Reduction of 2-chloro-*N*-phenylpropanamide and 2-methyl-*N*-phenylaziridine with lithium aluminium hydride†

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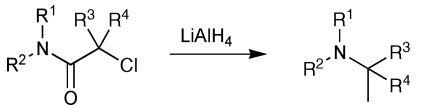
The reduction of 2-chloro-*N*-phenylpropanamide with $LiAlH_4$ has been re-examined. In contrast to previous findings, we obtain in almost equal quantities two amines from this reaction, namely *N*-propylaniline and the rearranged product *N*-isopropylaniline. 2-Methyl-*N*-phenylaziridine is an intermediate in the reduction and can be isolated from reactions with less $LiAlH_4$. Reduction of 2-methyl-*N*-phenylaziridine itself proceeds non-regioselectively to provide a mixture of propyl- and isopropylanilines. Formation of the amines by reduction of the aziridine is much slower than formation by reduction of the 2-chloropropanamide, which indicates that Lewis acid catalysis (by aluminium chlorohydrides) facilitates the reduction of the aziridine. In addition, Lewis acid catalysis increases the relative yield of the propylamine product. The reduction of 2-chloro-*N*-phenylpropanamide furnishes 2-phenylamino-1-propanol as a by-product, rather than the previously proposed 1-phenylamino-2-propanol.

Introduction

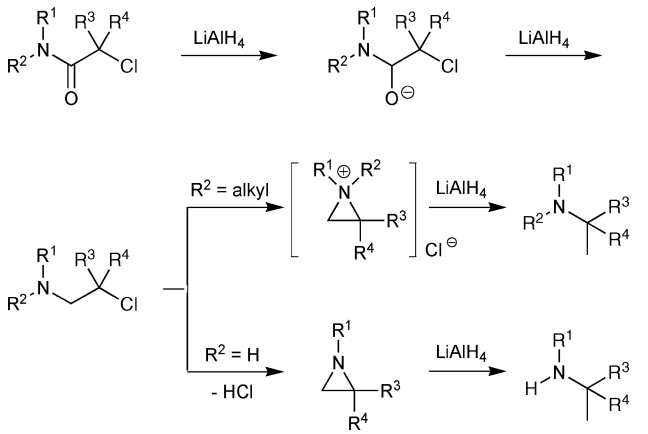
Reduction of amides with lithium aluminium hydride ($LiAlH_4$) is a textbook reaction that yields the corresponding amine by reduction of the C=O group to CH_2; it was reported for the first time in 1948 by Uffer and Schlittler.[1] This reaction is normally straightforward for tertiary amides, but can be sluggish for secondary and in particular primary amides.

Suzuki and co-workers[2] reported that the reduction of 2-chloroalkanamides proceeds *via* rearrangement to provide α-methyl aliphatic amines (Scheme 1). A mechanism was suggested (Scheme 2) that involves initial formation of a 2-chloroamine, which subsequently undergoes intramolecular nucleophilic substitution to give an aziridine or aziridinium intermediate. Finally, reductive ring opening furnishes the α-methyl amine product. Reduction of 2-chloro-*N*-phenylpropanamide provided *N*-isopropylaniline in an isolated yield of 36%. No mention was made of the possible formation also of *N*-propylaniline, the expected product in the absence of rearrangement; the two amines would be difficult to separate.



Scheme 1 Reduction of 2-chloropropanamides with $LiAlH_4$ according to Suzuki.[2]

Despite the modest yield, the ring opening mechanism is intriguing in view of the many reports that aziridines are formed by $LiAlH_4$ reduction of suitable precursors. Subsequent ring opening caused by the reducing agent does not seem to take place. For example, reduction of β-iodo azides provides a means of obtaining aziridines, as reported by Hassner *et al.*[3] Reduction of the primary iodide 2-azido-1-iodohexane gave, in addition to 2-butylaziridine, also 2-aminohexane. The two products were formed in a ratio of 1 : 1, and the amine was assumed to result from direct hydrogenolysis of the carbon–iodine bond. Along the same line, De Kimpe *et al.*[4] obtained an aziridine together with two isomeric secondary amines (derived from aniline) as by-products in the reduction of *N*-aryl α,α-dichloroalkyl aryl ketimines. The ring opening of chloroaziridine intermediates with $LiAlH_4$ was studied by De Kimpe,[5] who proposed that the reaction proceeds *via* an aziridinium intermediate that isomerized into an α-imino carbenium ion intermediate. Nevertheless, direct non-regioselective ring opening of aziridines was in fact proposed by De Kimpe[6] in an early paper, in which the reduction of *N*-2-(1,1-dichloroalkylidene)anilines was investigated. In this study, reaction *via* reductive ring opening was supported by the isolation of an aziridine in some cases, but otherwise no evidence for



