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Chlorination/Cyclodehydration of Amino Alcohols with $SOCl_2$: An Old Reaction Revisited

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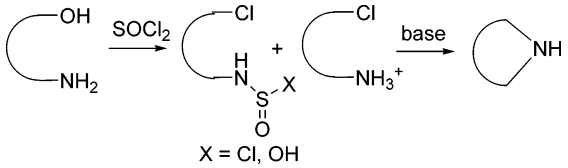
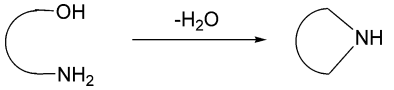


A simple, one-pot preparation of cyclic amines via efficient chlorination of amino alcohols with use of $SOCl_2$ has been developed. This approach obviates the need for the classical *N*-protection/*O*-activation/cyclization/deprotection sequence commonly employed for this type of transformation. The 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 reagents[4] such as $RuH_2(PPh_3)_4$ and $RhH(PPh_3)_4$, (2) exposure to acidic conditions[5] by generating a corresponding cation intermediate with suitable substrates, (3) phosphorus-assisted Mitsunobu reaction,[6] and (4) direct activation[3] 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 $SOCl_2$, which was discovered several decades ago, has not been well studied;[8,9] its application is underutilized due to the expected competition[10] between *N*- and *O*-sulfinylation, and subsequent "inevitable" side reactions. Low yields are typically an issue for this reaction.[11]



(1)

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 $SOCl_2$ 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 chlorosulfinyl ester intermediates during the chlorination of alcohols with $SOCl_2$ is well recognized. Isolation of the chlorosulfinyl ester has been reported.[13] It is also well-known that treatment of 1,2-amino alcohols with $SOCl_2$ *in the presence of bases* gives cyclic sulfamides, which are the products of subsequent intramolecular *O*- or *N*-sulfinylation of the initially formed chlorosulfinyl esters/amides.[14] After surveying the literature[15,16] related to chlorination

(1) For recent reviews, see: (a) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701. (b) Larock, R. C. *Comprehensive Organic Transformations*, 2nd ed.; Wiley-VCH: New York, 1999; pp 689−702 and 779−784.

(2) For recent examples and applications, see: (a) Smith, A. B., III; Kim, D.-S. *J. Org. Chem.* **2006**, *71*, 2547. (b) Trost, B. M.; Tang, W.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 14785. (c) Pyne, S. G.; Davis, A. S.; Gates, N. J.; Hartley, J. P.; Lindsay, K. B.; Machan, T.; Tang, M. *Synlett* **2004**, 2670. (d) Kan, T.; Kobayshi, H.; Fukuyama, T. *Synlett* **2002**, 697. (e) Ina, H.; Kibayashi, C. *J. Org. Chem.* **1993**, *58*, 52. (f) Burgess, K.; Chaplin, D. A.; Henderson, I.; Pan, Y. T.; Elbein, A. D. *J. Org. Chem.* **1992**, *57*, 1103. (g) Schink, H. E.; Pettersson, H.; Bäckvall, J.-E. *J. Org. Chem.* **1991**, *56*, 2769.

(3) For recent applications of direct cyclodehydration methods, see: (a) de Figueiredo, R. M.; Fröhlich, R.; Christmann, M. *J. Org. Chem.* **2006**, *71*, 4147. (b) Wu, T. R.; Chong, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 9646. (c) Pulz, R.; Al-Harrasi, A.; Reissig, H.-U. *Org. Lett.* **2002**, *4*, 2353 and references cited therein.

(4) (a) Nota, T.; Murahashi, S.-I. *Synlett* **1991**, 693. (b) Murahashi, S.-I.; Kondo, K.; Hakata, T. *Tetrahedron Lett.* **1982**, *23*, 229. (c) Grigg, R.; Mitchell, T. R. B.; Sutthivaiyakit S.; Tongpenyai, N. *Chem. Commun.* **1981**, 611.

(5) For examples, see: (a) Tanaka, H.; Murakami, Y.; Aizawa, T.; Torii, S. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3742. (b) Papageorgiou, C.; Borer, X. *Helv. Chim. Acta* **1988**, *71*, 1079.

(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.

(7) For reviews, see: (a) Castro, B. R. *Org. React.* **1983**, *29*, 1. (b) Appel, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 801.

