

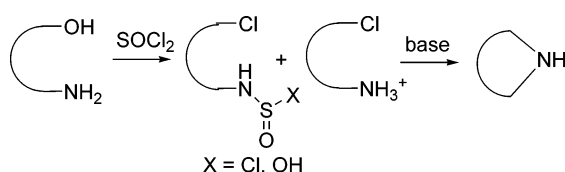
Chlorination/Cyclodehydration of Amino Alcohols with SOCl₂: An Old Reaction Revisited

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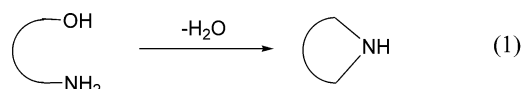
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A simple, one-pot preparation of cyclic amines via efficient chlorination of amino alcohols with use of SOCl₂ has been developed. This approach obviates the need for the classical *N*-protection/*O*-activation/cyclization/deprotection sequence commonly employed for this type of transformation. The reaction pathways and the general scope of this method have also been investigated.

Cyclodehydration of amino alcohols (eq 1) is an important and useful transformation for the preparation of nitrogen heterocycles. Many cyclodehydration methodologies^{1,2} have been developed; however, classical *indirect* cyclodehydration of amino alcohols typically involves a tedious sequence of protection/activation/cyclization/deprotection. Although commonly implemented,^{1,2} these indirect approaches require multiple chemical steps that reduce the overall efficiency of the transformation. The commonly used *direct* cyclodehydration methods^{3–7} of amino alcohols to the corresponding cyclic

amines include (1) redox organometallic reagents⁴ such as RuH₂-(PPh₃)₄ and RhH(PPh₃)₄, (2) exposure to acidic conditions⁵ by generating a corresponding cation intermediate with suitable substrates, (3) phosphorus-assisted Mitsunobu reaction,⁶ and (4) direct activation³ including halogenation to produce a halo-amine intermediate. For example, the use of the Appel reaction and its variants is widely applied,⁷ although there are drawbacks in large-scale production. Surprisingly, direct chlorination of amino alcohol free bases with SOCl₂, which was discovered several decades ago, has not been well studied;^{8,9} its application is underutilized due to the expected competition¹⁰ between *N*- and *O*-sulfonylation, and subsequent “inevitable” side reactions. Low yields are typically an issue for this reaction.¹¹



Recently during our asymmetric syntheses of (+)-bicifadine (**1a**) and DOV21947 (**1b**) (Scheme 1),¹² we developed a practical direct chlorination of amino alcohol **2** with SOCl₂ to prepare amino chloride **3**, which immediately cyclized to 3-azabicyclo[3.1.0]hexanes **1** upon pH adjustment during aqueous workup in nearly quantitative yield. Herein, we further detail our results including the reaction scope and mechanistic insights into the reaction pathway as revealed by NMR spectroscopic studies.

The formation of chlorosulfonyl ester intermediates during the chlorination of alcohols with SOCl₂ is well recognized. Isolation of the chlorosulfonyl ester has been reported.¹³ It is also well-known that treatment of 1,2-amino alcohols with SOCl₂ in the presence of bases gives cyclic sulfamides, which are the products of subsequent intramolecular *O*- or *N*-sulfonylation of the initially formed chlorosulfonyl esters/amides.¹⁴ After surveying the literature^{15,16} related to chlorination

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(6) For recent reviews, see: (a) Hughes, D. L. *Org. Prep. Proc. Int.* **1996**, 28, 127. (b) Hughes, D. L. *Org. React.* **1992**, 42, 335. (c) Mitsunobu, O. *Synthesis* **1981**, 1.

