using DMF as a reaction solvent. To our surprise the alkylated amines were isolated as the minor products of the reactions, the major product being the corresponding formate ester **2**. Reproduction of the experimental conditions in the absence of nucleophile gave **2** in 66% yield (Scheme 1). Under the same experimental conditions the bis-*t*-butyl ester analog, namely *tert*-butyl 2-((2-bromoethyl)(2-*tert*-butoxy-2-oxoethyl)amino)acetate (**3**) gave the corresponding formate in 76% yield.

To the best of our knowledge there is no previous report of such a transformation. The preparation of 2-aminoethyl-formates has been mentioned in the literature as a result of applications of general methods such as the conversion of primary alcohols or their *O*-*tert*-butyldimethylsilyl ethers to the corresponding formate esters in methylene chloride, using 2,4,6-trichloro-1,3,5-triazine and DMF in the presence of lithium fluoride.[2] Similarly, *O*-*tert*-butyldimethylsilyl or *O*-triethylsilyl alcohols were converted to their



Scheme 1. Conversion of 2-bromoamines to the corresponding formate esters.

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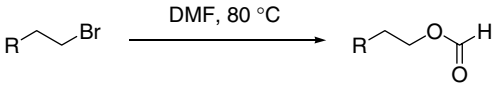
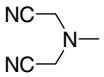
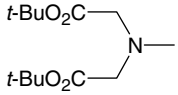
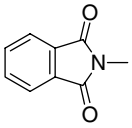
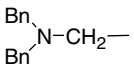
Table 1
Dependence of the formate ester yield on the type of substrate, the reaction time and the presence of base



R	Compound	Reaction time (h)	Product yield (%)
	**1**	20	66
	**3**	20	76
	**5**	20	44
	**6**	20	71
	6	40	97
	6	20[a]	68
	6	40[a]	74
	**7**	20	24
	7	40	61
	7	60	80
$PhCH_2Br$	**8**	20	7

[a] DIPEA was used as base in the reaction.

corresponding formates under Vilsmeier–Haack conditions ($POCl_3$/DMF).[3]

To explore the mechanism as well as the scope of the reaction we repeated the experiment using *N*-(2-bromoethyl)phthalimide (**5**) where the nitrogen is part of a conjugated system. The yield of the corresponding formate was reduced to 44%, presumably due to the reduced availability of the electron pair on the nitrogen (Table 1). A similar explanation was given for the lack of potency of *N*,*N*-bis-(2-chloroethyl)nitroanilines as nitrogen mustards.[4] The two-carbon distance between the nitrogen and bromine atoms appears crucial for the outcome of the reaction: while *N*,*N*-dibenzyl-*N*-(2-bromoethyl)amine (**6**) gave the desired formate in 97% yield after 40 h of heating, its homologue *N*,*N*-dibenzyl-*N*-(3-bromopropyl)amine (**7**) reacted much slower under the same conditions. The nitrogen base, used in the initial reaction, was not necessary, since it did not accelerate the conversion of bromide **6** to the desired product.

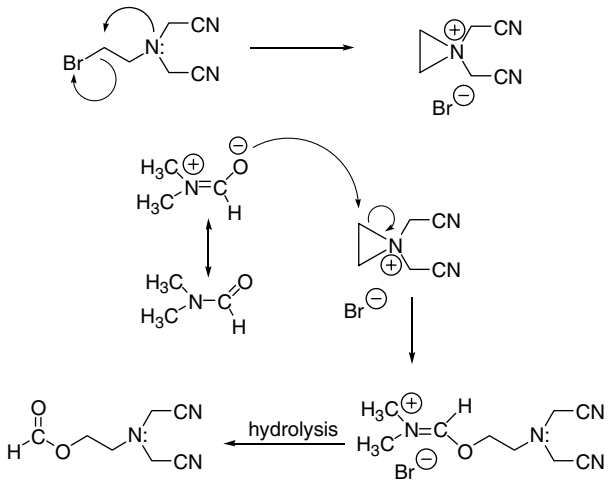
When benzyl bromide (**8**) was used as the substrate, benzyl formate was isolated in only 7% yield after 20 h. This compound was reported as a side-product in mixed carbonate preparations involving treatment of benzyl bromide with alcohols in the presence of K_2CO_3 and Bu_4NI, under a CO_2 atmosphere, using DMF as a solvent.[5] Formate esters were also formed as side-products upon the reaction of bromomethyl substituted 2-isoxazolines with $AgNO_3$ when DMF was used as a solvent.[6] 2-Bromopropanamides and acetamides also gave the corresponding formate esters as side-products in base promoted cyclocoupling reactions with DMF.[7] Besides these reports, there is no evidence that alkyl bromides are regularly converted to formyl esters via reaction with dimethyl formamide.

