9234 *J. Org. Chem.* **2000,** *65,* 9234−9237

One-Step Conversion of Urea to Tertiary Amines[†]

Navzer (Nozar) Sachinvala,[*,‡] David L. Winsor,[§]
Karol Maskos,[‖] Casey Grimm,[‡] Othman Hamed,[§]
Tyrone L. Vigo,[‡] and Noelie R. Bertoniere[‡]

Southern Regional Research Center (SRRC), USDA-ARS,
1100 Robert E. Lee Blvd., New Orleans, Louisiana 70124,
Hawaii Agriculture Research Center, New Orleans Office,
SRRC, USDA-ARS, 1100 Robert E. Lee Blvd.,
New Orleans, Louisiana 70124, and Coordinated
Instrumentation Facility, 604 Lindy Boggs Building,
Tulane University, New Orleans, Louisiana 70118

nozar@commserver.srrc.usda.gov

Received July 24, 2000

Introduction

Although tertiary amines are widely used in industry and new uses for them continue to emerge,[1−10] convenient one-step procedures for their direct preparation from urea (**1**) do not exist. To date, the chemical literature discusses stepwise methods for their preparation that involve the folowing: (1) N-alkylation of ammonia with alcohols in the presence of dehydrating agents to generate mixtures of primary, secondary, and tertiary amines;[11] (2) oxidation of alcohols to aldehydes, followed by the formation of imines (upon reaction with secondary amines), which are then reduced to tertiary amines;[12] (3) N-alkylation of ammonia and amines with alkyl halides in the presence of mineral acids and transition metals to generate mixtures of substituted amines;[13] (4) N-alkylation of ammonia with alkyl halides at high temperatures and pressures to obtain mixtures of mono-, di-, and trisubstituted amines;[14] (5) N-alkylation of secondary amines with alkyl halides in the presence of bases;[15] (6) disproportionation of quaternary ammonium salts (Hofmann degradation) to form trisubstituted amines (and alcohols or olefins).[16−18]

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[*] To whom correspondence should be addressed. Phone (fax): 504-286-4324 (4271).

[†] Dedicated to Professor Frederick W. Foss, on the occasion of his retirement from the Department of Chemistry, Winona State University, Winona, MN.

[‡] Southern Regional Research Center.

[§] Hawaii Agricultural Research Center.

[‖] Tulane University.

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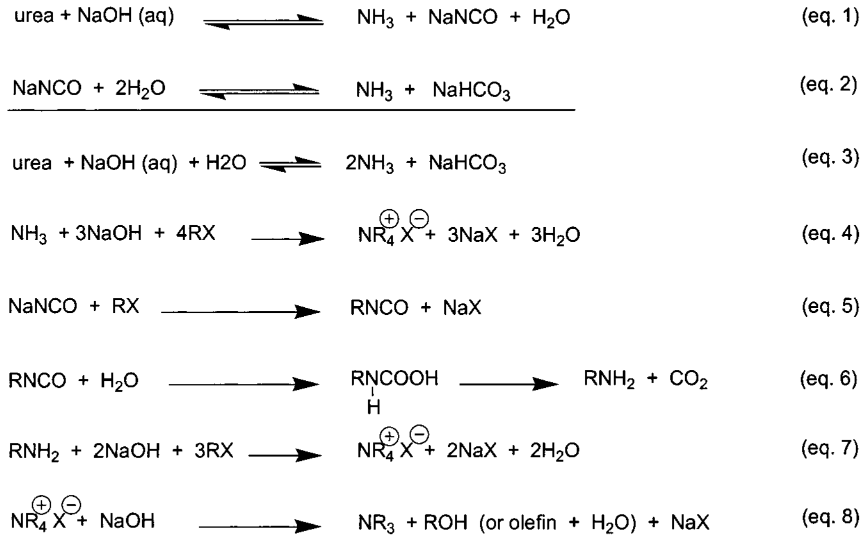

$$\text{urea} + \text{NaOH (aq)} \rightleftharpoons NH_3 + NaNCO + H_2O \qquad \text{(eq. 1)}$$

$$NaNCO + 2H_2O \rightleftharpoons NH_3 + NaHCO_3 \qquad \text{(eq. 2)}$$

$$\text{urea} + \text{NaOH (aq)} + H2O \rightleftharpoons 2NH_3 + NaHCO_3 \qquad \text{(eq. 3)}$$

$$NH_3 + 3NaOH + 4RX \longrightarrow NR_4^{\oplus}X^{\ominus} + 3NaX + 3H_2O \qquad \text{(eq. 4)}$$

$$NaNCO + RX \longrightarrow RNCO + NaX \qquad \text{(eq. 5)}$$

$$RNCO + H_2O \longrightarrow \underset{\text{H}}{\text{RNCOOH}} \longrightarrow RNH_2 + CO_2 \qquad \text{(eq. 6)}$$

$$RNH_2 + 2NaOH + 3RX \longrightarrow NR_4^{\oplus}X^{\ominus} + 2NaX + 2H_2O \qquad \text{(eq. 7)}$$

$$NR_4^{\oplus}X^{\ominus} + NaOH \longrightarrow NR_3 + ROH \text{ (or olefin } + H_2O) + NaX \qquad \text{(eq. 8)}$$

