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Improved Synthesis of Dialkylaminopyrrolines

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ABSTRACT

The literature synthesis of 5-dialkylamino-3,4-dihydro-2H-pyrroles from 5-methoxy-3,4-dihydro-2H-pyrrole has been much improved. In initial assays, the pyrrolinium salts obtained on alkylation of the dibutylaminoamide are excellent "naked halide" catalysts.

Key Words: Dialkylaminopyrrolines; Amidinium salts; Naked halide catalysts; Phase transfer catalysis; Chloroformates.

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INTRODUCTION

Hexabutylguanidinium chloride (HBGCl) 1 is an economical “naked chloride” catalyst with exceptional reactivity and high thermal stability.\[1\]

\[
\begin{array}{c}
\text{Bu}_2\text{N} \quad \text{Bu}_2\text{N} \\
\text{Bu}_2\text{N} \quad \text{Bu}_2\text{N}
\end{array}
\]

Resonance delocalization of the plus charge over four positions not only is responsible for the heat stability of 1 but also seems to be a key to its high anionic reactivity in phase transfer processes. Although “fat solubility” is a factor, steric shielding of the anion from the cation does not seem to be important. When solubility is not a significant problem, hexamethylguanidinium chloride (HMGCl) is nearly as active as 1.\[1,2\] In a recent study, biguanidinium chlorides (+ charge spread over 5 N’s and 2 C’s) were only slightly more effective than 1 as “naked chloride” catalysts.\[3\] This led to the efforts reported here to prepare and test low cost amidinium salts (+ spread over 2 N’s and 1 C) in this role.

RESULTS AND DISCUSSION

Because of its very low cost and economical conversion to the activated 2-methoxypyrroline 2, 2-pyrrolidinone seemed an ideal reactant in the preparation of the aminopyrroline precursor 3 of some desired amidinium salts to test as catalysts.

\[
\begin{align*}
\text{N} & \quad \text{O} \\
\text{Me}_2\text{SO}_4 & \quad 60 \degree \text{C} \\
\text{overnight} & \quad \text{Me}_2\text{NH.HCl} \\
\text{HCl cat.} & \quad \text{neat} \\
\text{R}_2\text{NH} & \quad \Delta \\
\text{NR}_2 & \quad \text{R}_2 = \text{dibutyl} \\
\text{R}_2 = \text{piperidino} \\
\text{R}_2 = \text{diethyl}
\end{align*}
\]

While treatment of neat 2-pyrrolidinone with Me₂SO₄ afforded 2 in the reported 71% distilled yield,\[4\] problems were encountered in the subsequent conversion of 2 to dibutylaminopyrroline 3. 2-Methoxypyrroline is reported to react with an equiv. of Me₂NH HCl in ethanol at rt for 24 h to give 2-dimethylaminopyrroline in 84% yield.
Dialkylaminopyrrolines

although the yield is only 43% in the same preparation of 5.\[^5\] Reaction of free Me\(_2\)NH requires a month to get 71% of product.\[^5\]

Because of its enhanced lipophilicity, 2-dibutylaminopyrroline 3 was the desired intermediate in the present research. However, since Bu\(_2\)NH·HCl is not commercially available, the reaction first was tried with Bu\(_2\)NH and an added equiv. of p-toluenesulfonic acid in ethanol (rt, 24 h). No product was obtained, implying that the reaction either required a weaker acid catalyst and/or a significant concentration of free amine nucleophile. When the reaction also was unsatisfactory with 0.1-0.2 equiv. of acetic acid (neat, rt-45°C, 24 h, ca. 30% 3), Bu\(_2\)NH·HCl was made by adding HCl gas to Bu\(_2\)NH. The yields of 3 and its congeners, 4 and 5, under varying conditions using catalytic amounts of HCl are summarized in Table 1.