(8) For recent reviews about $SOCl_2$, see: (a) El-Sakka, I. A.; Hassan, N. A. *J. Sulfur Chem.* **2005**, *26*, 33. (b) Wirth, D. D. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1995; p 4873. (c) Oka, K. *Synthesis* **1981**, 661.

(9) Chlorination of alcohols, excluding amino alcohols, with $SOCl_2$ is thoroughly studied in terms of both mechanism and practical applications.[8]

(10) For example, see: Pilkington, M.; Wallis, J. D. *Chem. Commun.* **1993**, 1857.

(11) For examples of chlorination of amino alcohol salts, see: (a) Back, T. G.; Nakajima, K. *J. Org. Chem.* **2000**, *65*, 4543. (b) Bubnov, Y. N.; Zykov, A. Y.; Ignatenko, A. V.; Mikhailovsky, A. G.; Shklyaev, Y. V.; Shklyaev, V. S. *Izv. Akad. Nauk., Ser. Khim.* **1996**, 935. (c) Dobler, M.; Beerli, R.; Weissmahr, W. K.; Borschberg, H.-J. *Tetrahedron*: *Asymmetry* **1992**, *11*, 1411. (d) Kóbor, J.; Fülöp, F.; Bernáth, G.; Sohár, P. *Tetrahedron* **1987**, *43*, 1887. (e) Bäckvall, J. E.; Renko, Z. D.; Byström, S. E. *Tetrahedron Lett.* **1987**, *28*, 4199. (f) Piper, J. R.; Johnston, T. P. *J. Org. Chem.* **1963**, *28*, 981. (g) Norton, T. R.; Seibert, R. A.; Benson, A. A.; Bergstrom, F. W. *J. Am. Chem. Soc.* **1946**, *68*, 1572.

(12) Xu, F.; Murry, J. A.; Simmons, B.; Corley, E.; Fitch, K.; Karady, S.; Tschaen, D. *Org. Lett.* **2006**, *8*, 3885.

(13) Gerrard, W. *J. Chem. Soc.* **1940**, 218

(14) For examples, see: (a) Lu, B. Z.; Jin, F.; Zhang, Y.; Wu, X.; Wald, S. A.; Senanayake, C. H. *Org. Lett.* **2005**, *7*, 1465. (b) Benson, S. C.; Snyder, J. K. *Tetrahedron Lett.* **1991**, *32*, 5885. (c) Lowe, G.; Reed, M. A. *Tetrahedron*: *Asymmetry* **1990**, *1*, 885.

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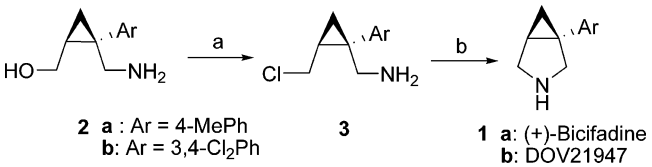
SCHEME 1. Preparation of DOV 21947 and (+) Bicifadine[a]



[a] Reagents and conditions: (a) 1.2 equiv of $SOCl_2$, *i*-PrOAc, 25 °C; (b) aq NaOH, pH 8.5−9.5.

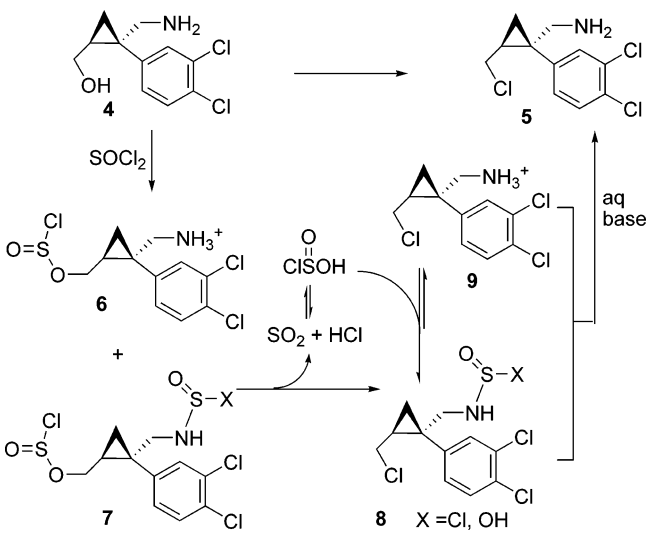
of amino alcohol free base with $SOCl_2$, we noticed that $SOCl_2$ was typically added to the solution of substrates in the presence or absence of bases. The reaction notoriously gave poor yields. In fact, we also obtained **3** in poor yield when $SOCl_2$ was added to a solution of free base **2** in *i*-PrOAc or $(MeOCH_2)_2$ slowly. The reaction turned dark red and formed gummy solids, which could be observed after about 0.3 equiv of $SOCl_2$ were introduced. HPLC analysis of the reaction revealed that many undesired byproducts were formed.