Scheme 2 Proposed mechanism for the reductive rearrangement according to Suzuki.[2]

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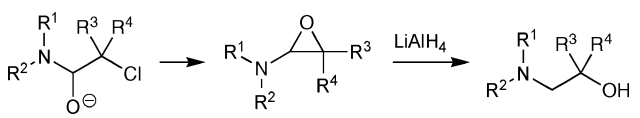
this mechanism was reported. However, the possibility that amines were in general formed by reductive opening of aziridines was discarded in several studies, as aziridines were recovered unchanged after refluxing in diethyl ether with $LiAlH_4$.[4,7] While reduction of 2-chloronitriles was shown to afford only aziridines,[8,9] primary amines were the major products obtained from the corresponding 2-bromonitriles.[9] However, reductive ring opening was rejected as the route to the amines, because reduction of 2-sulfonyloxynitriles gave the aziridines exclusively.[9] Aziridines have also been obtained by reduction of 2-azido-1-tosylates,[10] oximes,[11] as well as 2-isoxazolines,[12] with $LiAlH_4$. None of these reports[10–12] suggest subsequent reductive ring opening of the aziridine; in fact, $LiAlH_4$ has been used to reduce functional groups in compounds incorporating an aziridine unit, but leaving it intact.[13] However, activated aziridines are known to undergo reductive ring opening with a variety of hydride donors,[14] whereas the reaction appears not to have been reported for non-activated aziridines.

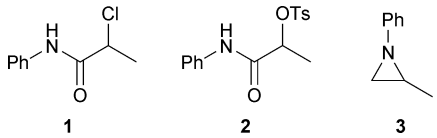
With these possibly contradicting results in mind, we decided to investigate the reduction of 2-chloroalkanamides in further detail, with a view also to examine whether amines can be obtained by direct reduction of simple aziridines using $LiAlH_4$ as reducing agent. The scarcity of studies of the $LiAlH_4$ reduction of aziridines is particularly striking in view of the large body of results available with regard to their oxygen counterparts, the oxiranes. Reduction of oxiranes with $LiAlH_4$ provides the corresponding alcohols by ring opening.[15] This reaction is an S_N2 process, and cleavage usually occurs so as to give the more highly substituted alcohol. With regard to aziridines, the outcome of reduction by $LiAlH_4$ can be deduced indirectly from the experiments of Suzuki[2] or from those of De Kimpe,[6] in which aziridines were assumed to be intermediates. We note that reductive ring opening of aziridines with lithium has been reported,[16] as has Pd-catalyzed reductive ring opening by hydrogenolysis or by reaction with formic acid;[17] samarium(II) iodide has been employed as well to effect reductive ring opening.[18] In general, however, the chemistry of aziridines[19] has not been as widely exploited as that of oxiranes, but aziridines have in recent years attracted an increasing interest owing to their biological activity.[20]

Suzuki[2] reports that 2-hydroxyalkylamines are formed as by-products in the reduction of 2-chloroalkanamides. The formation of these was taken to be the result of an intramolecular substitution in the tetrahedral oxyanion intermediate followed by reduction of the resulting oxirane with $LiAlH_4$ (Scheme 3). However, we find that the aminoalcohol formed as a significant by-product is a different isomer than that suggested.[2] Moreover, while our results confirm the intermediacy of an aziridine in the reduction of 2-chloroalkanamides, they do not support that the rearranged amine is formed selectively as reported by Suzuki.[2] The formation of 2-aminoalcohol by-products during aziridine synthesis, under similar conditions, was also observed by De Kimpe and co-workers.[7,21]



Scheme 3 Proposed mechanism to explain formation of aminoalcohol by-products according to Suzuki.[2]

We have chosen *N*-phenyl-2-chloropropanamide **1** as the key compound for our investigations. The outcome of the reduction of **1** under a variety of conditions is then compared to that obtained for reduction of 2-methyl-*N*-phenylaziridine **3**. We have also investigated the corresponding tosylate **2**, inspired by the previous reductions[9,10] of related azides and nitriles containing a sulfonyloxy group.