Key improvements over the literature process include the elimination of solvent thus simplifying workup and reduction in the amount of HCl (note increase in the yield of 5 from 43% to 84%). From Table 1, it is evident that HCl is a strong enough acid to be a good catalyst but not so strong (like pTosOH) that there is no equilibrium with free amine. Above a certain point, increasing the amount of acid reduces the yield. Also, the optimum temperature and acid concentration are functions of amine structure (likely due to differences in basicity and polarity). Since possible mechanisms for this process include several steps where both acid and free amine (as nucleophile and as base) participate, the data are as might be anticipated.

### Table 1. Conversion of 2-methoxypyrrole to various 2-dialkylaminopyrrolines.

<table>
<thead>
<tr>
<th>No.</th>
<th>Amine (R(_2)NH)(^a)</th>
<th>HCl (mol%)</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Distilled yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Dibutylamine</td>
<td>0.1</td>
<td>25</td>
<td>72</td>
<td>No reaction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.2</td>
<td>70</td>
<td>24</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.1</td>
<td>70</td>
<td>24</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.1</td>
<td>80</td>
<td>24</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.3</td>
<td>70</td>
<td>48</td>
<td>79</td>
</tr>
<tr>
<td>4</td>
<td>Piperidine</td>
<td>0.1</td>
<td>70</td>
<td>24</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.1</td>
<td>80</td>
<td>24</td>
<td>63</td>
</tr>
<tr>
<td>5</td>
<td>Diethylamine</td>
<td>0.1</td>
<td>70</td>
<td>24</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.1</td>
<td>60</td>
<td>24</td>
<td>No reaction(^b)</td>
</tr>
</tbody>
</table>

\(^a\)Ratio of amine plus its HCl salt to 2-methoxypyrrole is 1:1.
\(^b\)Diethylamine hydrochloride is insoluble in the reaction mixture at 60°C but soluble at 70°C.
When 3 was alkylated with bromooctadecane, the product salt 6 (54% yield) was stable above 200°C (thermogravimetric analysis at PPG). Alkylation of 3 with benzyl chloride afforded the amidinium salt 7 in 92% yield as an orange gum (used as 60% solution in o-dichlorobenzene in catalyst studies). (When tested, other alkyl and substituted benzyl salts had no advantages over 6 or 7.)

\[
\begin{align*}
6 & \quad (R = \text{octadecyl, } X = \text{Br}) \\
7 & \quad (R = \text{benzyl, } X = \text{Cl})
\end{align*}
\]

In a commercially valuable process, SNPE has converted octanethiol to its thiochloroformate 8 in 100% yield by treating the neat liquid with phosgene in the presence of only 0.2% mole HMGCl. After flushing away excess phosgene and HCl with N₂ followed by vacuum evaporation, the product 8 was effectively pure without distillation (too little catalyst to see by NMR). With other “Cl⁻” catalysts (R₄N⁺Cl⁻, anion exchange resins, and ureas and their products with phosgene, etc.), distillation always was required, because of increased catalyst amount (> 0.01 equiv.) and because yields were variable with by-products present. When this assay was repeated with 0.25 mol% of the new amidinium catalyst 7 at rt for 8 h with triphosgene as the phosgene source (converted to phosgene in the presence of “Cl⁻”[7]) the reaction again was quantitative, with 8 > 99% pure without distillation.

Olofson and Martz together with Senet and co-workers at SNPE obtained the industrially important 1-chloroethyl chloroformate 9 in 96% yield just by stirring acetaldehyde neat with phosgene in the presence of 3 mol% of benzyltributylammonium chloride (rt/1 h).[2a,8]
Also, the yield of 9 was 98% after an h with only 0.5 mol% of HBGCl.[2a] When this reaction was repeated using 4 mol% of 7 with triphosgene as the phosgene source (0 °C/3 h), the yield of 9 was quantitative. The assay also afforded pure 9 with 3 mol% of 6 as the catalyst. However, in both assays side products (acetaldehyde trimer) became significant when the catalyst concentration was reduced.

In conclusion, an understanding of the factors involved has permitted substantial improvement of the literature route to dialkylamino-pyrrolines 3-5. The salts 6 and 7 obtained on alklylation of 3 have useful activity as “naked halide” catalysts.

