Improvement upon a Largely Forgotten Method for the Synthesis of N-Alkyl Urazoles

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Article

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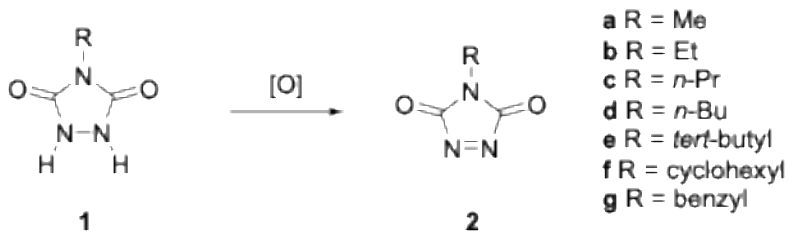
Abstract

N-Alkyl urazoles are important heterocyclic compounds that serve as important precursors to potent *N*-alkyl 1,2,4-triazoline-3,5-dione electrophiles. Traditional methods for urazole synthesis have relied upon the use of toxic isocyanates. We have modified and optimized an overlooked and poorly-described literature method for the synthesis of urazoles that now avoids the use of isocyanates, limits the use of solvents, and provides urazoles without the need for purification steps. A variety of urazoles are afforded in good to high yields.

Keywords: 1,2,4-triazoline-3,5-dione; urazole; semicarbazide; sustainable

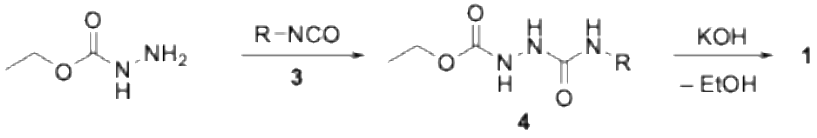
1. Introduction

N-Alkyl urazoles (**1**, Scheme 1) are direct precursors, via oxidation, to the corresponding azo compounds *N*-alkyl 1,2,4-triazoline-3,5-diones (**2**, RTADs) [1]. RTADS are potent electrophilic reagents that readily engage in a variety of useful reactions including Diels-Alder cycloadditions with dienes, [2+2] cycloadditions with suitably-substituted alkenes, and ene reactions [1]. Such general organic reactivity has recently been directed towards practical applications such as "click"-type reactivity, polymer coupling, and surface modification [1,2].



Scheme 1. The oxidation of *N*-alkyl urazoles **1** to the corresponding triazolinediones **2**.

The traditional method for the synthesis of *N*-alkyl urazoles was devised by Zinner in 1961 [3], and then refined and developed into an established Organic Synthesis procedure by Cookson in 1971 (Scheme 2) [4]. Unfortunately, however, this synthetic method relies upon access to appropriate alkyl isocyanates (**3**) as starting materials [5]. Due to the known dangers of working with isocyanates, the commercial availability of isocyanates has severely diminished, thereby hindering direct access to urazole compounds via the Cookson route. This has led to the development of alternative routes for the synthesis of urazoles that have been recently summarized by Du Prez [1].



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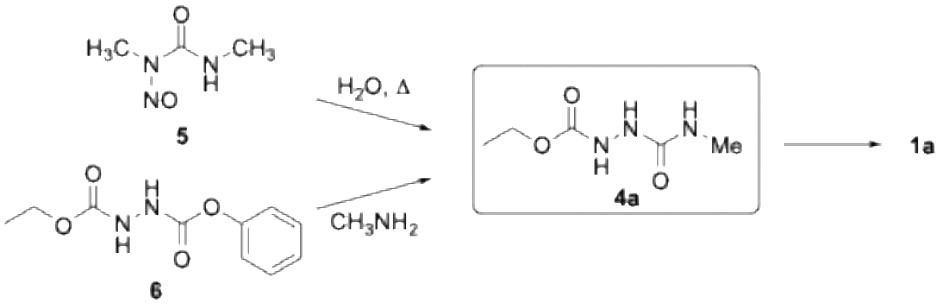
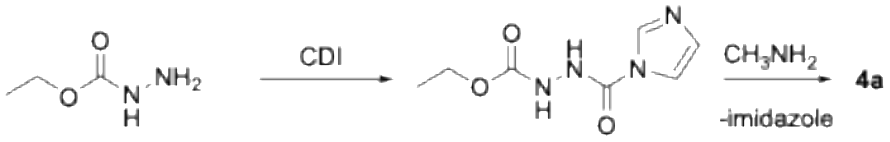
Scheme 2. Zinner and Cookson method for the synthesis of urazoles.