However, we reasoned that a clean cyclodehydration transformation could still be achieved by utilizing $SOCl_2$ as an OH activation/chlorination reagent if the nucleophilic amine species could be "protected/quenched" through rapid protonation and/or *N*-sulfinylation under acidic reaction conditions. Thus, the sulfinamide byproducts formed via nucleophilic amine attacking the *N*- or *O*-sulfinylated species could be minimized.[17]

To test this hypothesis, the HCl salt **2b** was treated with $SOCl_2$ in *i*-PrOAc. The formation of byproducts was significantly suppressed since the nucleophilic NH_2 was protonated. However, incomplete chlorination reaction was observed due to the poor solubility of the corresponding HCl amine salts, which precipitated from the reaction mixture. Interestingly, a clear homogeneous reaction solution was obtained,[18] if an *inverse* addition of a solution of the free base **2b** in *i*-PrOAc to $SOCl_2$ was carried out. Under these inverse addition conditions, complete conversion of **2b** to the corresponding chloride **3b** was observed by HPLC analysis.

To better understand the difference between the two modes of addition, we studied the reaction using in situ NMR

SCHEME 2. Reaction Pathways for Chlorination of 4 with $SOCl_2$



spectroscopy (Scheme 2). When $SOCl_2$ (1.5 equiv) was quickly mixed with a solution of the cis amino alcohol **4**[12] in d_8-THF at 0 °C, the formation of the chlorosulfinate ester and amide was immediately observed. As expected, **4** was partially converted to the chlorosulfinylate ester **6** while the NH_2 was protonated by the HCl formed during the reaction right after $SOCl_2$ was introduced. Although it was expected that the initial contact of $SOCl_2$ with amine **4** under the above quick mixing conditions was not well controlled and would also result in the formation of the corresponding bissulfinylated ester **7**, the fact of the formation of a fair amount of bissulfinylated ester **7** under acidic conditions indicated that the *O*-sulfinylation is competitively faster than the formation of intermolecular sulfamide byproducts (RNHS(O)OR′) via subsequently coupling between the free OH/NH_2 with the corresponding monosulfinylated intermediates (vide infra).

The structures of **6**−**9** were unambiguously elucidated by applying various NMR techniques (1-D TOCSY, HMQC, and ^{13}C NMR). The proton spin−spin coupling networks were easily identified by 1-D TOCSY experiments and these protons could then correlate with ^{13}C via 2-D HMQC experiments. The ^{13}C NMR data for $-CH_2OS(O)Cl$ (69.4 and 69.2 ppm for intermediates **6** and **7**, respectively) and $-CH_2Cl$ (46.4 and 46.5 ppm for intermediates **9** and **8**, respectively) further supported the formation of these intermediates.

Conversion of the chlorosulfinate esters **6**/**7** to the corresponding chlorides **9**/**8** was slow at 0 °C, as confirmed by NMR studies. After the sample was aged (Figure 1, spectrum a) at 0 °C, chlorosulfinate intermediates, as expected, turned to a mixture of **8**/**9** (Figure 1, spectrum d). However, further aging of the reaction mixture at ambient temperature for several hours resulted in **8** as the major product while **9** was partially converted to **8** (Figure 1, spectrum f). Surprisingly, the sulfinylation of the protonated NH_3^+ group of **9** with ClS(O)OH, which was liberated as the chlorosulfinate intermediates were converted to the chloride intermediates, could still happen under these acidic reaction conditions to form the sulfamic acid **8**.

The *N*-sulfinylation of the protonated NH_3^+ with $SOCl_2$/$ClSO_2H$ was also unambiguously confirmed when the chlorination of **2b** was carried out in the presence of $SOCl_2$. After a solution of **2b** in d_8-THF was added slowly to a solution of

(15) For examples of chlorination of amino alcohols with $SOCl_2$ in the presence of bases, see: (a) Muratake, H.; Natsume, M. *Tetrahedron Lett.* **2002**, *43*, 2913. (b) Howarth, N. M.; Malpass, J. R.; Smith, C. R. *Tetrahedron* **1998**, *54*, 10899. (c) Bosch, J.; Mestre, E.; Bonjoch, J.; López, F.; Granados, R. *Heterocycles* **1984**, *22*, 767. (d) Mousseron, M.; Winternitz, F.; Mousseron-Canet, M. *Bull. Soc. Chim. Fr.* **1953**, 737.

