One-Step Synthesis of Chiral Guanidinium Salts from Phosgeniminium Salts

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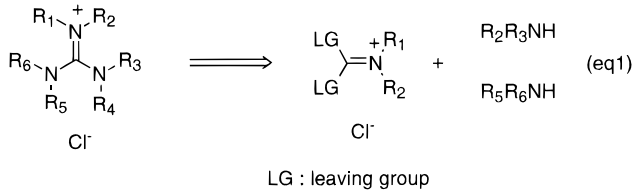
Introduction

Guanidinium salts have attracted increasing interest in recent years. The importance of guanidinium salts is featured in many biologically active compounds where they are widely used for molecular recognition of oxyanions such as carboxylates or phosphates, due to their ability to set a pair of strong zwitterionic hydrogen bonds with the guanidinium moiety.[1,2] This property has been recently exploited in the preparation of guanidinium-based catalysts for many transformations.[3]

Classically, guanidinium salts are obtained by protonation or alkylation of guanidines. Various methods have been developed to access the guanidine moiety through intermediates such as thioureas,[4] aminoiminomethanesulfonic acids,[5] chloroformamidines,[6] dichloroisocyanides,[7] carbodiimides,[8] or cyanamides[1b] and through Mitsunobu protocol.[9] However, methods which involve two or more steps can restrict the range of substituents that can be introduced on the guanidinium moiety.

In this paper, we describe the first one-step synthesis of guanidinium salts from non-guanidine precursors. Indeed, we anticipated that guanidinium salts should be readily accessible by a convergent process combining two secondary amines with a highly reactive electrophilic iminium synthon (eq 1).



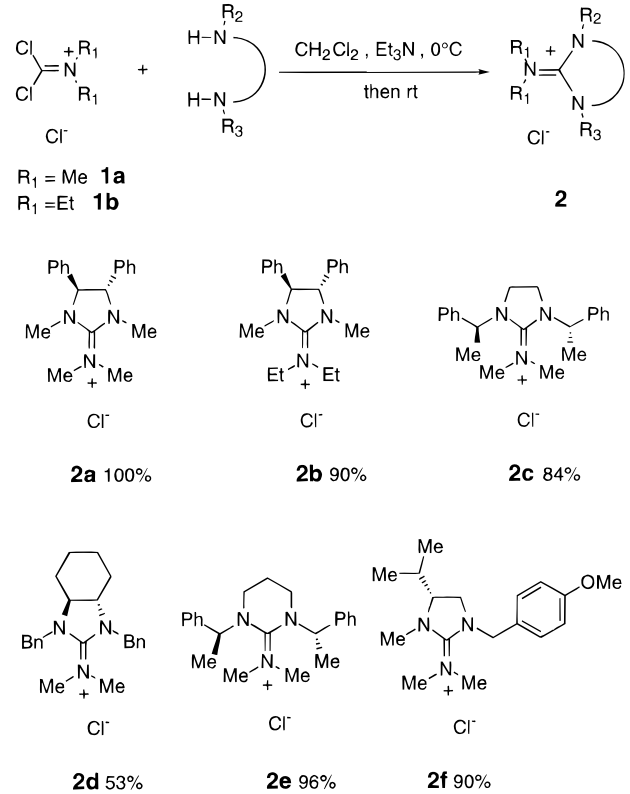
Results and Discussion

The iminium synthons of choice are *N,N*-dialkylphosgeniminium salts **1**. Several reviews have brought to light the use of those powerful electrophilic reagents in synthesis.[10] Phosgeniminium salts can be easily prepared by chlorination of the corresponding dithiurams or thiocarbamoyl chlorides following the procedure previously detailed in the literature.[11]

The reactions of phosgeniminium salts **1** with chiral secondary diamines were performed by adding a mixture of 1 equiv of the appropriate diamine and 2 equiv of triethylamine to a suspension of phosgeniminium salt **1** in dichloromethane at 0 °C. Complete solubilization of the starting iminium salt indicated that the reaction was complete. Treatment of the reaction mixture with 15% NaOH and evaporation of the organic phase afforded a crude oil which was allowed to stand overnight in dry ether. The guanidinium salts **2** were isolated in 53−100% yields (Scheme 1).

