Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 4947–4949

Lewis acid mediated [1,2]-rearrangement of ammonium ylides

Pavel Tuzina and Peter Somfai*

Organic Chemistry, KTH Chemical Science and Engineering, SE-100 44 Stockholm, Sweden

Received 24 March 2007; revised 15 April 2007; accepted 26 April 2007
Available online 10 May 2007

Abstract—The first example of Lewis acid mediated [1,2]-rearrangement of various glycine derivatives has been developed. A brief study of steric and electronic properties of the migrating group is presented. The corresponding amides were obtained in good yields and in the case of substrate **4d**, moderate diastereoselectivity was observed.

The [1,2] Stevens rearrangement of ammonium ylides is a useful transformation, since it serves as a tool for converting readily accessible C–N bonds into new C–C bonds, and it has been used extensively in organic synthesis.[1] However, its asymmetric versions still remain a challenge, probably reflecting the radical character of the process.[2] The rearrangement proceeds via a homolytic cleavage of the carbon–nitrogen bond, generating a radical pair, which is held tightly together by a solvent cage. This is then followed by rapid recombination of the radicals thus providing the product of the [1,2]-rearrangement.[1] It has been shown, however, that for cyclic ammonium ylides, having a stereogenic nitrogen nucleus, high levels of stereoselectivity can be obtained.[3,4]

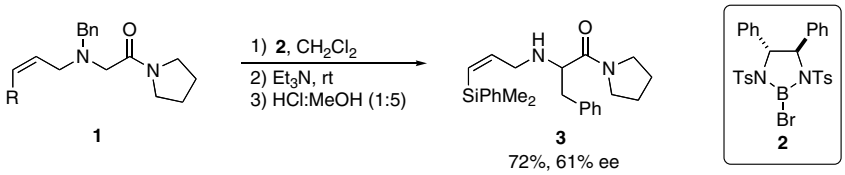
We have recently demonstrated that activation of *N*-allyl-*N*-Bn amines derived from glycine with BBr_3, followed by deprotonation of the complex formed in situ, results in the formation of the corresponding homoallylic amines, the products of [2,3]-sigmatropic rearrangement.[5] It was also shown that, when using a chiral boron Lewis acid, this is easily transformed into an asymmetric process.[6] It is known that the [2,3]-rearrangement can be accompanied by formation of the products derived from a [1,2]-rearrangement, and this can be particularly pronounced when elevated reaction temperatures are used or in cases where unfavorable steric interactions prevent the desired reaction pathway.[7,8] In line with this, it was observed that the asymmetric [2,3]-rearrangement of **1** (R = H), using chiral Lewis acid **2**, which is sterically more demanding than BBr_3, increased amounts of the products derived from a [1,2]-shift were sometimes obtained (Scheme 1). Indeed, attempts at the [2,3]-rearrangement of allylic amine **1** (R = $SiMe_2Ph$), having a bulky vinyl substituent, gave only **3** in good yield and moderate enantioselectivity, the product of a [1,2]-shift.[6,9] These observations warranted a more thorough study of the Lewis acid mediated [1,2]-rearrangements of various glycine derivatives and also an investigation of the possibilities of developing an asymmetric process. Herein, we report our preliminary findings.

In order to favor the [1,2]-shift over the [2,3] reaction manifold, model substrate **4a**, in which only the benzyl group is capable of N→C migration, was employed (Scheme 2).[10] Based on the previous results,[5] it was envisioned that mixing **4a** with BBr_3 would result in the formation of oxazaborolidine **5**. Subsequent deprotonation would then yield ylide **6**, which could participate in a [1,2]-rearrangement, ultimately yielding secondary amine **7a** (Scheme 2).

Initial attempts were directed toward developing optimal reaction conditions that would effect the rearrangement of compound **4a**. In the first attempt, BBr_3 and the non-ionic base Et_3N were employed, since such conditions were successfully used in our previous investigation. Thus, when subjecting amine **4a** to BBr_3 (1.2 equiv) and Et_3N (5 equiv),[5,11] secondary amine **7a** was obtained in low yield together with starting material (Table 1, entry 1). Increasing the amount of BBr_3 (2 equiv) resulted in a somewhat higher yield but a long reaction time was still required, indicating that the homolysis of the carbon–nitrogen is slow under these

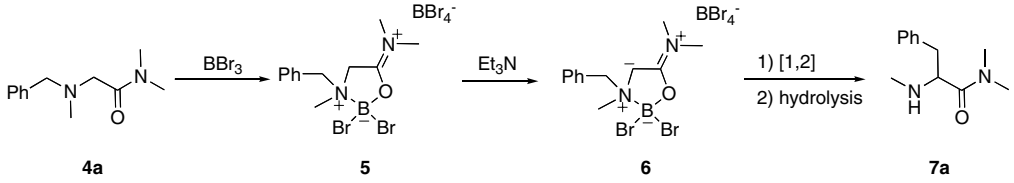
Keywords: [1,2]-Rearrangement; Ammonium ylide; Lewis acid; Microwave irradiation; Amide.
* Corresponding author. Tel.: +46 8 790 6960; fax: +46 8 791 2333; e-mail: somfai@kth.se

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.04.151



1 3 72%, 61% ee 2

Scheme 1. [1,2]-Rearrangement of allylic amine **1**.