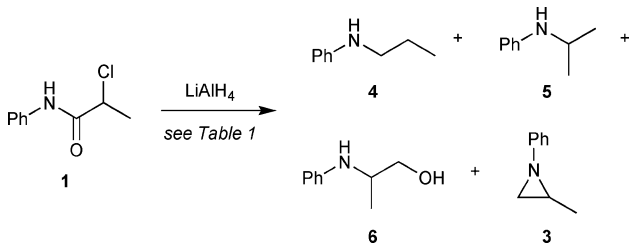


1 **2** **3**

Results and discussion

i. Reduction of 2-chloro-*N*-phenylpropanamide (1)

First, the reduction was performed with three molar equivalents of $LiAlH_4$ in Et_2O (suspension) under conditions similar to those employed by Suzuki[2] (refluxing for 20 h). According to gas chromatography–mass spectrometry (GC–MS), three major products were obtained, *N*-propylaniline **4**, *N*-isopropylaniline **5**, and 2-phenylamino-1-propanol **6** (Scheme 4) in the relative amounts indicated in entry 1, Table 1. In addition, we observed traces of 2-(phenylamino)propanal and two other unidentified by-products. The expected[2] aminoalcohol by-product, 1-phenylamino-2-propanol **7**, was not observed. Changing to THF as solvent (entry 2) had only little influence on the product distribution. In order to examine the influence of the exact amount of reducing agent actually in solution, we instead added the amide to a 1.0 M solution of $LiAlH_4$ (from Aldrich) (entries 3, 4), this having only little influence on the product distribution. However, the aziridine **3** was among the products isolated when the molar ratio of $LiAlH_4$ to amide was reduced to 1 : 1 (entry 5). This result implies that **3** is an intermediate in the reaction leading to the two propylanilines. Corroborating evidence is obtained from the outcome of reduction with $LiAlD_4$, which yields the two amines $PhNH\text{-}CD_2\text{-}CDH\text{-}CH_3$ and $PhNH\text{-}CH(CH_3)\text{-}CD_3$ (identified from the MS and ^{1}H-NMR spectra).



1 **4** **5** **6** **3**

Scheme 4 Reduction of 2-chloro-*N*-phenylpropanamide with $LiAlH_4$.

The GC trace of the reaction mixture from entry 3 (after work-up as described in the Experimental) is shown in Fig. 1 together with the most important fragmentation reaction of the ionic products as observed in the mass spectra. The identity of the products was also confirmed by ^{1}H-NMR spectroscopy. Our results are different from those previously reported[2] on two counts. First, we find that propylaniline is formed alongside isopropylaniline in almost the same amount. Suzuki *et al.*[2] do not elaborate on the by-products and possibly both amines

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Table 1 Products from reduction of 2-chloro-*N*-phenylpropanamide (**1**)[a]

Entry	Solvent	$LiAlH_4$	Time	Product distribution (%)[b] 4	5	6	3
1	Et_2O	3 equiv.[c]	20 h	46.5	32.5	21	0
2	THF	3 equiv.[d]	18 h	40	39	21	0
3	THF	3 equiv.[e]	22 h	44	37	19	0
4	THF	2 equiv.[e]	22 h	41	45	14	0
5	THF	1 equiv.[e]	20 h	28	19	34	19

[a] *Reagents and conditions*: reflux in the solvent indicated for the time shown, using $LiAlH_4$. [b] Percentages according to GC–MS. The given products correspond in all entries to *ca.* 95% of the total outcome of the reaction, the remaining by-products being unidentified. [c] Addition of solid $LiAlH_4$ to the amide in Et_2O. [d] Addition of amide in THF to a suspension of $LiAlH_4$ in THF. [e] Addition of amide in THF to a solution of $LiAlH_4$ (1 M) in THF.

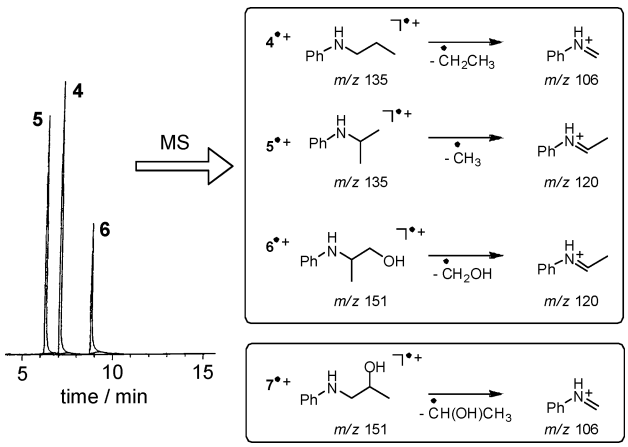


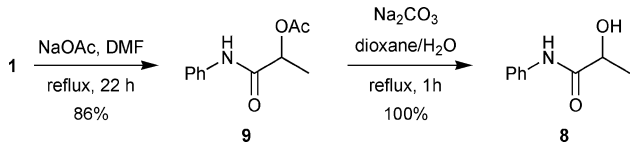
Fig. 1 Gas chromatograph (GC) trace obtained from entry 3, Table 1, and assignment of peaks to products according to fragment ions (base peaks) observed in the mass spectra.