(16) For examples of chlorination of amino alcohols with $SOCl_2$ in the absence of bases by adding $SOCl_2$ to amino alcohol solution, see: (a) Gursky, M. E.; Ponomarev, V. A.; Pershin, D. G.; Bubnov, Y. N.; Antipin, M. Y.; Lyssenko, K. A. *Russ. Chem. Bull.* **2002**, *51*, 1562. (b) Foubelo, F.; Gómez, C.; Gutiérrez, A.; Yus, M. *J. Heterocycl. Chem.* **2000**, *37*, 1061. (c) Howarth, N. M.; Malpass, J. R.; Smith, C. R. *Tetrahedron* **1998**, *54*, 10899. (d) Gursky, M. E.; Potapova, T. V.; Bubnov, Y. N. *Izv. Akad. Nauk., Ser Khim.* **1998**, 1450. (e) Bubnov, Y. N.; Zykov, A. Y.; Ignatenko, A. V.; Mikhailovsky, A. G.; Shklyaev, Y. V.; Shklyaev, V. S. *Izv. Akad. Nauk., Ser Khim.* **1996**, 935. (f) Granier, C.; Guilard, R. *Tetrahedron* **1995**, *51*, 1197. (g) Grigg, R.; Santhakumar, V.; Sridharan, V.; Thornton-Pett, M.; Brideg, A. W. *Tetreahedron* **1993**, *49*, 5177. (h) Takano, S.; Inomata, K.; Sato, T.; Ogasawara, K. *Chem. Commun.* **1989**, 1591. (i) Barbry, D.; Couturier, D.; Ricart, G. *Synthesis* **1980**, 387. (j) Sturm, P. A.; Cory, M.; Henry, D. W. *J. Med. Chem.* **1977**, *20*, 1333. (k) Giacet, C.; Bécue, G. *C. R. Acad. Sci., C* **1967**, *264*, 103.

(17) It is known that the formation of sulfinamides from the corresponding *N*- or *O*-sulfinylated species is accelerated in the presence of bases.[8,14]

(18) Although a slurry was obtained after prolonged agitation of the reaction mixture at ambient temperature, the precipitation of the HCl salt, which can be isolated and characterized, was believed to be a result of solubility-driven equilibrium shift. See more discussion in the text.

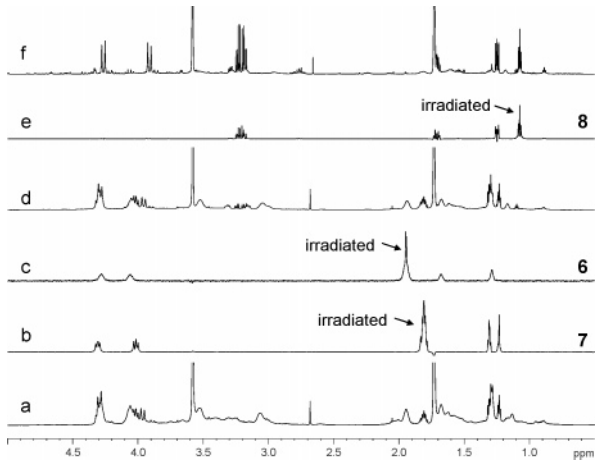
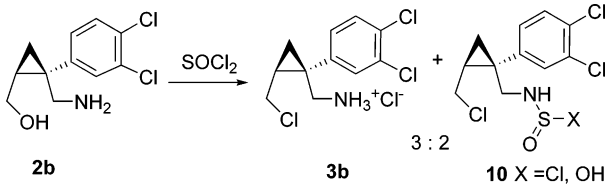


FIGURE 1. NMR spectra of the reaction sequence in the chlorination of **4** in d_8-THF. (a) ^{1}H NMR spectrum at $t = 45$ min at 0 °C, after 1.5 equiv of $SOCl_2$ was added to a solution of **4** in one portion at 0 °C. (b) TOCSY spectrum obtained by irradiating the solution from part a at 1.81 ppm.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

