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Tetrahedron Letters 47 (2006) 2209–2211
Tetrahedron Letters

Reductive ring opening of 2-azetidinones promoted by sodium borohydride

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Received 11 January 2006; revised 19 January 2006; accepted 19 January 2006
Available online 13 February 2006

Abstract—Variously substituted 2-azetidinones **3** and **4** were reacted with sodium borohydride in aqueous isopropanol giving 3-aminopropan-1,2-dioles **5** and **7**. Reaction extent was dependent upon the substitution pattern in the 3- and 4-positions of the 2-azetidinone ring and revealed good correlation with carbonyl LUMO energies of starting **3**.

The 2-azetidinone (β-lactam) ring represent the key structural feature of the main class of antibacterial agents, namely the β-lactam antibiotics.[1] In the light of their relevance both in industrial and academic fields, several strategies devoted to the synthesis of new β-lactams have been developed,[2] giving rise to a lot of compounds featuring enhanced antibacterial activity[3] or better resistance towards β-lactamases.[4] Within this developing picture, new evidences on the chemical behaviour of the 2-azetidinone ring should be highly valuable. In this field, the reductive ring opening of β-lactams giving β-amino alcohols have been exploited in the presence of several hydrides, namely monochloroalane[5] or lithium aluminium hydride.[6] At a first glance, sodium borohydride seems not a suitable reagent for this transformation, since only one literature example is available describing the ring fission of compound **1**[7] (Fig. 1), which is strongly activated towards nucleophilic attack by the presence of the *N*-benzyloxycarbamate moiety. When tricarbonyl(η^6-arene) chromium(0) complex in the 4-position of the azetidinone ring acts as the activating group, although an acyclic (ring-fission

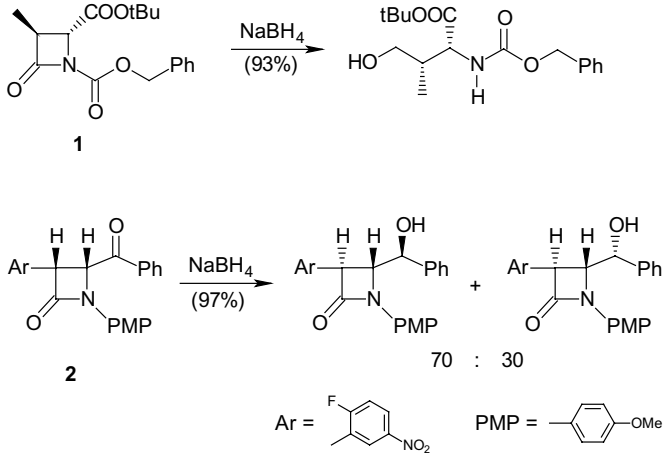

Figure 1.

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doi:10.1016/j.tetlet.2006.01.103

derived) product was not isolated, its occurrence was recently postulated by us in the sodium borohydride promoted conversion 2-azetidinones → dihydrobenzopyranes.[8] Less activated substrates are prone to side-chain transformations, which leaves the 2-azetidinone ring unchanged,[9] as is shown in Figure 1 for the stereoselective carbonyl reduction of compound **2**.[10]

The aim of this letter is to show that sodium borohydride can behave as an effective reagent in the reductive ring opening of β-lactams, and to illustrate which structural features of the starting four-membered heterocycle allows the above transformation.

(3*S**,4*S**)-2-Azetidinones **3** and **4** were synthesized through standard [2+2] (Staudinger) cycloaddition as is depicted in Scheme 1. Subsequent treatment of the latter products with sodium borohydride[11] gave 2-phenoxy-3-aryl-3-aminopropan-1-ols **5**[12] or 2-hydroxy-3-aryl-3-aminopropan-1-ols **7**[13] according to the substitution pattern in the 3-position of the 2-azetidinone ring. Products and product yields are reported in Table 1. Mixtures of the starting β-lactam and the open-chain product **5** were obtained from 3-phenoxy-2-azetidinones **3** (Table 1, entries 1–4). It can be added that the ratio **5**:**3** increases according to the electron withdrawal character of R^1. The behaviour of 3-acetoxy-2-azetidinones **4** was different since (i) sodium borohydride first hydrolizes **4** to 3-hydroxy-2-azetinones **6**, and (ii) open-chain products **7** were obtained with very good yields independently from the electronic features of R^1 (Table 1, entries 5–8). The rationale to these findings are apparent from the carbonyl LUMO energies of both **3** and **4** calculated with the AM1[14] method (Table 2).[15] Decreasing of the LUMO energies in the series **3a**→**3d** justifies the better reactivity of electron-poor substrates towards hydride, while the much lower LUMO energies of **4** accounts for their better reactivity and the lack of sensitivity towards R^1.