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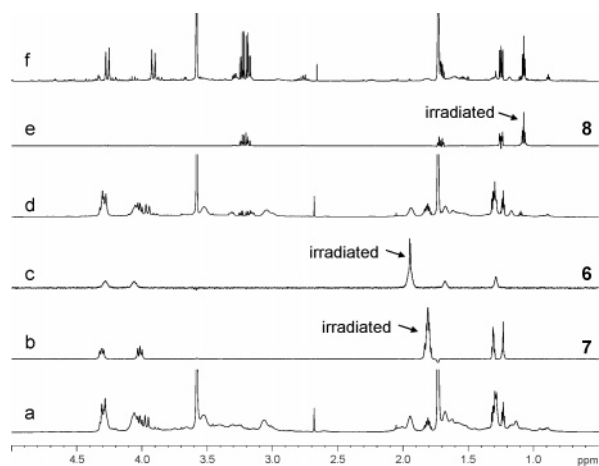
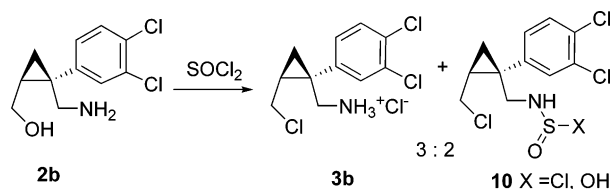


FIGURE 1. NMR spectra of the reaction sequence in the chlorination of **4** in d_8 -THF. (a) ^1H NMR spectrum at $t = 45$ min at 0°C , after 1.5 equiv of SOCl_2 was added to a solution of **4** in one portion at 0°C . (b) TOCSY spectrum obtained by irradiating the solution from part a at 1.81 ppm. (c) TOCSY spectrum obtained by irradiating the solution from part a at 1.95 ppm. (d) ^1H NMR spectrum at $t = 3.5$ h at 0°C . (e) TOCSY spectrum obtained by irradiating the solution from part d at 1.07 ppm. (f) ^1H NMR spectrum at $t = 18$ h at ambient temperature.

SCHEME 3. Chlorination of **2b** with SOCl_2



SOCl_2 (1.2 equiv) in d_8 -THF, NMR studies (see the Supporting Information, Figure S1) of the crude reaction mixture before aqueous base quench clearly showed the complete formation of the two products, protonated salt **3b** and sulfamic intermediate **10**, in about 3:2 ratio (Scheme 3).¹⁹ The observed ratio of protonated salt **3b**:**10** clearly indicated that ClSO_2H formed during the reaction is responsible for the formation of **10**, since only 1.2 equiv of SOCl_2 total was charged during the reaction.

Thus, a rational conclusion for the most desirable way to run the reaction would be *slow inverse-addition* of the amino alcohol solution in an appropriate solvent to a solution of SOCl_2 . The amino alcohol substrate would become instantly protonated upon contact with adventitious HCl in the SOCl_2 solution or the HCl generated during the *O*-sulfonylation step as well as the “inevitable” *N*-sulfonylation step. Because the amino alcohol substrate is added slowly to keep a low concentration of its protonated salt in the reaction mixture, the protonated amino alcohol substrate would be expected to react with excess SOCl_2 before it crystallizes.¹⁸ Thus, complete conversion could be achieved. In addition, the minor *N*-

(19) In principle, protonation of amine moiety would attenuate nitrogen's reactivity and allow the hydroxyl group to react preferentially over the ammonium group. If these protonated amine salts are soluble, a good conversion can be achieved. However, the solubility of protonated amino alcohols as well as their corresponding protonated amino chloride salts in these solvents, which are compatible to SOCl_2 , would often create an undesirable slurry-to-slurry reaction (even formation of a gummy reaction mixture as mentioned above) accompanied by low conversion. Similarly, we observed incomplete conversion when the HCl salt **2** was treated with SOCl_2 in solvents such as *i*-PrOAc, $(\text{MeOCH}_2)_2$, and CHCl_3 .