are formed in their experiments as well. They describe the isolation of the pure product; however, we did not succeed in separating the two anilines. Moreover, 2-phenylamino-1-propanol **6** was obtained in significant amount, rather than the isomeric aminoalcohol 1-phenylamino-2-propanol **7**. We synthesized the isomeric aminoalcohol **7** according to a literature procedure.[22] The mass spectra of these two aminoalcohols differ significantly and allow for an unambiguous assignment (Fig. 1).

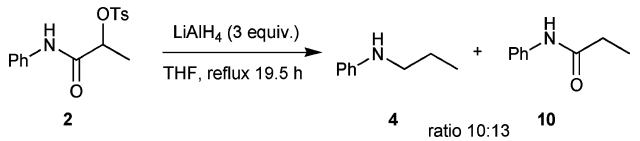
The aziridine is possibly a precursor for the 2-phenylamino-1-propanol product **6** by reaction between the aziridine and OH^- during alkaline hydrolysis of the reaction mixture. However, methanolysis (with KOH dissolved in MeOH) did not produce the corresponding methyl ether, which would arise after nucleophilic attack by MeO^-. We therefore take the alcohol to be formed during the reduction of **1** in a competing reaction.

ii. Reduction of 1-(phenylcarbamoyl)ethyl tosylate (2)

The tosylate **2** was prepared by tosylation of 2-hydroxy-*N*-phenylpropanamide **8** according to Shahak and Bergmann.[23] The alcohol **8** was prepared in two steps according to Scheme 5. The chloride **1** was converted to the ester **9**, which was then hydrolyzed under mild conditions to afford **8**.[24]



Scheme 5 Synthesis of 2-hydroxy-*N*-phenylpropanamide.

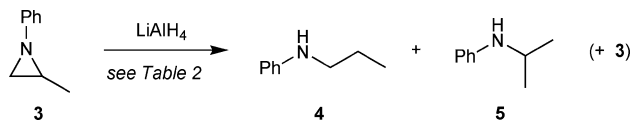


Scheme 6 Reduction of tosylate with $LiAlH_4$.

Reduction of **2** in THF with 3 molar equivalents of $LiAlH_4$ (using a 1.0 M solution) gave the propylamine **4** and the amide **10** in a ratio of 10 : 13 (GC–MS) (Scheme 6). The absence of any isopropylamine product as well as any aziridine product indicates that the tosylate is reduced before the amide. It is well-known that tosylates are reduced faster than chlorides.[25]

iii. Reduction of 2-methyl-*N*-phenylaziridine (3)

Reduction of the known aziridine **3**[26,27] in THF with 3.5 molar equivalents of $LiAlH_4$ (using a 1.0 M solution) (Scheme 7) yielded the two amines **4** and **5** in a ratio of *ca.* 1 : 2, together with unreacted aziridine (Table 2, entry 1). The outcome of this experiment illustrates that the reduction of aziridines by $LiAlH_4$ is a slow reaction; 43% of the aziridine is unchanged after refluxing for 20 h. Moreover, the reaction is apparently not regioselective, in contrast to the case for oxiranes.



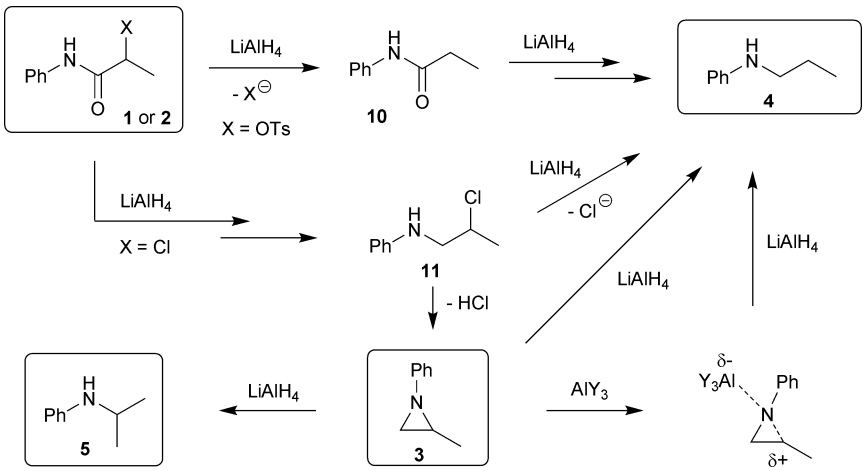
Scheme 7 Reduction of 2-methyl-*N*-phenylaziridine.