4a **5** **6** **7a**

Scheme 2. The Lewis acid mediated [1,2]-rearrangement of **4a**.

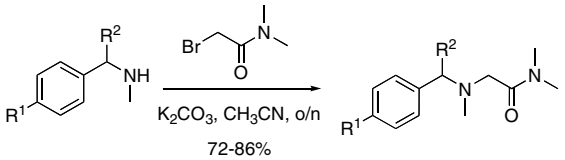
Table 1. Optimization of the reaction conditions for [1,2]-rearrangement of **4a**[a]

Entry	Lewis acid	Equiv	Temp (°C)	Reaction time (h)	Yield[b] **7a** (%)
1	BBr_3	1.2	rt	48	39 (30)
2	BBr_3	2	rt	24	48 (32)
3	BBr_3	2	60[c]	1	52 (0)
4	$BF_3{\cdot}Et_2O$	2	60[c]	1	n.r.[d] (96)
5	BBr_3	1.2	60[c]	1	60 (12)

[a] Reaction conditions: To **4a** (1.0 equiv) in CH_2Cl_2 at 0 °C was added BBr_3 (1.2 equiv) and Et_3N (5 equiv) and the mixture was stirred at the indicated temperature for the time given, see Ref. 13.
[b] Isolated yield. Yield of recovered starting material in parenthesis.
[c] Microwave-assisted heating.
[d] n.r. = no reaction.

reaction conditions (entry 2). The reaction time could be decreased by heating the reaction mixture to 60 °C for 1 h in a microwave reactor, providing **7a** in 52% yield (entry 3). Interestingly, even though only a moderate yield was achieved, no starting material could be recovered, suggesting that either **7a** (in case of full conversion) or starting material **4a** decomposed during the reaction. Attempts to promote the [1,2]-shift by using the weaker Lewis acid $BF_3{\cdot}Et_2O$ resulted in no rearrangement and only starting material was recovered (entry 4). This is surprising since we have previously shown that $BF_3{\cdot}Et_2O$ promotes the formation of oxazaborolidines corresponding to **5**, and the reasons why the subsequent C–N bond homolysis is unfavored are not clear.[11] Finally, using BBr_3 (1.2 equiv) together with Et_3N (5 equiv) and heating to 60 °C in a microwave reactor for 1 h proved to be superior and gave **7a** in 60% yield together with recovered starting material (12%, entry 5). It should be noted that the yield obtained is in accordance with the proposed reaction pathway (Scheme 2). When using 1.2 equiv of BBr_3 a maximum of 60% of **4a** can be converted into oxazaborolidine **5**, the formation of which is a prerequisite for the subsequent [1,2]-shift. Somewhat surprisingly, using larger amounts of BBr_3 (2 equiv), in an attempt to promote a complete conversion of **4a** into **5**, resulted in only a low yield of product **7a**.

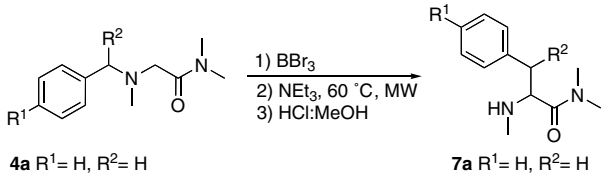
With the optimized reaction conditions in hand, the influence of varying the steric and electronic properties of the migrating group was briefly studied. Substrates **4b–d** were selected and their preparation is summarized in Scheme 3.[9,12]



4a R^1= H, R^2= H
b R^1= *t*-Bu, R^2= H
c R^1= F, R^2= H
d R^1= H, R^2= Me

Scheme 3. Synthesis of rearrangement precursors **4a–d**.

Rearrangement of glycine derivatives **4b–d** provided the corresponding products **7b–d** in moderate yields (Scheme 4, Table 2); steric and electronic effects do not appear to have any dramatic impact on the reaction outcome.[13,14] It is also noted that for substrate **4d**, which has an α-methylbenzyl moiety, product **7d** was obtained as a 2:1 mixture of diastereomers.