Figure 1. Proposed reaction pathways for the transformation of urea to trisubstituted amines.

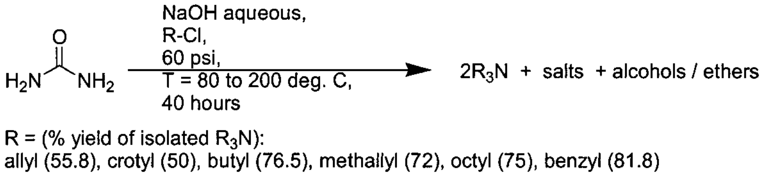

Figure 2. Synthesis of trisubstituted amines from urea.

Recently, we needed research quantities of functionalized trisubstituted amines for the development of new flame-resistant compounds that are also formaldehyde free cross-linking agents for permanent-press textile fabrics, polymers, and composites. We decided not to prepare them in a stepwise manner from ammonia because the procedures are not convenient. We also decided not to prepare them from amines, because amine-based starting materials are expensive for bulk industry applications. Furthermore, we need a one-step procedure that could easily and safely be reproduced by personnel in textile and fiber processing industries who may neither be proficient in organic synthesis nor have the facilities for elaborate synthetic procedures. Therefore, our need for various trisubstituted amines transformed into an agenda to obtain them in good yields without using ammonia or amines.

Our insight into their syntheses was guided by the realization that in aqueous base urea (**1**) decomposes to ammonia, isocyanates, and carbonate salts (Figure 1, eqs 1–3).[19] However, in anhydrous media under phase transfer conditions, the acyl amine group in urea can be exchanged or N-alkylated.[20] Both anhydrous reactions generate *N*-alkylureas. We conjectured that tertiary amines could be generated from urea, if **1** was first decomposed to ammonia upon reaction with aqueous sodium hydroxide and the ammonia then reacted with the alkylating agents present in the aqueous mixture at low (to moderate) pressures and temperatures. Alternatively, urea could hydrolyze to sodium isocyanate (Figure 1, eq 1),[19] which could then alkylate to produce alkyl isocyanates (Figure 1, eq 5).[21] Thereafter, following conversion to *N*-alkylcarbamic acid and decarboxylation, we surmised that the resulting alkylamines could react further to form tertiary amines (Figure 1, eqs 6–8).[22] To restrict the formation of tetrasubstituted ammonium salts, we postulated that slightly above 3 molar equiv of alkylating agent and hydroxide base per nitrogen would be needed to keep their concentration negligible. Furthermore, in situ disproportionation of quaternary ammonium salts to tertiary amines (Hofmann degradation, Figure 1, eq 8)[16] by hydroxides,[16] hydrides,[17] ammonia, and other amines[18] could be exploited to obtain tertiary amines. Therefore, we decided to explore our postulates to develop a general method for making the trisubstituted amines from urea (Figure 2).

Results and Discussion

Urea was added to an aqueous solution of NaOH in a glass-lined Parr vessel. To this was added the alkyl, allyl, or benzyl halide, the vessel was sealed and pressurized to ~60 psi with nitrogen gas at ambient temperature, and the mixture was stirred at the required temperature (see Experimental Section and Table 1) for 40 h. The organic contents (tertiary amines, alcohols, and ethers) were then separated from the inorganic salts in the aqueous phase by extraction with ether. Liquid trisubstituted amine products were purified by fractional distillation, and tribenzylamine was purified by recrystallization from methanol. All tertiary amines reported herein are known compounds and were confirmed by GC-MS, carbon-13 NMR spectrometry, and elemental analysis.