The above method provides a direct route to enantiomerically pure guanidininum salts from numerous readily available chiral diamines. Attempts to extend this protocol to secondary tosylated diamines were unsuc-

Scheme 1



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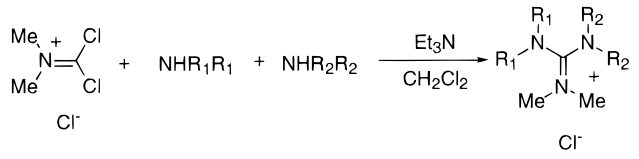
Scheme 2



1a **2**

Table 1. Condensation of Secondary Amines on Compound 1a

NHR_1R_1	NHR_2R_2	compd	yield (%)
$NH(Et)_2$	pyrrolidine	**2g**	100
$NH(Bn)_2$	pyrrolidine	**2h**	88
$NH(iPr)_2$	pyrrolidine	**2i**	76

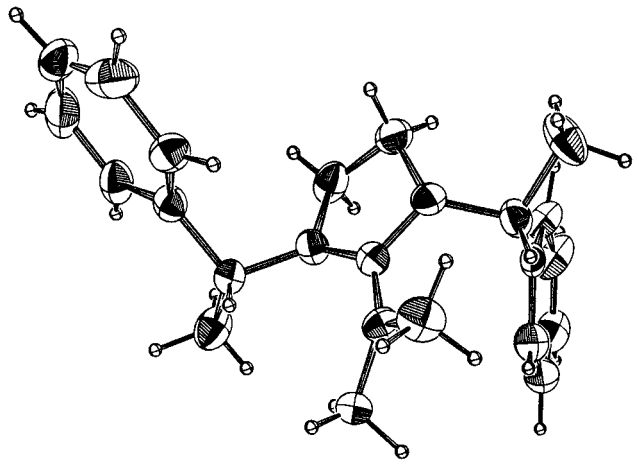


Figure 1.

cessful due to rapid detosylation under the reaction conditions.[12]

However, it was possible to prepare differentially substituted acyclic guanidinium salts by sequentially introducing two different secondary amines (Scheme 2, Table 1). The above procedure had to be modified in order to control the product outcome of the reaction. For two amines of markedly different reactivity, this was achieved by adding 1 equiv of the less reactive amine admixed with 1 equiv of triethylamine to a suspension of the phosgeniminium salt in dichloromethane or chloroform. After complete dissolution, the more reactive amine admixed with an equimolar amount of triethylamine was added to the now *in situ* prepared less electrophilic chloroamidinium intermediate. The desired guanidinium salts were isolated in good to excellent yields.

Guanidinium chlorides **2a**−**i** are hygroscopic and need to be kept under argon at 0 °C. However, these salts can be made more stable by substituting the counterion with PF_6^- or BF_4^-. All compounds were fully characterized by the usual spectroscopic data. Compound **2c** after counterion exchange with PF_6^- has been further characterized by X-ray diffraction analysis (Figure 1).[13]

This crystal structure is particularly interesting because the two phenyl groups interact in plane with the guanidinium moiety. This result suggests that the stacked geometry is more favorable and constitutes a new example of cation-Π interactions that are among the many noncovalent forces that contribute to biological structure.[14]

In summary, this paper describes the first convergent one-step synthesis of racemic and chiral guanidinium salts. The key feature of this strategy is the use of highly electrophilic phosgeniminium salts as precursors. It provides direct access to cyclic as well as acyclic guanidinium salts. Moreover, this new strategy has the added advantage of obtaining guanidinium salts derived from three different secondary amines in a one-step reaction.

Experimental Section

Materials. (*S*)-α-Phenylethylamine was purchased from Aldrich. (1*S*,2*S*)-*N*,*N*′-Dibenzyl-1,2-cyclohexanediamine,[15] (1*S*,2*S*)-*N*,*N*′-dimethyl-1,2-cyclohexanediamine,[15] (1*S*,2*S*)-*N*,*N*′-dimethyl-1,2-diphenyl-1,2-ethanediamine,[15] *N*-methyl-*N*′-(*p*-methoxybenzyl)-1(*R*)-isopropyl-1,2-ethanediamine,[16] *N*,*N*′-bis-(1(*S*)-phenylethyl)-1,2-ethanediamine,[17] *N*,*N*′-bis(1(*S*)-phenylethyl)-1,3-propanediamine,[17] and phosgeniminium salts **1a** and **1b**[11] were prepared as described in the literature. ^1H and ^{13}C NMR spectra were recorded in either $CDCl_3$ or CD_3OD with a 200 or 300 MHz spectrometer. Melting points could not be measured because guanidinium salts are hygroscopic.

General Procedure for the Preparation of Cyclic Guanidinium Salts. To a suspension of 1 equiv of phosgeniminium salt in dry CH_2Cl_2 (0.3 M) at 0 °C was added dropwise a mixture of 1 equiv of diamine and 2 equiv of triethylamine in CH_2Cl_2 (0.3 M). After 10 min at 0 °C, stirring was maintained at room temperature until completion of the reaction (complete solubilization of the phosgeniminium salt). The mixture was treated with 15% NaOH and brine. The organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure. The residue was then allowed to stand in dry ether overnight. The upper ethereal layer of the resulting biphasic mixture was removed, and the lower phase containing the guanidinium salt was washed with ether. The guanidinium salt was finally obtained as a solid or as an oil and was stored at 0 °C under an inert atmosphere. Analytically pure compounds were obtained by crystallization or by preparative reverse phase HPLC purification (ZORBAX SB C18, reverse phase). Only compound **2d** could not be prepared in a satisfactory state of purity because of partial decomposition on the column or during crystallization.