Table 1. Reaction of 2-azetidinones **3** and **4** with $NaBH_4$ in aq isopropanol[a]

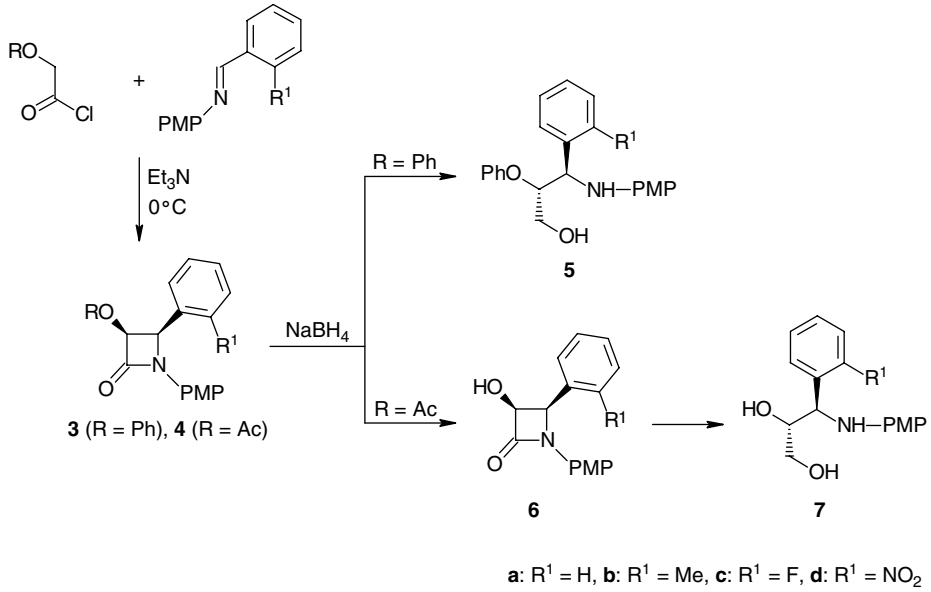
Entry	R^1	Products and yields (%)[b]			
		3	**5**	**6**	**7**
1	H	85	15	—	—
2	Me	68	32	—	—
3	F	29	71	—	—
4	NO_2	13	87	—	—
5	H	—	—	26	74
6	Me	—	—	8	92
7	F	—	—	5	95
8	NO_2	—	—	5	95

[a] 5 mol equiv of $NaBH_4$.
[b] As determined from ^1H NMR analyses of reaction crudes.

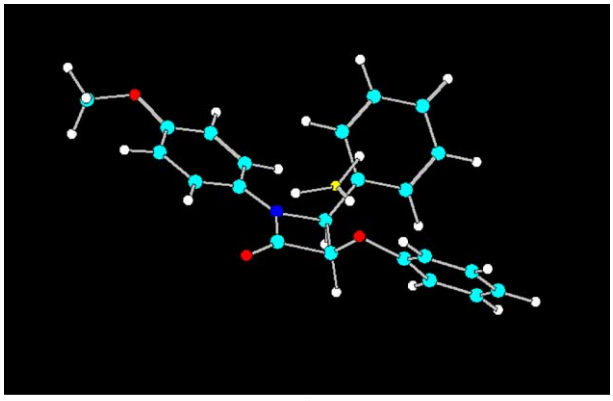
Table 2. AM1 computed carbonyl LUMO energies of 2-azetidinones **3** and **6**

R^1	**3** *E* (eV)	**6** *E* (eV)
H	+0.346	−3.422
Me	+0.336	−3.408
F	+0.321	−3.448
NO_2	+0.263	−3.647

The facile reductive ring opening of 2-azetidinones **3** and **4** points to some kind of complexation between the substrate and the borohydride reagent. To this point, we perceived model **A** (Fig. 2) as a reasonable reaction intermediate. Structure optimization of **A** at the AM1[14] level showed two main interactions: (i) between boron and the oxygen in the 3-position of the 2-azetidinone ring (distance B–O = 1.85 Å), and (ii) between a hydride and the LUMO of the aromatic ring in the 4-position (distance H–Ar = 2.59 Å). This latter π-H interaction, which finds precedents in the literature,[16] allows one hydride to be close enough to the



Scheme 1.