Following each reaction, the stainless steel stirring shaft and paddles were observed to darken. This may be due to the reaction of hot concentrated sodium hydroxide with stainless steel.[23] While reaction temperatures for the synthesis of triallyl- (**2**), tricrotyl- (**3**), and trimethallyl- (**4**) amines were low (80 °C), the synthesis of tributyl- (**5**) and trioctyl- (**6**) amines with chloride reagents

Table 1. General Conditions for Tertiary Amine Synthesis from Urea

R_3N no.	halide used	°C[a]	product bp or mp	% yield
2	allyl chloride, 244.9 g	80	148−150 °C, atm (lit.[24] 150−151)	55.8
3	crotyl chloride, 290 g	80	106−107 °C, ~70 mmHg	50.0
4	methallyl chloride, 290 g	80	101−103 °C, ~70 mmHg	72.0
5	butyl bromide, 438.5 g	120	56−58 °C, ~4.0 mmHg	76.5
6	octyl bromide, 681 g	200	200−202 °C, ~4.0 mmHg	75.0
7	benzyl chloride, 783 g	120	93.4 (DSC)	81.8

[a] Reaction temperature.

required 200 °C to proceed in less than 50% yields. Use of butyl and octyl bromides generated the desired tertiary amines in ~80 and ~75% yields at 120 and 200 °C, respectively. Tribenzylamine (**7**) was produced by the reaction of urea with benzyl chloride in aqueous base at 120 °C. Triallyl, trimethallyl, and tricrotylamines were found in water even after the aqueous layers were extracted three times with ether (observed by GC-MS). It appeared that the water-soluble byproducts of these amines might be increasing their solubility in water. Byproducts (isolated by fractional distillation) of all trisubstituted amine syntheses were alcohols and ethers as determined by ^{13}C NMR and GC-MS. When reactions were conducted at ambient pressures, mixtures of mono-, di-, and trisubstituted amines were obtained. When times were less than about 30 h for reactions conducted in the pressure vessel, yields of the trisubstituted amines were lower. Thereafter, the reaction time of 40 h was set for convenience. Quaternary ammonium salts were detected

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in appreciable concentrations (>10%) in product mixtures when the molar ratio of alkylating agent and base to nitrogen was >4:1.

While the approaches for the synthesis of tertiary amines in the literature (1850 to present) are ingenious, none afford access to trisubstituted amines directly from urea in good yields in aqueous media. Hereafter, we want to explore combinations of electrophiles to obtain unsymmetrical (di- and trisubstituted) and polymeric amines via this new method. In addition we are converting some tertiary amine products to flame-resistant permanent-press finishes for textiles. This method is flexible and affords environmental and cost benefits; therefore, we expect it to find easy acceptance in industrial syntheses.

Experimental Section

Reactions were conducted in a glass-lined Parr pressure vessel model 4522M (2L) under a positive pressure of N_2. All organic reagents and solvents (reagent grade) were purchased from the Aldrich Chemical Co. and were used without further purification. ^{13}C spectra were obtained at 125.776 MHz (on a GE Omega 500) using a 5-mm dual probe and recorded at 25 °C in $CDCl_3$. For GC-MS, samples were dissolved in hexane at a concentration of ~1 part per thousand. A 1 μL aliquot of each sample was analyzed by GC/MS using an HP 5970 quadrupole mass filter. The samples were injected into the GC in split mode at a ratio of ~50:1 and employing helium as the carrier gas. The injector temperature was held at 270 °C. The capillary column was 25 m in length, with a 0.25 mm i.d., and a stationary phase of 95% dimethylsiloxane and 5% diphenylsiloxane. The GC oven temperature was held for 1 min at 50 °C and then ramped at 5 °C/min to 100 °C. A second ramp of 10 °C/min was then used to a final temperature of 300 °C, where the oven was held for 4 min, giving a total run time of 35 min. The mass filter was scanned from *m/z* 45 to *m/z* 450 under electron ionization conditions. IR spectra of neat liquid films (KBr plates) were recorded on a MIDAC Prospect IR (model PRS) in transmission mode at a resolution of 4 cm^{-1}. Melting point was determined using a Shimadzu differential scanning calorimeter (DSC-50) under nitrogen (flow rate, 20 mL/min). Elemental analyses were performed by Desert Analytics, Tucson, AZ.

For the preparations of triallyl-, tricrotyl-, trimethallyl-, tributyl-, and trioctylamines the following procedure was used: Urea (30.0 g, 0.5 mol) was suspended in aqueous NaOH (50% w/w, 169 mL, 128 g of NaOH in solution, 3.2 mol, 3.2 equiv/N). The organic halide (3.2 mol, 3.2 equiv/N) was added to the vessel in one portion, the vessel was sealed and pressurized with nitrogen gas (60 psi, 20 °C), and the contents were stirred and allowed to react for 40 h at the temperature specified in Table 1. The mixture was then cooled to room temperature and the vessel depressurized. The mixture was then diluted with water (~1 L) and extracted with ethyl ether (3 × 250 mL). The organic layer was then washed with brine (500 mL), dried over anhydrous sodium sulfate, filtered, and distilled under reduced pressure to isolate the desired triamine (Table 1). Details for the synthesis of tribenzylamine are given below.