Although limited, these initial results indicate that the reaction proceeds via initial neighboring group participation of the nitrogen atom, most likely leading to the formation of an aziridinium intermediate (Scheme 2). Reaction of the aziridinium ion with DMF produces an alkoxymethaniminium salt (a Vilsmeier-type intermediate) which, either in the presence of traces of water or during work-up, is hydrolyzed to the corresponding formate ester. In a parallel example, *N*,*N*-bis-(2-chloroethyl)amides of aliphatic acids were reported to rearrange to the corresponding esters via an intermediate oxazolinium ion.[4]

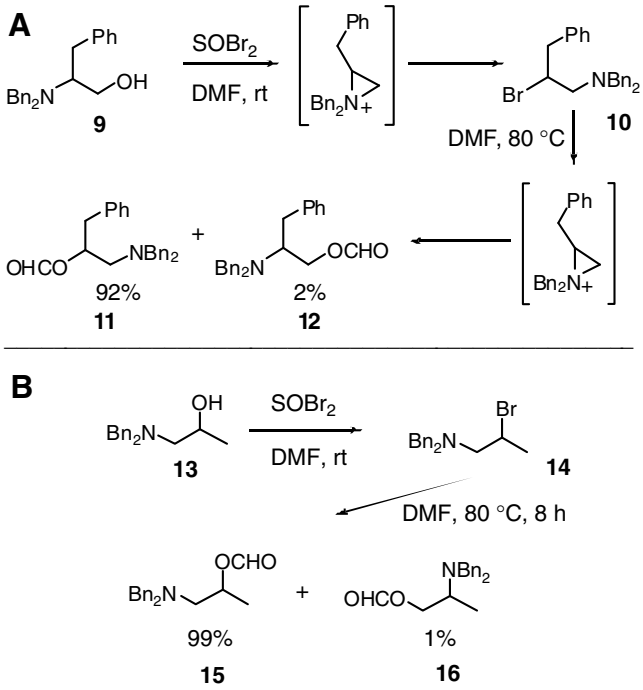
To test the validity of this hypothesis, we used substrates that contained bromoethylamino-analogs with the amino group at a secondary center. As mentioned in the literature, diprotected 2-aminoalcohols with the amino group at a secondary center lead to the exclusive formation of rearranged bromoamines with complete stereochemical inversion at the secondary centers via translocation through aziridinium salt intermediates.[8]

Following a published procedure,[8] we synthesized *N*,*N*-dibenzyl-2-bromo-3-phenyl-1-propanamine (**10**, Scheme 3A) and subjected this compound to the formylation reaction conditions. The result verified our initial hypothesis: since the reaction proceeds via a substituted aziridinium intermediate, reaction with DMF took place predominantly in the same fashion as in the bromination step, yielding the unrearranged formate **11** as the major product. The minor product **12**, identified by GC/MS as the rearranged formate, is apparently the result of the reaction of DMF with the methylene carbon of the aziridinium system.

The study was extended by the conversion of 1-dibenzylamino-2-propanol (**13**) to the corresponding secondary bromide,[8] which was in turn treated with DMF to



Scheme 2. Proposed mechanism for the conversion of 2-bromoamines into formate esters.



Scheme 3. Conversion of secondary 2-bromoamines into formate esters.

yield, as expected, the secondary as well as the primary formate esters in 99% and 1% yields, respectively. In this case, the bromide was completely converted to products within 8 h due to the reduced steric hindrance of the compound (Scheme 3B).