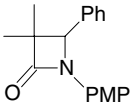
A

Figure 2.

2-azetidinone carbonyl (distance H–C = 2.14 Å) to promote reaction.

On the basis of the above findings, it is apparent that β-lactams can undergo reductive ring opening in the presence of sodium borohydride provided that two structural features are met. First, a donor heteroatom in the 3-position of the 2-azetidinone ring should be present in order to allow complexation with boron. Second, an aromatic ring in the 4-position and cis with respect to the donor heteroatom is required to ensure the π-H interaction, which provides the arrangement of intermediate **A**.

To test the latter rules, 2-azetidinones **8**, **9** and **10** were synthesized and then submitted to treatment with sodium borohydride. Unchanged starting products were isolated according to our expectations.



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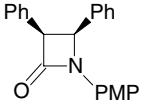

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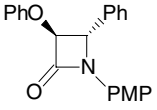

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Acknowledgements

Thanks are due to MURST (COFIN) for financial support.

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11. For a typical run: A suspension of **3** or **4** (0.87 mmol) in isopropanol (11 mL) was treated with sodium borohydride (0.16 g, 4.3 mmol) in water (2 mL) and then stirred under nitrogen for 20 h. The crude was partly evaporated under reduced pressure and taken up with dichloromethane (40 mL). The organic layer was washed with water to neutrality, dried over sodium sulfate and evaporated. The residue was chromatographed on silica gel column giving open-chain products **5** or **7**.
12. Selected ^{1}H NMR data of compounds **5** in $CDCl_3$ solutions. Compound **5a**: δ 3.75 (3H, s), 3.80 (1H, dd, *J* 11.8, 4.2), 3.95 (1H, dd, *J* 11.8, 4.8), 4.5–4.6 (1H, m), 4.75 (1H, d, *J* 4.9), 6.6–7.5 (14H, m). Compound **5b**: δ 2.53 (3H, s), 3.70 (3H, s), 3.80 (1H, dd, *J* 11.6, 4.4), 3.95 (1H, dd, *J* 11.6, 5.4), 4.4–4.5 (1H, m), 4.96 (1H, d, *J* 4.0), 6.5–7.4 (13H, m). Compound **5c**: δ 3.75 (3H, s), 3.80 (1H, dd, *J* 11.6, 4.2), 3.95 (1H, dd, *J* 11.6, 5.2), 4.5–4.6 (1H, m), 4.97 (1H, d, *J* 4.3), 6.6–7.5 (13H, m). Compound **5d**: δ 3.70 (3H, s), 4.0–4.1 (1H, m), 4.8–4.9 (1H, m), 5.5–5.6 (1H, m), 4.97 (1H, d, *J* 4.3), 6.5–7.9 (13H, m).
13. Selected ^{1}H NMR data of compounds **7** in $CDCl_3$ solutions. Compound **7a**: 3.60 (1H, dd, *J* 10.7, 6.0), 3.70 (3H, s), 3.75 (1H, dd, *J* 10.7, 3.7), 3.9–4.0 (1H, m), 4.42 (1H, d, *J* 6.5), 6.5–7.3 (9H, m). Compound **7b**: 2.42 (3H, s), 3.60 (1H, dd, *J* 11.4, 6.0), 3.70 (3H, s), 3.75 (1H, dd, *J* 11.4, 3.7), 3.9–4.0 (1H, m), 4.70 (1H, d, *J* 6.0), 6.5–7.4 (8H, m). Compound **7c**: 3.60 (1H, dd, *J* 10.7, 5.2), 3.70 (3H, s), 3.8–4.0 (2H, m), 4.70 (1H, d, *J* 6.6), 6.7–7.3 (8H, m). Compound **7d**: δ 3.70 (3H, s), 3.8–4.1 (3H, m), 5.35 (1H, d, *J* 5.8), 6.5–7.9 (8H, m).
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