Triallylamine (2). ^{13}C NMR ($CDCl_3$): δ 56.7, 117.8, 135.9. GC MS (EI) for $C_9H_{15}N$ (*m/e*): calcd 137.12; found molecular ion 137; base peak 110 (loss of 27, C_2H_3, a vinyl radical fragment). Retention time: 11.28 min. Anal. Calcd for $C_9H_{15}N$: C, 78.77; H, 11.02; N, 10.21. Found: C, 77.66; H, 11.03; N, 9.98.

Tricrotylamine (3). ^{13}C NMR: trans isomer ($CDCl_3$), δ 18.1, 55.5, 128.6, 128.7; cis isomer, δ 13.3, 49.6, 126.7, 128.0. GC MS (EI) for $C_{12}H_{21}N$ (*m/e*): calcd 179.17; found molecular ion $M^+ - 1 = 178$; base peak 178 (loss of 1, H). Retention time: 20.48–21.91 min (mixture of isomers). Anal. Calcd for $C_{12}H_{21}N$: C, 80.38; H, 11.81; N, 7.81. Found: C, 78.78; H, 11.89; N, 7.60.

Trimethallylamine (4). ^{13}C NMR ($CDCl_3$): δ 21.0, 61.0, 112.9, 144.4. GC MS (EI) for $C_{12}H_{21}N$ (*m/e*): calcd 179.17; found molecular ion 179, base peak 138 (loss of 41, C_3H_5, a 2-propenyl radical fragment). Retention time: 16.07 min. Anal. Calcd for $C_{12}H_{21}N$: C, 80.38; H, 11.81; N, 7.81. Found: C, 79.33; H, 11.67; N, 7.80.

Tributylamine (5). ^{13}C NMR ($CDCl_3$): δ 14.4 21.1, 29.6 54.3. GC MS (EI) for $C_{12}H_{27}N$ (*m/e*): calcd 185.21; found molecular ion 185, base peak 142 (loss of 43, C_3H_7, a propyl radical fragment). Retention time: 17.28 min. Anal. Calcd for $C_{12}H_{27}N$: C, 77.76; H, 14.69; N, 7.56. Found: C, 76.63; H, 15.03; N, 7.69.

Trioctylamine (6). ^{13}C NMR ($CDCl_3$): δ 14.4, 23.0, 24.5, 28.0, 29.7, 30.0, 32.2, 54.6. GC MS (EI) for $C_{24}H_{51}N$ (*m/e*): calcd 353.40; found molecular ion 353, base peak 254 (loss of 99, C_7H_{15}, a heptyl radical fragment). Retention time: 30.79 min. Anal. Calcd for $C_{24}H_{51}N$: C, 81.51; H, 14.53; N, 3.96. Found: C, 80.70; H, 15.00; N, 4.13.

Tribenzylamine (7). Urea (60.0 g, 1.0 mol), aqueous NaOH (50% w/w, 337.0 mL, 6.4 mol, 3.2 equiv/N), and benzyl chloride (712 mL, 783 g, 6.2 mol, 3.1 equiv/N) were pressurized (60 psi, 20 °C), and the contents were allowed to react at 120 °C for 40 h. The reaction mixture was then filtered through a sintered glass funnel. The insoluble tribenzylamine was washed serially with water (2 × 2 L, to remove inorganic salts) and then methanol (1 L) to remove benzyl alcohol and benzyl ether. Thereafter, the product was dried in vacuo (50 °C, 0.1 mmHg, overnight) and then recrystallized from methanol in 81.8% yield (470 g, 1.64 mol). Differential scanning calorimetry showed the compound to melt at 93.4 °C (peak temperature, nitrogen flow rate = 20 mL/min.; heating rate = 5 °C/min.; lit.[24] 91–94 °C). ^{13}C NMR ($CDCl_3$): δ 140.1, 129.2, 128.7, 127.3, 58.3. GC MS (EI) for $C_{21}H_{21}N$ (*m/e*): calcd 287.16; found molecular ion 287, base peak 91 (loss of 27, C_7H_7, a benzyl radical fragment). Retention time: 31.99 min. Anal. Calcd for $C_{21}H_{21}N$: C, 87.76; H, 7.37; N, 4.87. Found: C, 88.05; H, 7.50; N, 4.92.

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