Triazolinedione **2a** is one of the most commonly used triazolinediones in the literature [6]. The lack of commercial availability of methylisocyanate, the Cookson precursor to *N*-methyl urazole (**1a**), is especially problematic because compound **2a** is a convenient TAD derivative with which to work. Its particular usefulness derives from the unique chemical shift of the *N*-methyl signal in the ^{1}H NMR spectrum (a singlet at ~3 ppm) that makes following reactions, and analyzing crude reaction mixtures, relatively straightforward [6]. Therefore, several years ago our group developed a method for the synthesis of urazole **1a** via the *in situ* generation of methyl isocyanate from *N*-nitroso dimethylurea **5** (see Scheme 3), as well as via the reaction of methylamine with ethyl phenyl hydrazine-1,2-dicarboxylate **6** [6]. These reactions afforded semicarbazide **4a** which could then be cyclized to the urazole **1a** under standard Cookson conditions (see Scheme 2). Gratifyingly, we also found that derivatives of **4** other than just the *N*-methyl were also accessible from compound **6** (i.e., **1d**-**g**) [6].

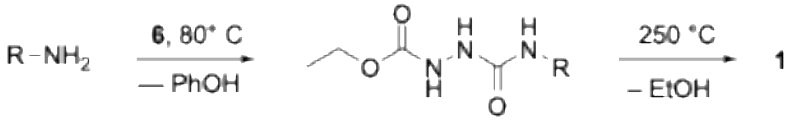


Scheme 3. Two other reported methods for the synthesis of semicarbazide **4a** (R = Me), the precursor to urazole **1a**.

Recently, Sarlah reported a "scalable" synthesis of *N*-methyl urazole **1a** that accessed semicarbazide intermediate **4** (R = Me) using carbonyl diimidazole (CDI) as the reactive carbonyl component (Scheme 4) [7]. While this method permits a multigram synthesis of *N*-methyl urazole, the process requires concentration of a reaction mixture under high vacuum followed by several recrystallization steps to afford the desired **4a**. While still an excellent method for large scale synthesis of **1a**, it is not particularly convenient for ordinary lab use, nor was it expanded to urazole substituents other than that of *N*-methyl. Finally, in related work Du Prez reported what was described as a "sustainable" synthetic route for urazoles [8]. This synthetic route eliminated the use of reaction solvents by substituting bulk heating of intermediate compounds (Scheme 5). The major limitation to the method was that the amines needed to be of relatively high boiling point (the smallest being butylamine) for the method to be viable.



Scheme 4. Synthesis of semicarbazide **4a** via the use of CDI.



Scheme 5. Du Prez's method for the synthesis of urazoles.

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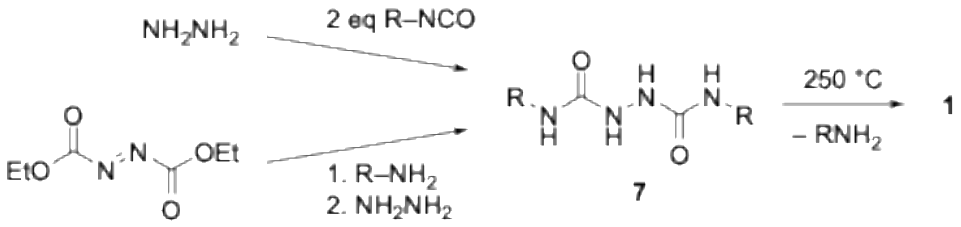
We were recently fortunate to come across a previously described method for the synthesis of urazoles that seems to have been overlooked in the literature (or at least underappreciated). In a 1967 paper, Priehradny reported that heating neat 1,6-dialkylbiureas **7** to relatively high temperatures (~ 250 °C) resulted in spontaneous cyclization to form the corresponding *N*-alkyl urazoles (Scheme 6) [9]. Therefore, this synthesis can be considered to be a "sustainable" method akin to that described earlier by Du Prez (Scheme 5) in that solvent use is avoided in the cyclization step. The major downside to this method is that the synthesis of the required starting 1,6-dialkylbiureas **7** relied upon either the same toxic isocyanates as were used in the Cookson method, or the use of similarly toxic dialkyl azodicarboxylates via a two-step method (see Scheme 6). Additionally, there have also been some reports that the Priedhradny urazole synthesis method has been hard to reproduce [1,4,10]. The lack of reproducibility could be due to the lack of experimental detail provided in the original paper [9]. Therefore, for these reasons the use of Priehradny's synthetic method for urazoles has been largely ignored.