TABLE 1. Direct Chlorination/Cyclization of Amino Alcohols

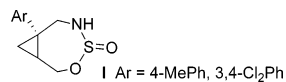
Entry	Starting Material	Conditions ^a		Product	Yield (%) ^b
		Chlorination	Cyclization		
1		$(\text{MeOCH}_2)_2$ r.t.	r.t.		83 ^c
2		$(\text{MeOCH}_2)_2$ r.t.	r.t.		94
3		CH_2Cl_2 40 °C	$(\text{MeOCH}_2)_2$ 40 °C, 3h		95
4		$(\text{MeOCH}_2)_2$ or <i>i</i> -PrOAc r.t.	60 °C overnight		94
5		CH_2Cl_2 r.t.	$(\text{MeOCH}_2)_2$ 80 °C, 5 days		90
6		$(\text{MeOCH}_2)_2$ r.t.	r.t.		92 ^c
7		$(\text{MeOCH}_2)_2$ r.t.	40 °C		96 ^c
8		$(\text{MeOCH}_2)_2$ r.t.	r.t.		79
9		$(\text{MeOCH}_2)_2$ r.t.	N/A		99
10		$(\text{MeOCH}_2)_2$ 40 °C	N/A		99

^a Unless otherwise mentioned, the cyclization was carried out in the same solvent as the chlorination. ^b Isolated yield. ^c Isolated as its HCl salt.

sulfonylated intermediates (such as sulfamic chloride **7**) that could be formed “inevitably” by reacting with SOCl_2 are also preserved and further converted to the corresponding chlorides (such as **8** and **10**, $\text{X} = \text{Cl}$) in the acidic inverse-addition reaction media, because the nucleophilic amine species that could react with these *N*-sulfonylated intermediates are either quenched by HCl or converted to sulfamic acids with ClSO_2H . Finally, the formation of sulfamic chlorides/acids (such as **8** and **10**) is also believed to partially contribute to retaining a kinetically homogeneous reaction solution during the inverse-addition of amine substrate **2b** to SOCl_2 since they do not readily precipitate from the reaction mixture like the HCl salt does (vide supra).^{18,19}

Building on these mechanistic insights, an optimal, one-pot process for converting amino alcohols to the corresponding cyclized products was developed. A solution of amino alcohol **2** in either *i*-PrOAc or $(\text{MeOCH}_2)_2$ was slowly added over 2 h to a solution of SOCl_2 in the same solvent at ambient temperature. No sticky solids, discoloration, or significant undesired side products were observed. The reaction mixture was directly quenched with aqueous base after a complete conversion was achieved. The trans chloride **3** was cyclized to

(20) The formation of possible sulfamide intermediate **I** was not observed.



1 immediately upon adjusting the pH to >8.5.²⁰ The cyclized pyrrolidine **1** was isolated in 95% yield following workup.²¹

To further explore the chlorination/cyclodehydration scope, a variety of amino alcohols were examined. The results are summarized in Table 1. In a typical experiment, a solution of amino alcohol (ca. 0.2 M) in solvents such as (MeOCH₂)₂ or *i*-PrOAc or CH₂Cl₂ was added over several hours to a solution of SOCl₂ (1.2 equiv, 0.2 M based on amino alcohol) in the same solvent. We were gratified to observe that all of the amino alcohols examined were cleanly and efficiently converted to the corresponding amino chloride in nearly quantitative yield. Full conversion to the desired chloride was observed within 5 h for most examples; however, compounds **13** and **20** required heating at 40 °C for several hours to achieve complete conversion to the corresponding chloride, respectively.

For direct cyclodehydration transformation, the above crude chloro amine intermediates were treated with base. The intramolecular cyclization rate is dependent on the substrates, as expected. Upon addition of excess alkaline aqueous base to the reaction mixture, pyrrolidines **21**, **22**, and (±)-crispine A **23**²² (Table 1, entries 1–3) were formed instantaneously from the corresponding 1,4-amino chlorides. Complete formation of pyrrolidines **24** and **25** required thermal instigation over an extended period (Table 1, entries 4 and 5). These slower rates can be rationalized by the attenuated nucleophilicity of the aniline nitrogen on **14** and the ring strain presumed to be present in **15**. The formation of piperidines **26**–**28** (Table 1, entries 6–8) was easily achieved after aging the corresponding 1,5-amino chloride free bases for several hours at ambient temperature. However, a cleaner cyclization to **28** could be obtained by diluting the reaction solution to 0.01 M from 0.1 M before the addition of aqueous base. Attempts to cyclize the readily formed 1,2- and 1,3-chloroamines **29** and **30** even at elevated temperatures resulted in complicated mixtures containing only small amounts of desired cyclized product.²³