It should be noted that the tendency of the formation of the aziridinium system is so great that it is practically impossible to convert such substrates to the corresponding aminoethyl halides or sulfonate esters in satisfactory yields. When primary alcohol **9** was treated with tosyl chloride in the presence of 4-dimethylaminopyridine, the sole product isolated was the secondary chloride. The conversion of alcohols to the corresponding chlorides under these conditions is a known process and its mechanism has been described earlier.[9] The result may be explained by a similar mechanism involving initial conversion to the primary tosylate, the formation of the aziridinium intermediate and its subsequent attack by the chloride anion in a similar fashion to that described in Scheme 3A.

A strong indication that participation by the β-amino group may not only promote the regioselectivity but also the stereoselectivity of the reaction sprang from the following simple experiment. (*R*)-**13** was transformed to (*R*)-**15** $[\alpha]_D^{20}$ 33.0 (*c* 1.0, EtOH) via direct esterification with formic acid. The enantiomeric purity of the product was verified by ^{1}H NMR studies using Eu(hfc)$_3$. Reaction of (*R*)-**13** with CBr_4/PPh_3, yielded (*R*)-**14** $[\alpha]_D^{20}$ 12.7 (*c* 1.0, EtOH). The absolute stereochemistry of (*R*)-**14** was verified by X-ray structure analysis[10] (Fig. 1, 35% probability ellipsoids). When (*R*)-**14** was treated with DMF at room temperature the bromide was converted in 72 h to (*R*)-**15** with identical optical rotation to that of the esterification product, indicating that both reactions proceed via an aziridinium intermediate with retention of configuration (Scheme 4).

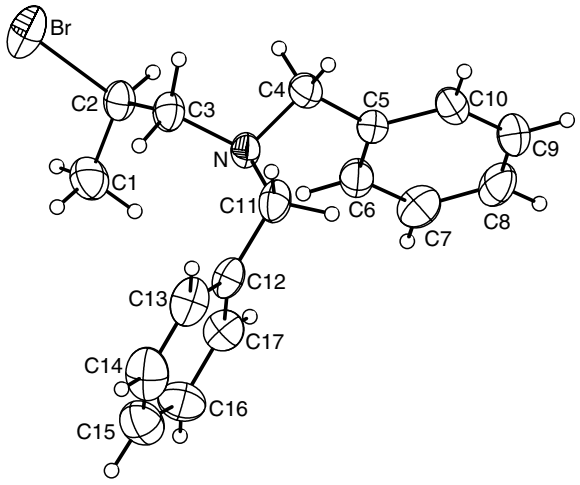
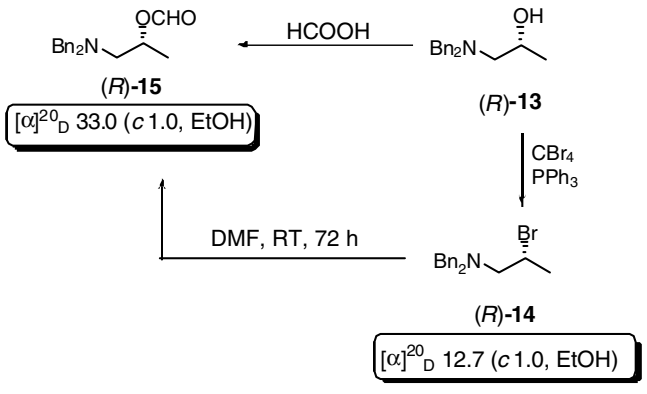


Fig. 1. X-ray structure of (*R*)-**14** (35% probability ellipsoids).