Considering that reduction of 2-chloropropanamide in all likelihood involves an aziridine intermediate (*vide supra*) and that it is complete under the same reaction conditions, it would appear that a catalyst for the aziridine ring opening is generated *in situ* in the amide reduction. Chloride ions are released as the aziridine is formed, which opens the possibility that mixed aluminium chlorohydrides are formed during the reaction and that these act as Lewis acid catalysts. It is well-known that the reductive power of mixed aluminium halohydrides is considerably lower than that of aluminium hydride and that aluminium halides are stronger Lewis acids than aluminium hydrides.[28,29] In order to investigate

Table 2 Products from reduction of 2-methyl-1-phenylaziridine (**3**) with and without $AlCl_3$[a]

Entry	Additive	Product distribution (%)[b] 4	5	3
1	None	21	36	43
2	$AlCl_3$	52	48	0

[a] *Reagents and conditions*: reflux in THF for 20 h, using 3.5 equiv. of $LiAlH_4$ and 0.3 molar equiv. of the additive. [b] According to GC-MS.



Scheme 8 Possible routes leading to *N*-propylaniline **4** and *N*-isopropylamine **5**. Y = chloride, hydride, alkoxide.

whether the reaction is facilitated by the presence of Lewis acids, reduction of aziridine **3** was repeated in the presence of $AlCl_3$ (Table 2, entry 2). Complete conversion is observed, and the propylamine/isopropylamine ratio is higher than in the absence of Lewis acid catalyst; in fact it is similar to that obtained for reduction of the amide **1**. Formation of the propylamine is best explained by a reductive ring opening of S_N1 type promoted by the Lewis acid. Reversal of the direction of ring opening is known to occur also for substituted oxiranes in the presence of aluminium halides.[28,30] Reducing triphenyloxirane with a $LiAlH_4$ solution in which one mole of allyl bromide had been reduced previously to release bromide ions resulted in exclusive formation of 1,2,2-triphenylethanol rather than 1,1,2-triphenylethanol.[28] Similarly, we find that the aziridine is converted more rapidly when the reduction is performed after reduction (in the same reaction mixture) of either *t*-BuCl or AcCl, which would allow mixed aluminium chlorohydrides to be generated *in situ*. The effect of the presence of electrophilic catalysts on the rate of ring opening agrees well with Tanner's observation that aziridines activated by tosylation are rapidly ring-opened by hydride reagents.[14]

The presence of unreacted aziridine, but complete absence of aminoalcohol products, confirms that the aziridine does not react with OH^- during alkaline hydrolysis of the reaction mixture. To examine if the aziridine would be a precursor for the aminoalcohol **6** by reaction with partly hydrolyzed $LiAlH_4$ as a possible oxygen source, we added one to two molar equivalents of H_2O (relative to the aziridine) to the $LiAlH_4$ reducing agent. However, this addition of H_2O did not promote the formation of detectable amounts of aminoalcohols. This observation suggests that intermolecular ring opening of the aziridine intermediate by attack of oxygen nucleophiles present in the reaction mixture during reduction of **1** does not occur.

iv. Revised mechanism

Inasmuch as the outcome of reduction of 2-chloro-*N*-phenylpropanamide differs from that originally reported,[2] the original mechanistic proposal (Schemes 2 and 3) has to be revised. Indeed, the aziridine **3** appears to be an intermediate in the reaction, but reduction of **3** yields both the propylaniline **4** and the isopropylaniline **5**. In Scheme 8, we have summarized possible routes to the two amines. In addition to the aziridine route to the propylaniline, a path involving initial reductive removal of the chloride can be considered. The reduction of the corresponding tosylate exclusively follows this path, with *N*-phenylpropanamide **10** as an intermediate. Generation of the isopropylaniline **5** is likely to follow the original mechanism. The routes depicted in Scheme 8 are in agreement with the outcome of the deuterium labeling experiment.