EXPERIMENTAL

1H and 13C (proton decoupled) NMR spectra were recorded on a Bruker WP 200, DPX 300, or AMX 360 spectrometer. Mass spectral (MS) data were obtained at 70 eV on a Kratos MS-9/50 double-focusing high resolution mass spectrometer.

5-Dialkylamino-3,4-dihydro-2H-pyrroles 3–5

A neat mixture of 5-methoxy-3,4-dihydro-2H-pyrrole 2 (4.95 g, 0.0500 mol), Bu2NH (5.17 g, 0.0400 mol), and Bu2NH·HCl (1.65 g, 0.0100 mol, 20 mol%) (anhyd HCl bubbled into ethereal Bu2NH) was stirred at 70 °C for 24 h. The cooled mixture was neutralized with 21% NaOEt in ethanol (0.75 g, 0.011 mol), then concentrated and distilled to obtain, after a 1.0 g forerun of dibutylamine, 7.80 g (80% yield) of pure 3, b.p.: 100 °C at 1.5 mm. 1H NMR (CDCl3): δ 3.66 (t, 2H, J = 7.4 Hz), 3.22 (t, 4H, J = 7.5 Hz), 2.49 (t, 2H, J = 7.9 Hz), 2.0–1.8 (m, 2H), 1.6–1.2 (m, 8H), 0.92 (t, 6H, J = 7.4 Hz). 13C NMR (CDCl3): δ 167.8, 56.6, 48.6, 31.7, 30.6, 24.0, 20.3, 14.0. MS (EI): m/z (%) 196 (M⁺, 29), 181 (9), 167 (26), 139 (18).

Reaction as above of 2 (4.95 g, 0.0500 mol), piperidine (3.83 g, 0.0450 mol), and piperidine·HCl (0.61 g, 0.0050 mol, 10 mol%) at 70 °C for 24 h, followed by neutralization with 21% NaOEt/EtOH (0.41 g, 0.006 mol) afforded 7.20 g (95% yield) of pure 4, b.p.: 90–91 °C at 2.5 mm (lit.[5]: 90–91 °C at 2.5 mm). 1H NMR (CDCl3): δ 3.65 (t, 2H, J = 7.1 Hz), 3.4–3.2 (m, 4H), 2.48 (t, 2H, J = 8.2 Hz), 2.1–1.8 (m, 2H), 1.7–1.4 (m, 6H). 13C NMR (CDCl3): δ 168.4, 56.5, 47.2, 31.4, 25.7, 24.6, 23.7. MS (EI): m/z (%) 152 (M⁺, 100).
Similar reaction of 2 (5.94 g, 0.0600 mol), Et₂NH (3.29 g, 0.0450 mol), and Et₂NH·HCl (0.55 g, 0.0050 mol, 10 mol%) (Aldrich) at 70°C for 24 h, then neutralization with 21% NaOEt/EtOH (0.41 g, 0.006 mol) yielded 5.90 g (84%) of pure 5, b.p.: 98–101°C at 25 mm (lit. [5]: 98–101°C at 25 mm). ¹H NMR (CDCl₃): δ 3.67 (t, 2H, \( J = 7.2 \text{ Hz} \)), 3.32 (q, 4H, \( J = 6.9 \text{ Hz} \)), 2.51 (t, 2H, \( J = 8.3 \text{ Hz} \)), 2.0–1.9 (m, 2H), 1.13 (t, 6H, \( J = 7.2 \text{ Hz} \)).

N-Alkylpyrrolinium Halides 6, 7

A mixture of 3 (2.5 g, 0.013 mol) and 1-bromooctadecane (5.3 g, 0.016 mol) in CH₃CN (20 mL) was stirred at 90°C (18 h) and then concentrated. A solution of the residue in CH₂Cl₂ (65 mL) was extracted with water (2 × 65 mL), dried (Na₂SO₄), concentrated, and the remaining residue dried in vacuo for 18 h to obtain 3.7 g (54% yield) of pure 6, m.p.: 75–78°C. ¹H NMR (CDCl₃): δ 3.97 (t, 2H, \( J = 7.2 \text{ Hz} \)), 3.6–3.3 (m, 8H), 2.3–2.1 (m, 2H), 1.9–1.7 (m, 6H), 1.5–1.2 (m, 34H), 1.1–0.8 (m, 9H). IR (NaCl): 2368 (sh, w), 1669 cm⁻¹ (s). Thermogravimetric analysis (PPG): stable above 200°C.