SCHEME 3. Chlorination of 2b with $SOCl_2$

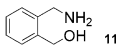
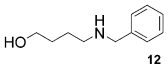
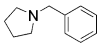
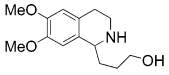
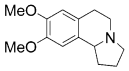
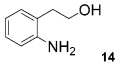
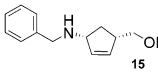
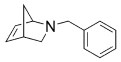
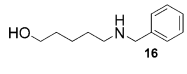
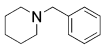
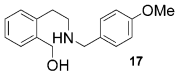
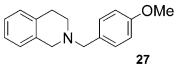
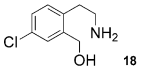
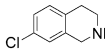
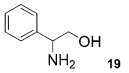
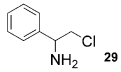
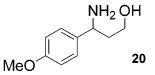
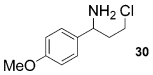


$SOCl_2$ (1.2 equiv) in d_8-THF, NMR studies (see the Supporting Information, Figure S1) of the crude reaction mixture before aqueous base quench clearly showed the complete formation of the two products, protonated salt **3b** and sulfamic intermediate **10**, in about 3:2 ratio (Scheme 3).[19] The 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*-sulfinylation step as well as the "inevitable" *N*-sulfinylation 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*-sulfinylated 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**, X = Cl) in the acidic inverse-addition reaction media, because the nucleophilic amine species that could react with these *N*-sulfinylated 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 $(MeOCH_2)_2$ 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

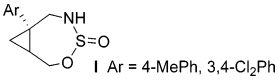
TABLE 1. Direct Chlorination/Cyclization of Amino Alcohols

Entry	Starting Material	Conditions[a] Chlorination	Conditions[a] Cyclization	Product	Yield (%)[b]
1	 11	$(MeOCH_2)_2$ r.t.	r.t.	 21	83[c]
2	 12	$(MeOCH_2)_2$ r.t.	r.t.	 22	94
3	 13	CH_2Cl_2 40 °C	$(MeOCH_2)_2$ 40 °C, 3h	 23	95
4	 14	$(MeOCH_2)_2$ or *i*-PrOAc r.t.	60 °C overnight	 24	94
5	 15	CH_2Cl_2 r.t.	$(MeOCH_2)_2$ 80 °C, 5 days	 25	90
6	 16	$(MeOCH_2)_2$ r.t.	r.t.	 26	92[c]
7	 17	$(MeOCH_2)_2$ r.t.	40 °C	 27	96[c]
8	 18	$(MeOCH_2)_2$ r.t.	r.t.	 28	79
9	 19	$(MeOCH_2)_2$ r.t.	N/A	 29	99
10	 20	$(MeOCH_2)_2$ 40 °C	N/A	 30	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.

(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, $(MeOCH_2)_2$, and $CHCl_3$.

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



I Ar = 4-MePh, 3,4-Cl_2Ph

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/cyclodeydration 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 $(MeOCH_2)_2$ or *i*-PrOAc or CH_2Cl_2 was added over several hours to a solution of $SOCl_2$ (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 $SOCl_2$. 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.

(21) This process was successfully and reproducibly carried out in 5 kg scale with 1.2 equiv of $SOCl_2$.

(22) **13** is commercially available. For leading references of the synthesis of crispine A, see: (a) King, F. D. *Tetrahedron* **2007**, *63*, 2053. (b) Knöelker, H.-J.; Agarwal, S. *Tetrahedron Lett.* **2005**, *46*, 1173.

(23) For examples of relative rates of cyclization as a function of ring size, see: (a) Mandolini, L. *Adv. Phys. Org. Chem.* **1986**, *22*, 1. (b) Winnik, M. A. *Chem. Rev.* **1981**, *81*, 491. (c) Galli, C.; Illuminati, G.; Mandolini, L.; Tamborra, P. *J. Am. Chem. Soc.* **1977**, *99*, 2591.

Experimental Section

General Procedure. To a solution of $SOCl_2$ (1.2−3 equiv) in a solvent such as *i*-PrOAc or $(MeOCH_2)_2$ or CH_2Cl_2 (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 Na_3PO_4. For these substrates cyclized at ambient temperature, the separated organic layer was washed with water and brine, and then dried over Na_2SO_4. 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.

(1*R*,5*S*)-1-(4-Methylphenyl)-3-azabicyclo[3,10]hexane [(+)-Bicifadine, 1a]. To a solution of $SOCl_2$ (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). ^{1}H 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). ^{13}C 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 $C_{12}H_{16}ClN$: 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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