4a R^1= H, R^2= H
b R^1= *t*-Bu, R^2= H
c R^1= F, R^2= H
d R^1= H, R^2= Me

7a R^1= H, R^2= H
b R^1= *t*-Bu, R^2= H
c R^1= F, R^2= H
d R^1= H, R^2= Me

Scheme 4. Lewis acid mediated [1,2]-rearrangement of **4a–d**.

Table 2. Lewis acid mediated [1,2]-rearrangement of amines **4**[a]

Entry	Substrate	Product	Yield[b] (%)
1	**4a**	**7a**	60
2	**4b**	**7b**	46
3	**4c**	**7c**	51
4	**4d**	**7d**	60[c]

[a] For reaction conditions, see Ref. 13.
[b] Isolated yield.
[c] Isolated as 2:1 mixture of diastereomers.

In conclusion, we have presented the first example of a Lewis acid mediated [1,2]-rearrangement of various glycine derivatives. The effect when changing the steric and electronic properties of the migrating group was briefly studied and these parameters do not seem to have any appreciable effect on the reaction outcome. Development of an asymmetric version of the Lewis acid mediated [1,2]-rearrangement is currently underway in our laboratory.

Acknowledgments

This work was supported financially by the Swedish Research Council and the Knut and Alice Wallenberg foundation.

References and notes

1. For reviews see: (a) Vanecko, J. A.; Wan, H.; West, F. G. *Tetrahedron* **2006**, *62*, 1043–1062; (b) Pine, S. H. *Org. React. (NY)* **1970**, *18*, 403–464; (c) Lepley, A. R.; Giumanini, A. G. In *Mechanisms of Molecular Migrations*; Thygarajan, B. S., Ed.; Interscience: New York, 1971; Vol. 3, pp 297–440; (d) Markó, I. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, pp 913–973.
2. Ollis, W. D.; Rey, M.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1009–1027.
3. Glaeske, K. W.; West, F. G. *Org. Lett.* **1999**, *1*, 31–33.
4. Tayama, E.; Nanbara, S.; Nakai, T. *Chem. Lett.* **2006**, *35*, 478–479.
5. Blid, J.; Brandt, P.; Somfai, P. *J. Org. Chem.* **2004**, *69*, 3043–3049.
6. Blid, J.; Panknin, O.; Somfai, P. *J. Am. Chem. Soc.* **2005**, *127*, 9352–9353.
7. Jemison, R. W.; Laird, T.; Ollis, W. D.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1436–1449.
8. Jemison, R. W.; Laird, T.; Ollis, W. D.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1450–1457.
9. Blid, J.; Panknin, O.; Tuzina, P.; Somfai, P. *J. Org. Chem.* **2007**, *72*, 1294–1300.
10. Formation of the most stable potential carbon-centered radical is favored.
11. Blid, J.; Somfai, P. *Tetrahedron Lett.* **2003**, *44*, 3159–3162.
12. *N*-Methyl-*p*-*t*-butylbenzylamine was prepared according to the procedure by Pigge, F. C.; Coniglio, J. J.; Fang, S. *Organometallics* **2002**, *21*, 4505–4512.
13. *Typical procedure*: To **4b** (113.8 mg, 0.434 mmol) in dry CH_2Cl_2 (2 mL) at 0 °C was added BBr_3 (442 μL, 0.520 mmol, 1.178 M solution in CH_2Cl_2). The resultant mixture was stirred for 1.5 h (0 °C→rt) and then Et_3N (302 μL, 2.165 mmol) was added and the mixture was heated to 60 °C in a microwave reactor for 1 h. After cooling to rt, MeOH–HCl (2 mL, 5:1) was added and the resultant mixture was stirred overnight. The mixture was then basified by addition of 2 M NaOH (2 mL) and aq $NaHCO_3$ (2 mL). The mixture was then extracted with CH_2Cl_2 (3 × 10 mL), the organic phases dried (K_2CO_3), and the resultant crude material purified by chromatography (SiO_2, 40:1 CH_2Cl_2–MeOH with 0.5% of *i*-$PrNH_2$) to provide **7b** (52.3 mg, 46%). ^1H NMR ($CDCl_3$, 500 MHz): δ_H 7.29 (d, 2H, $J = 8.2$ Hz), 7.12 (d, 2H, $J = 8.1$ Hz), 3.65 (dd, 1H, $J = 6.0$, 8.5 Hz), 2.91 (dd, 1H, $J = 5.9$, 13.3 Hz), 2.90 (s, 3H), 2.77 (dd, 1H, $J = 8.6$, 13.2 Hz), 2.54 (s, 3H), 2.31 (s, 3H), 1.93 (s, 1H), 1.31 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C 174.2, 149.4, 134.7, 128.7, 125.0, 61.2, 39.8, 36.3, 35.4, 34.6, 31.3.
14. All new compounds showed spectroscopic data (^1H, ^{13}C, NMR, IR, HRMS) in accordance with their structure.