***N*,*N*,*N*′,*N*″-Tetramethyl-*N*′,*N*″-(1(*S*),2(*S*)-diphenylethylene)guanidinium Chloride (2a).** Crude compound **2a** was obtained as a white solid (100%): analytically pure compound was obtained by preparative HPLC purification; $[\alpha]^{25}_D = -90.3$ ($c = 0.034$, $CHCl_3$); ^1H NMR (CD_3OD, 300 MHz) δ 7.47−7.31 (m, 10H), 4.64 (s, 2H), 3.27 (s, 6H), 3.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 165.2, 135.6, 129.4, 127.1, 75.2, 41.5, 36.9; IR (neat) 1642, 1536 cm^{-1}; HRMS calcd for $C_{19}H_{24}N_3$ (cation) 294.1970, found 294.1964; HPLC (CH_3OH/H_2O, 40/60, 0.1% TFA, 1.5 mL/min) t_R 7 min.

***N*,*N*-Diethyl-*N*′,*N*″-dimethyl-*N*′,*N*″-(1(*S*),2(*S*)-diphenylethylene)guanidinium Chloride (2b).** Crude compound **2b** was obtained as a white solid (90%): analytically pure compound was obtained by preparative HPLC purification; $[\alpha]^{25}_D = -74.5$ ($c = 0.07$, $CHCl_3$); ^1H NMR (CD_3OD, 300 MHz) δ 7.50−7.31 (m, 10H), 4.72 (s, 2H), 3.62 (q, $J = 7.0$ Hz, 4H), 3.00 (s, 6H), 1.39 (t, $J = 7.2$ Hz, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 165.8, 135.5, 129.4, 127.5, 74.9, 44.4, 36.6, 13.6; IR (neat) 1608, 1547 cm^{-1}; HRMS calcd for $C_{21}H_{28}N_3$ (cation) 322.2283, found 322.2271; HPLC (CH_3OH/H_2O, 40/60, 0.1% TFA, 1.5 mL/min) t_R 9 min.

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(13) The authors have deposited atomic coordinates for this structure in the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

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***N,N*-Dimethyl-*N′,N″*-bis((*S*)-α-phenylethyl)-*N′,N″*-ethyleneguanidinium Chloride (2c).** Compound **2c** was purified by crystallization (C_6H_6/$CHCl_3$ 1/1) and obtained as a white solid (84%): $[\alpha]^{25}_D = +50.7$ ($c = 0.065$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.41−7.23 (m, 10H), 5.10 (q , $J = 6.9$ Hz, 2H), 3.48 (s, 4H), 3.23 (s, 6H), 1.64 (d, $J = 7.0$ Hz, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 162.7, 138.1, 128.8, 128.1, 125.7, 55.8, 41.9, 40.8, 17.7; IR (neat) 1609, 1546 cm^{-1}; HRMS calcd for $C_{21}H_{28}N_3$ (cation) 322.2283, found 322.2281. X-ray for compound **2c** with PF_6^- as counterion: orthorombic, $P2_12_12_1$, $a = 8.686$ Å, $b = 12.252$ Å, $c = 21.419$ Å, $V = 2279$ Å^{-3}, $Z = 4$.

***N,N*-Dimethyl-*N′,N″*-dibenzyl-1(*S*),2(*S*)-phenyleneguanidinium Chloride (2d).** This compound isolated as a white solid could not be obtained with satisfactory purity after several crystallizations (CH_2Cl_2/ether) or HPLC purification: yield: 53%; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.37−7.27 (m, 10H), $\delta_A = 4.98$ and $\delta_B = 4.59$ (AB system, $J_{AB} = 17.6$ Hz, 2H), 3.68 (m, 2H), 3.03 (s, 6H), 1.89−0.97 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.2, 135.7, 128.9, 127.6, 125.7, 67.6, 51.3, 41.3, 27.8, 23.6; IR (neat) 2941, 1692, 1632 cm^{-1}; HRMS calcd for $C_{23}H_{30}N_3$ (cation) 348.2440, found 348.2453.