In summary, modifications to an “old” method for activating OH have resulted in a simple process for the chlorination of amino alcohols in the presence of SOCl₂. This reaction has been extended to cyclodehydration of amino alcohols in a practical one-pot process. In situ NMR studies provided useful insights

into the reaction pathway. The general scope of this approach and its practical efficiency were demonstrated on a wide variety of amino alcohols.

Experimental Section

General Procedure. To a solution of SOCl₂ (1.2–3 equiv) in a solvent such as *i*-PrOAc or (MeOCH₂)₂ or CH₂Cl₂ (ca. 0.2 M) was subsurface-added a solution of amino alcohol (1.0 equiv, ca. 0.2 M) in the same solvent dropwise over 1 h. The reaction mixture was allowed to stir for additional 1–5 h, then quenched with a base such as aqueous NaOH or Na₃PO₄. For these substrates cyclized at ambient temperature, the separated organic layer was washed with water and brine, and then dried over Na₂SO₄. Upon concentration in vacuum, the product was purified on silica gel column to give the desired product. For these substrates cyclized at elevated temperature, the organic phase could be separated and the corresponding chloride was then cyclized under the conditions as specified in Table 1.

(1R,5S)-1-(4-Methylphenyl)-3-azabicyclo^{3.10}hexane [(+)-Bicifadine, 1a]. To a solution of SOCl₂ (4.08 mL, 55.85 mmol) in *i*-PrOAc (50 mL) was slowly subsurface-added a solution of amino alcohol **2a** (8.89 g, 46.54 mmol) in *i*-PrOAc (50 mL) at ambient temperature over 1 h. After an additional 2 h, 5.0 N NaOH (45 mL) was added over 1 h while the batch temperature was maintained at <30 °C with external cooling. The two-phase reaction mixture was stirred for 1 h at ambient temperature to allow pH to stabilize (usually to 8.5–9.0) with NaOH pH titration. The organic phase was washed with water (2 × 20 mL). Concentrated HCl (4.0 mL) was added to the organic phase while the internal temperature was kept <30 °C. The aqueous *i*-PrOAc was azeotropically concentrated in vacuum to a final volume of ca. 50 mL. The solid was filtered and washed with *i*-PrOAc (2 × 20 mL). Suction dry gave 9.0 g of the desired HCl salt (92% isolated yield). ¹H NMR (400 MHz, *d*₄-MeOH): δ 7.17 (m, 4 H), 3.73 (d, *J* = 11.4 Hz, 1 H), 3.66 (dd, *J* = 3.8, 11.4 Hz, 1 H), 3.58 (d, *J* = 11.4 Hz, 1 H), 3.51 (d, *J* = 11.4 Hz, 1 H), 2.31 (s, 3 H), 2.10 (m, 1 H), 1.22 (t, *J* = 7.5 Hz, 1 H), 1.12 (t, *J* = 5.4 Hz, 1 H). ¹³C NMR (100 MHz, *d*₄-MeOH): δ 138.3, 136.8, 130.6, 128.3, 52.3, 49.3, 32.3, 24.2, 21.2, 16.0. Anal. Calcd for C₁₂H₁₆ClN: C, 68.73; H, 7.69; N, 6.68. Found: C, 68.52; H, 7.69; N, 6.64.

Supporting Information Available: Experimental procedures and spectral data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(21) This process was successfully and reproducibly carried out in 5 kg scale with 1.2 equiv of SOCl₂.

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