Conclusions

We have shown that aziridines can be reductively ring-opened by $LiAlH_4$ to furnish either of the two possible amine products. Intriguingly, reduction of aziridines appears not to exhibit the same high degree of regioselectivity as reduction of oxiranes. Addition of $AlCl_3$ as a Lewis acid speeds up the reduction considerably and promotes cleavage at the most substituted carbon, presumably *via* an S_N1-type pathway. Reductive aziridine ring opening was in fact proposed in an early study by De Kimpe[6] to account for the products obtained from reduction of *N*-2-(1,1-dichloroalkylidene)aniline starting materials, but in later studies on α,α-dichloroketimines, a mechanism involving an aziridinium intermediate that isomerized into an α-imino carbenium ion was adopted instead.[5]

We have identified an aziridine as intermediate in the reduction of 2-chloro-*N*-phenylpropanamide, and in agreement to the observed lack of selectivity in the reduction of aziridines, both the propyl- and isopropylanilines are obtained as the final products of reduction. The reduction is accompanied by the formation of considerable amounts of a β-aminoalcohol that is easily separated from the amines and that has been unambiguously identified as the primary alcohol instead of the originally proposed isomeric, secondary alcohol.

Experimental

General methods

Chemicals were purchased from Sigma-Aldrich, Merck, and Fluka, and used as received. THF was distilled from sodium or obtained from a Puresolv drying apparatus. Thin-layer

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chromatography (TLC) was carried out using aluminium sheets pre-coated with silica gel 60F (Merck 5554). Column chromatography was carried out using silica gel 60 (Merck 9385, 0.040–0.063 mm). Melting points were measured on a Reichert melting point apparatus equipped with a microscope and are uncorrected. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Varian instrument. Samples were dissolved in $CDCl_3$ purchased from Cambridge Isotope Labs. Gas chromatography–mass spectrometry (GC–MS) was performed on an HP 5890 Gas chromatograph/5972 Mass Selective Detector or an HP 6890 Gas chromatograph/5973 Mass Selective Detector; RT = retention time. Fast atom bombardment (FAB) spectra were obtained on a Jeol JMS-HX 110 Tandem Mass Spectrometer in the positive ion mode using 3-nitrobenzyl alcohol (NBA) as matrix. Microanalyses were performed at the Microanalytical Laboratory at the Department of Chemistry, University of Copenhagen.

Synthesis of 1-(phenylcarbamoyl)ethyl acetate (9)

To a solution of 2-chloro-*N*-phenylpropanamide **1** (5.46 g, 29.7 mmol) in DMF (60 mL) was added NaOAc (2.95 g, 36.0 mmol). The mixture was refluxed overnight, whereupon the precipitate was filtered off and washed with DMF. The filtrate was concentrated at reduced pressure using an oil pump. The residue was subjected to column chromatography (SiO_2, 5% MeOH in CH_2Cl_2) to provide the product (5.3 g, 86%) as white solid. Mp 120–121 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.57$ (d, $J = 7.5$ Hz, 3 H), 2.21 (s, 3 H), 5.34 (q, $J = 7.5$ Hz, 1 H), 7.14 (t, $J = 7.9$ Hz, 1 H), 7.34 (t, $J = 7.9$ Hz, 2 H), 7.54 (d, $J = 8.2$ Hz, 2 H), 7.81 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.0$, 21.4, 71.2, 120.3, 125.1, 129.3, 137.2, 168.4, 169.7. MS(FAB): $m/z = 207$ (M^+). Found: C, 63.67; H, 6.26; N, 6.70. $C_{11}H_{13}NO_3$ requires C, 63.76; H, 6.32; N, 6.76%.

Synthesis of 2-hydroxy-*N*-phenylpropanamide (8)

To a suspension of compound **9** (735 mg, 3.55 mmol) in dioxane (40 mL) was added Na_2CO_3 (5.31 g, 50.1 mmol) in H_2O (20 mL). The mixture was refluxed overnight. After cooling to room temperature, the mixture was extracted with Et_2O (3 × 20 mL). The combined organic phase was dried (Na_2SO_4), filtered, and concentrated *in vacuo.* Drying at oil pump provided the analytically pure product as white crystals in nearly quantitative yield. Mp 50–52 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.53$ (d, $J = 6.9$ Hz, 3 H), 2.55 (s, 1 H), 4.37 (q, $J = 6.9$ Hz, 1 H), 7.12 (t, $J = 8.2$ Hz, 1 H), 7.33 (t, $J = 8.2$ Hz, 2 H), 7.56 (d, $J = 8.2$ Hz, 2 H), 8.44 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.4$, 69.1, 119.9, 124.7, 129.2, 137.3, 172.4. MS(FAB): $m/z = 165$ (M^+). Found: C, 65.40; H, 6.65; N, 8.45. $C_9H_{11}NO_2$ requires C, 65.44; H, 6.71; N, 8.48%.