Scheme 6. Priehradny's synthesis of urazoles (**1**) via thermal cyclization of 1,6-dialkylbiureas **7**.

In this paper we revitalize Priedhradny's synthetic method by finding a general and highly convenient (i.e., free of purification steps) route for the synthesis of the 1,6-dialkylbiureas precursors (**7**) that eliminates the need for isocyanates and azodicarboxylates. We also refine the solvent-free cyclization of compounds **7** to the corresponding urazoles and provide important reaction details missing from the Priehradny paper that now allow for practical and reproducible results. We hope that by avoiding toxic reagents, optimizing reaction steps, and providing key details to the cyclization step that ensures reproducibility that this very convenient, but previously overlooked method, might enjoy greater use.

2. Materials and Methods

2.1. General Methods

All solvents and reagents were obtained commercially and used as received. Heating of 1,6-dialkylbisureas **7** were conducted in 5 mL conical vials left open to the atmosphere (in a suitable hood) using a metal hot plate whose temperature was closely controlled by a digitally-controlled unit. Chemical shifts (^{1}H and ^{13}C) are reported in units of parts per million downfield from TMS. IR spectra were collected as solids pressed against a ZnSe ATR crystal. High-resolution mass spectra (HRMS) were acquired via electron spray ionization on an LTQ-FTMS hybrid mass spectrometer.

2.2. Experimental Procedures

2.2.1 *N,N*-Diphenyl-1,2-hydrazinedicarboxamide (8). To a stirring mixture of 1.05 g (12.6 mmol) of hydrazine hydrate (60% by weight) and 2.76 g (2 equiv) of sodium carbonate in 125 mL of THF at 0 °C was added 4 g (25.5 mmol) of phenyl chloroformate dropwise via Pasteur pipette. The mixture was allowed to warm to room temperature and stirred overnight after which a white precipitate appeared. 50 mL of 0.5 M aq. HCl was added to the mixture and the THF removed via rotary evaporation to leave the white solid suspended in the aqueous layer. The mixture was filtered and the separated solid rinsed well with 100 mL of water. After air drying, the product was dried in the oven at 90 °C for at least two hours after which 84.7 g (96%) of **8** was isolated as a fluffy white solid,

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m.p. 153-154 °C: ^{1}H NMR (DMSO-d$_6$) δ 9.44-10.10 (multiple s, 2H, *N*H), 7.42 (t, *J* = 7.8 Hz, 4H), 7.25 (t, *J* = 7.8 Hz, 2H), 7.13 (d, *J* = 7.8 Hz, 4H); ^{13}C NMR (DMSO-d$_6$) δ 154.8, 150.5, 129.6, 125.6, 121.6. The spectra were consistent with those reported in the literature [11].

2.2.3 1,6-Dimethylbisurea (7a). To a stirring solution of 0.5 g (1.83 mmol) of compound **8** in 15 mL of CH_3CN was added 5.50 mL (6 eq) of a 2 M solution of methyl amine in THF via syringe. A precipitate began to form some minutes later and stirring was continued overnight. The resulting white precipitate was isolated via vacuum filtration and washed with 10 mL of water. Air drying afforded 0.25 g (94% yield) of **7a** as a white powder, m.p. 243-244 °C: IR (ATR) cm^{-1} 3311.6, 1662.0, 1561.1, 1413.9, 1325.6,; ^{1}H NMR (CF_3CO_2D) δ 11.82 (br s, 4H, *N*H), 2.99 (s, 6H); ^{13}C NMR (CF_3CO_2D) δ 164.2, 28.1; HRMS (ESI) m/z [M+H]+ Calcd for $C_4H_{11}N_4O_2$ 147.08765; Found 147.08695.

2.2.4 1,6-Diethylbisurea (7b). To a stirring solution of 0.5 g (1.83 mmol) of compound **8** in 15 mL of CH_3CN was added 5.50 mL (6 eq) of a 2 M solution of ethyl amine in THF via syringe. A precipitate began to form some minutes later and stirring was continued overnight. The resulting white precipitate was isolated via vacuum filtration and washed with 10 mL of water. Air drying afforded 0.28 g (88% yield) of **7b** as a white powder, m.p. 238-239 °C: IR (ATR) cm^{-1} 3297.7, 1665.0, 1554.2, 1328.6,; ^{1}H NMR (CF_3CO_2D) δ 11.73 (br s, 4H, *N*H), 3.47 (q, *J* = 7.7 Hz, 4H), 1.28 (t, *J* = 7.7 Hz, 6H); ^{13}C NMR (CF_3CO_2D) δ 160.3, 34.9, 11.7; HRMS (ESI) m/z [M+H]+ Calcd for $C_6H_{15}N_4O_2$ 175.11895; Found 175.11874.