A solution of 3 (8.9 g, 0.045 mol) and benzyl chloride (7.5 g, 0.059 mol) in CH₃CN (30 mL) was stirred at 90°C overnight. After concentration, the remaining orange gum was dried in vacuo at 60°C for 2 h, then dissolved in CH₂Cl₂ (50 mL), extracted with water (2 × 15 mL), and back extracted with CH₂Cl₂ (2 × 15 mL). The combined organic layers were dried (Na₂SO₄) and concentrated, and the orange gum was triturated in ether and dried in vacuo at 80°C overnight to obtain 13.3 g (92% yield) of pure 7. ¹H NMR (CDCl₃): δ 7.6–7.2 (m, 6H), 4.98 (s, 2H), 4.00 (t, 2H, \( J = 7.2 \text{ Hz} \)), 3.6–3.3 (m, 6H), 2.4–2.3 (m, 2H), 2.0–1.6 (m, 4H), 1.5–1.1 (m, 4H), 1.1–0.7 (m, 6H). When the water wash was skipped, 7 was contaminated with the HCl salt of 3.

Catalyst Evaluations

A 60% solution of 7 (0.020 g, 0.062 mmol, 0.25 mol%) in o-dichlorobenzene was added to stirred, cooled (0°C, ice bath) triphosgene (3.0 g, 0.010 mol) under a −70°C condenser. After 5 min, octanethiol (3.7 g, 0.025 mol) (Aldrich) was injected into the yellow liquid and the mixture stirred for 8 h under the −70°C condenser. The excess phosgene was flushed away with N₂ (20–30 s) followed by short vacuum evaporation.
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...to yield pure 1-octyl thiochloroformate. $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 2.93 (t, 2H, $J = 6.0$ Hz), 1.7–1.6 (m, 2H), 1.5–1.2 (m, 10H), 0.89 (t, 3H). $^{13}$C NMR (CDCl$_3$): $\delta$ 166.0, 34.0, 31.8, 29.1, 29.0, 28.7, 28.6, 22.7, 14.1.

A 60% solution of 7 (0.10 g, 0.30 mmol, 0.7 mol%) in $o$-dichlorobenzene was added to stirred, cooled ($-20^\circ$C bath) triphosgene (5.1 g, 0.017 mol) and acetaldehyde (1.9 g, 0.043 mol) under a $-20^\circ$C condenser. After 15 min, more of the catalyst (0.47 g, 1.4 mmol, 3.3 mol%) solution was added. The bath temperature was increased (ice bath), and the mixture was stirred at this temperature for 3 h under the $-20^\circ$C condenser. When the excess phosgene was removed with an N$_2$ stream, 1-chloroethyl chloroformate was obtained in quantitative yield. $^1$H NMR (CDCl$_3$): $\delta$ 6.48 (q, 1 H, $J = 6.0$ Hz), 1.88 (d, 3 H, $J = 6.3$ Hz). $^{13}$C NMR (CDCl$_3$): $\delta$ 148.5, 85.9, 24.4. Yield determined by $^1$H NMR (360 MHz) analysis using the benzylic H’s of the catalyst at $\delta$ 4.91 as an internal standard.

Because the stirred, cooled ($0^\circ$C) mixture of triphosgene (2.1 g, 0.0067 mol) and 6 (0.32 g, 0.60 mmol, 3 mol%) contained two solids, acetaldehyde (5 drops) was added to initiate reaction. After 5 min, the remaining acetaldehyde (0.89 g, 0.020 mol) was added, and the mixture was stirred at $0^\circ$C (3 h). The excess phosgene was evacuated with N$_2$ to yield 9 free of side products ($^1$H NMR analysis).

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