Reduction of 2-chloro-*N*-phenylpropanamide (1)

Entry 1, Table 1. To a solution of the amide **1** (9.15 g, 49.8 mmol) prepared according to Suzuki[2] in Et_2O (100 mL) was added $LiAlH_4$ (5.70 g, 150 mmol) over 1 h, cooling the reaction mixture on an ice bath under an inert atmosphere. Then the mixture was refluxed for 20 h, cooled, and diluted with Et_2O (55 mL), and hydrolyzed with aqueous 10% NaOH (*ca.* 50 mL). To the resulting gel was added another portion of Et_2O (100 mL), and the organic phase was decanted off and then dried (K_2CO_3), filtered and concentrated *in vacuo.* GC–MS revealed three major products: **5** [RT = 6.36 min; MS: $m/z = 135$ (M^+, 22%), 120 (100%), 93 (8%), 77 (12%)], **4** [RT = 7.19 min; MS: $m/z = 135$ (M^+, 21%), 106 (100%), 77 (19%)], **6** [RT = 8.90 min; MS: $m/z = 151$ (M^+, 12%), 120 (100%), 93 (6%), 77 (16%)]. The amines **4** and **5** were isolated from the aminoalcohol **6** by column chromatography (SiO_2, CH_2Cl_2–EtOAc 1 : 1), and the product assignment was then confirmed by ^{1}H NMR spectroscopy.

Entries 2–5, Table 1. The amide **1** in THF was added to a suspension (entry 2) or solution (1 M, entries 3–5) of $LiAlH_4$ in THF. The addition was performed under inert atmosphere. The concentration of amide was the same in entries 2–5 after complete addition (1.85 g in a total of 52 mL THF for entry 2; 1.84 g in a total of 50 mL THF for entries 3–5). The mixture was hydrolyzed with conc. aqueous NaOH (*ca.* 5 mL) (Caution), and the mixture stirred for 1 h. To the resulting gel was added another portion of Et_2O (100 mL), and the organic phase was filtered through a layer of Na_2SO_4 and concentrated *in vacuo.*

Reduction of 1-(phenylcarbamoyl)ethyl tosylate (2). Performed in a similar way, using a solution of $LiAlH_4$ (1 M) in THF.

Reduction of 2-methyl-*N*-phenylaziridine (3). Performed in a similar way, using a solution of $LiAlH_4$ (1 M) in THF and the additive given in Table 2.

References

1 A. Uffer and E. Schlittler, *Helv. Chim. Acta*, 1948, **31**, 1397–1400.
2 K. Suzuki, K. Okano, K. Nakai, Y. Terao and M. Sekiya, *Synthesis*, 1983, 723–725.
3 A. Hassner, G. J. Matthews and F. W. Fowler, *J. Am. Chem. Soc.*, 1969, **91**, 5046–5054.
4 N. De Kimpe, R. Verhé, L. De Buyck and N. Schamp, *J. Org. Chem.*, 1980, **45**, 5319–5325.
5 N. De Kimpe, R. Verhé, L. De Buyck and N. Schamp, *J. Org. Chem.*, 1981, **46**, 2079–2081; N. De Kimpe, R. Verhe, L. De Buyck and N. Schamp, *Bull. Soc. Chim. Belg.*, 1983, **92**, 233–239.
6 N. De Kimpe, R. Verhé and N. Schamp, *Bull. Soc. Chim. Belg.*, 1975, **84**, 701–707.
7 N. De Kimpe, R. Verhé, L. De Buyck and N. Schamp, *Recl. Trav. Chim. Pays-Bas*, 1977, **96**, 242–246.
8 K. Ichimura and M. Ohta, *Bull. Chem. Soc. Jpn.*, 1967, **40**, 432.
9 K. Ichimura and M. Ohta, *Bull. Chem. Soc. Jpn.*, 1970, **43**, 1443–1450.
10 J. Cleophax, J. Hildesheim, A.-M. Sepulchre and S. D. Géro, *Bull. Soc. Chim. Fr.*, 1969, 153–156.
11 K. Kitahonoki, K. Kotera, Y. Matsukawa, S. Miyazaki, T. Okada, H. Takahashi and Y. Takano, *Tetrahedron Lett.*, 1965, **6**, 1059–1065; K. Kotera, T. Okada and S. Miyazaki, *Tetrahedron*, 1968, **24**, 5677–5690; K. Kotera, Y. Matsukawa, H. Takahashi, T. Okada and K. Kitahonoki, *Tetrahedron*, 1968, **24**, 6177–6184; K. Kotera, S. Miyazaki, H. Takahashi, T. Okada and K. Kitahonoki, *Tetrahedron*, 1968, **24**, 3681–3696; H. Tanida, T. Okada and K. Kotera, *Bull. Chem. Soc. Jpn.*, 1973, **46**, 934–938.
12 K. Kotera, Y. Takano, A. Matsuura and K. Kitahonoki, *Tetrahedron*, 1970, **26**, 539–556.
13 J. L. Pierre, H. Handel and P. Baret, *Tetrahedron*, 1974, **30**, 3213–3223; P. Baret, P. M. Bourgeois, C. Gey and J. L. Pierre, *Tetrahedron*, 1979, **35**, 189–196; J. M. Concellón, J. R. Suárez, S. García-Granda and M. R. Díaz, *Angew. Chem., Int. Ed.*, 2004, **43**, 4333–4336; L. Yu, A. Kokai and A. K. Yudin, *J. Org. Chem.*, 2007, **72**, 1737–1741.
14 D. Tanner, H. M. He and P. Somfai, *Tetrahedron*, 1992, **48**, 6069–6078; D. Tanner and P. Somfai, *Tetrahedron Lett.*, 1987, **28**, 1211–1214; D. Tanner and T. Groth, *Tetrahedron*, 1997, **53**, 16139–16146; D. Tanner and O. R. Gautun, *Tetrahedron*, 1995, **51**, 8279–8288.