***N,N*-Dimethyl-*N′,N″*-bis((*S*)-α-phenylethyl)-*N′,N″*-trimethyleneguanidinium Chloride (2e).** Crude compound **2e** was obtained as a white solid (96%): analytically pure compound was obtained by preparative HPLC purification; $[\alpha]^{25}_D = +196.0$ ($c = 0.15$, $CHCl_3$); ^{1}H NMR (CD_3OD, 200 MHz) δ 7.47−7.33 (m, 10H), 5.17 (q, $J = 7.1$ Hz, 2H), 3.24 (s, 6H), 3.11 (m, 2 H), 2.90 (m, 2H), 1.76 (d, $J = 7.1$ Hz, 6H), 1.15 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 160.9, 136.9, 128.5, 128.1, 126.1, 76.4, 58.5, 40.4, 39.3, 23.7, 15.4; IR (neat) 1547 cm^{-1}; HRMS calcd for $C_{22}H_{30}N_3$ (cation) 336.2440, found 336.2417; HPLC (CH_3OH/H_2O, 40/60, 0.1% TFA, 1.5 mL/min) t_R 14 min.

***N,N*-Dimethyl-*N′*-methyl-*N″*-(*p*-methoxybenzyl)-*N′,N″*-(1(*R*)-isopropylethylene)guanidinium Chloride (2f).** Crude compound **2f** was obtained as a white solid (90%): analytically pure compound could be obtained by preparative HPLC purification or crystallization (C_6H_6/$CHCl_3$ 1/1); $[\alpha]^{25}_D = +71.6$ ($c = 0.07$, $CHCl_3$); ^{1}H NMR (CD_3OD, 300 MHz) δ 7.26 (d, $J = 8.6$ Hz, 2H), 6.97 (d, $J = 8.4$ Hz, 2H), 4.54 (δ_A) and 4.48 (δ_B) (AB system, $J_{AB} = 15.8$ Hz, 2H), 3.94 (t, 1H), 3.60 (s, 3H), 3.57 (m, 1H), 3.23 (m, 1H), 3.13 (s, 6H), 3.12 (s, 3H), 1.78 (m, $J = 6.6$ Hz, 1H), 0.88 (d, $J = 6.8$ Hz, 3H), 0.77 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 163.3, 159.4, 128.5, 125.5, 114.3, 66.9, 55.1, 51.8, 49.1, 47.6, 40.2, 37.2, 30.6, 17.2, 16.1; IR (neat) 1634, 1551 cm^{-1}; HRMS calcd for $C_{17}H_{28}N_3O_1$ (cation) 290.2232, found 290.2214; HPLC (CH_3OH/H_2O 50/50, 0.1% TFA, 1.5 mL/min) t_R 10 min.

***N,N*-Dimethyl-*N′,N′*-diethyl-*N″,N″*-tetramethyleneguanidinium Chloride (2g).** Crude compound **2g** was obtained as a colorless oil (90%): analytically pure compound was obtained by preparative HPLC purification; yield 100%; ^{1}H NMR (CD_3OD, 300 MHz) δ 3.44 (m, 4H), 3.29 (q, $J = 7.0$ Hz, 4H), 2.96 (s, 6H), 2.02 (m, 4H), 1.20 (t, $J = 7.2$ Hz, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 159.3, 49.4, 45.6, 43.3, 42.0, 40.1, 24.8, 24.3, 12.8; IR (neat) 1573 cm^{-1}; HRMS calcd for $C_{11}H_{24}N_3$ (cation) 198.1970, found 198.1966; HPLC (CH_3OH/H_2O, 25/75, 0.1% TFA, 1.5 mL/min) t_R 4 min.

***N,N*-Dimethyl-*N′,N′*-dibenzyl-*N″,N″*-tetramethyleneguanidinium Chloride (2h).** Crude compound **2h** was obtained as a white solid (88%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.40−7.15 (m, 10H), 4.04 (br s, 4H), 3.39 (m, 4H), 2.90 (s, 6H), 1.95 (m, 2H), 1.81 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 159.5, 133.9, 129.1, 128.6, 53.7, 49.9, 49.2, 39.9, 24.8, 24.4; IR (neat) 1584, 1537 cm^{-1}; HRMS calcd for $C_{21}H_{28}N_3$ (cation) 322.2283, found 322.2309.

***N,N*-Dimethyl-*N′,N′*-diisopropyl-*N″,N″*-tetramethyleneguanidinium Chloride (2i).** Crude compound **2i** was obtained as a white solid (76%): analytically pure compound was obtained by preparative HPLC purification; ^{1}H NMR (CD_3OD, 300 MHz) δ 3.71 (h, $J = 7.0$ Hz, 2H), 3.46 (m, 4H), 3.01 (s, 6H), 2.05 (m, 4H), 1.37 (d, $J = 6.8$ Hz, 12H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 160.4, 51.9, 50.0, 47.8, 46.3, 24.7, 24.1, 22.4; IR (neat) 1578, 1518 cm^{-1}; HRMS calcd for $C_{13}H_{28}N_3$ (cation) 226.2283, found 226.2287; HPLC (CH_3OH/H_2O, 30/70, 0.1% TFA, 1.5 mL/min) t_R 5 min.

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Supporting Information Available: ^{1}H NMR spectrum of compounds **2a**−**i** (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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