These results are in agreement with recently reported data describing aziridinium ion formation from β-aminotrifluoroacetates and subsequent attack of the liberated trifluoroacetate anion onto the more substituted carbon of the aziridinium ion with the same stereospecificity described above.[11] Similarly, *N*,*N*-dibenzyl-*O*-methylsulfonyl serine methyl ester reacted with a variety of heteronucleophiles to yield, via an aziridinium intermediate, the corresponding β-amino esters.[12]

In conclusion, we have investigated the conversion of 2-bromoethylamines to the corresponding formate esters in the presence of DMF. Both primary and secondary bromides were esterified smoothly in satisfactory yields.[13] The reaction mechanism involves the formation of an aziridinium ion which, upon reaction with DMF, forms a Vilsmeier-type intermediate that is further hydrolyzed to the corresponding formate esters. Participation of the β-amino group appears to control not only the regioselectivity but also the stereoselectivity of the reaction. The reaction presented facilitates the stereocontrolled formation of protected β-amino alcohols (vicinal amino alcohols), a



Scheme 4. Conversion of chiral 2-bromoamines into chiral formate esters.

moiety widely used in modern pharmacopoeia.[14] The use of vicinal amino alcohols in the synthesis of natural or synthetic biologically active compounds has been reviewed[15] and studies on asymmetric aminohydroxylation have revealed the importance of methodologies introducing chirality in this system.[16] Studies aimed at the exploitation of this reaction in the synthesis of amino acid derivatives are in progress in our laboratory.

Acknowledgment

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Supplementary data

A general procedure for the conversion of 2-bromoethylamines to the corresponding formate esters, ^{1}H NMR, ^{13}C NMR, and mass spectra of compounds **1**–**15**, DEPT-135 NMR spectra of compounds **11** and **15**, and ^{1}H NMR spectra of **15** in the presence of $Eu(hfc)_3$ are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.01.002.

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10. (*R*)-**14** ($C_{17}H_{20}BrN$): Stoe IPDS diffractometer, $M_m = 318.25$ g mol^{-1}, crystal size $0.35 \times 0.10 \times 0.05$ mm, monoclinic, space group $P2_1$ (No. 4), $a = 9.7188(9)$, $b = 7.2139(6)$, $c = 12.3783(11)$, $\beta = 111.624(10)°$, $V = 806.8(1) \times 10^6$ pm^3, $Z = 2$, $T = 213(2)$ K, $\rho_{ber} = 1.310$ g cm^{-3}, $\mu = 2.535$ mm^{-1}, $\lambda = 71.073$ pm (Mo-K_α), numerical absorption correction, $T_{min} = 0.582$, $T_{max} = 0.419$, 5233 measured, 2927 independent reflections, $R_{int} = 0.0285$, 2264 with $I > 2\sigma(I)$, 173 parameters, H atoms in idealized positions, R_1 (observed reflections)=0.032, wR_2 (all data) = 0.069, *Flack* parameter $x = -0.001(10)$, max./min. residual electron density peaks 0.28/-0.17 e$^-$/10^6 pm^3. Programs for structure solution and refinement: SHELXS-97 (Sheldrick, 1990) and SHELXL-97 (Sheldrick, 1997); Graphical presentation: Diamond2 (Brandenburg, 1999).
11. For a related mechanism, see: Metro, T.-X.; Appenzeller, J.; Pardo, D. G.; Cossy, J. *Org. Lett.* **2006**, *8*, 3509 and references cited therein.
12. Couturier, C.; Blanchet, J.; Schlama, T.; Zhu, J. *Org. Lett.* **2006**, *8*, 2183. In this case, the diprotected 2-aminoalcohols, with the amino group at a secondary center, lead to the exclusive formation of the corresponding rearranged β-amino esters with complete stereochemical inversion at the secondary centers.
13. Representative experimental procedure for the conversion of 2-bromoethylamines to the corresponding formate esters: The 2-bromoethylamine (1 mmol) was dissolved in 4 ml of DMF. The mixture was continuously stirred and heated at 80 °C, unless otherwise stated, under an argon atmosphere. A typical reaction was complete within 8 h as determined by thin layer chromatographic analysis. Longer reaction times up to 60 h were used as necessary until complete reaction of starting material was obtained. The reaction mixture was diluted with dichloromethane (30 ml) and washed with water (3×50 ml) and brine (1×50 ml). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. Products were purified by flash chromatography using 10% ethyl acetate in petroleum ether. The identity and the purity of the reaction products were established by their spectral (^{1}H, ^{13}C NMR, IR and MS) data. Crystallographic data (excluding structure factors) for (*R*)-**14** have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication Number CCDC 661281. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
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