15 N. G. Gaylord, *Reduction with Complex Metal Hydrides*, Interscience Publishers, Inc., New York, 1956.
16 J. Almena, F. Foubelo and M. Yus, *J. Org. Chem.*, 1994, **59**, 3210–3215.
17 H. Ohno, N. Mimura, A. Otaka, H. Tamamura, N. Fujii, T. Ibuka, I. Shimizu, A. Satake and Y. Yamamoto, *Tetrahedron*, 1997, **53**, 12933–12946; J.-W. Chang, J. H. Bae, S.-H. Shin, C. S. Park, D. Choi and W. K. Lee, *Tetrahedron Lett.*, 1998, **39**, 9193–9196; D. Savoia, G. Alvaro, R. Di Fabio, A. Gualandi and C. Fiorelli, *J. Org. Chem.*, 2006, **71**, 9373–9381; T. Manaka, S.-I. Nagayama, W. Desadee, N. Yajima, T. Kumamoto, T. Watanabe, T. Ishikawa, M. Kawahata and K. Yamaguchi, *Helv. Chim. Acta*, 2007, **90**, 128–142.
18 G. A. Molander and P. J. Stengel, *Tetrahedron*, 1997, **53**, 8887–8912.
19 For recent reviews on the chemistry of aziridines, see: J. B. Sweeney, *Chem. Soc. Rev.*, 2002, **31**, 247–258; G. S. Singh, M. D'hooghe and N. De Kimpe, *Chem. Rev.*, 2007, **107**, 2080–2135.
20 R. S. Coleman, J.-S. Kong and T. E. Richardson, *J. Am. Chem. Soc.*, 1999, **121**, 9088–9095; S. Fürmeier and J. O. Metzger, *Eur. J. Org. Chem.*, 2003, 649–659; R. Vicik, V. Hoerr, M. Glaser, M. Schultheis, E. Hansell, J. H. McKerrow, U. Holzgrabe, C. R. Caffrey, A. Ponte-Sucre, H. Moll, A. Stich and T. Schirmeister, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 2753–2757.
21 N. De Kimpe, R. Verhé, L. De Buyck and N. Schamp, *Synth. Commun.*, 1975, **5**, 269–274.
22 A. K. Chakraborti, S. Rudrawar and A. Kondaskar, *Eur. J. Org. Chem.*, 2004, 3597–3600.
23 I. Shahak and E. D. Bergmann, *J. Chem. Soc.*, 1967, 319–320.
24 Hydrolysis of the ester **9** has previously been reported (using alcoholic KOH): M. Passerini, *Gazz. Chim. Ital.*, 1924, **54**, 529–540.
25 J. March, *Advanced Organic Chemistry*, 4th edn, John Wiley & Sons, USA, 1992, pp. 441–442.
26 D. R. Arnold and V. Y. Abraitys, *Tetrahedron Lett.*, 1970, **11**, 2997–3000.
27 The aziridine was synthesized by a Mitsunobu reaction following a general protocol: J. R. Pfister, *Synthesis*, 1984, 969–970.
28 E. L. Eliel and D. W. Delmonte, *J. Am. Chem. Soc.*, 1958, **80**, 1744–1752.
29 S.-C. Chen, *Synthesis*, 1974, 691–703.
30 E. L. Eliel and D. W. Delmonte, *J. Am. Chem. Soc.*, 1956, **78**, 3226.

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