2.2.5 1,6-Di-n-propylbisurea (7c). To a stirring solution of 0.5 g (1.83 mmol) of compound **8** in 20 mL of CH_3CN was added 0.64 g (6 eq) of n-propyl amine dropwise via Pasteur pipette. The solution became cloudy after approximately 10 mins, and stirring was continued overnight. The resulting white precipitate was isolated via vacuum filtration and washed with 10 mL of water. Air drying afforded 0.32 g (87% yield) of **7c** as a white powder, m.p. 243-244 °C: IR (ATR) cm^{-1} 3290.0, 2961.8, 1658.5, 1560.2, 1335.3; ^{1}H NMR (CF_3CO_2D) δ 11.72 (br s, 4H, *N*H), 3.39 (t, *J* = 7.3 Hz, 4H), 1.68 (h, *J* = 7.3 Hz, 4H), 0.99 (t, *J* = 7.3 Hz, 6H); ^{13}C NMR (CF_3CO_2D) δ 164.1, 44.8, 24.1, 11.5; HRMS (ESI) m/z [M+H]+ Calcd for $C_8H_{19}N_4O_2$ 203.15025; Found 203.15006.

2.2.6 1,6-Di-n-butylbisurea (7d). To a stirring solution of 0.5 g (1.83 mmol) of compound **8** in 20 mL of CH_3CN was added 0.80 g (6 eq) of n-butyl amine dropwise via Pasteur pipette. The solution became cloudy after approximately 10 mins, and stirring was continued overnight. The resulting white precipitate was isolated via vacuum filtration and washed with 10 mL of water. Air drying afforded 0.38 g (90% yield) of **7d** as a white powder, m.p. 246-247 °C: IR (ATR) cm^{-1} 3295.0, 2956.6, 1659.6, 1555.3, 1377.0,; ^{1}H NMR (CF_3CO_2D) δ 11.82 (br s, 4H, *N*H), 3.43 (t, *J* = 7.3 Hz, 4H), 1.63 (p, *J* = 7.3 Hz, 4H), 1.42 (h, *J* = 7.3 Hz, 4H), 0.98 (t, *J* = 7.3 Hz, 6H); ^{13}C NMR (CF_3CO_2D) δ 163.5, 42.8, 32.9, 21.3, 14.0; HRMS (ESI) m/z [M+H]+ Calcd for $C_{10}H_{23}N_4O_2$ 231.18155; Found 231.18157.

2.2.7 1,6-Di-*tert*-butylbisurea (7e). To a stirring solution of 0.5 g (1.83 mmol) of compound **8** in 20 mL of CH_3CN was added 0.80 g (6 eq) of *tert*-butyl amine dropwise via Pasteur pipette. After stirring overnight, the solution was concentrated via rotary evaporation to afford a pale orange solid. The solid was taken up in 20 mL of CH_2Cl_2 and washed 2 x 20 mL 0.5 M aq. NaOH. The organic layer was then dried over Na_2SO_4, filtered, and concentrated to afford 0.24 g (57% yield) of **7e** as a white solid, m.p. 189-190 °C: IR (ATR) cm^{-1} 3314.7, 2968.1, 1654.9, 1558.4, 1363.3, 1217.6; ^{1}H NMR ($CDCl_3$) δ 6.88 (br s, 2H, *N*H), 5.62 (br s, 2H, *N*H), 1.34 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 158.1, 50.6, 29.1; HRMS (ESI) m/z [M+H]+ Calcd for $C_{10}H_{23}N_4O_2$ 231.18155; Found 231.18111.

2.2.8 1,6-Dicyclohexylbisurea (7g). To a stirring solution of 0.5 g (1.83 mmol) of compound **8** in 20 mL of CH_3CN was added 1.09 g (6 eq) of cyclohexyl amine dropwise via Pasteur pipette. After stirring overnight, the resulting white precipitate was isolated via vacuum filtration and washed with 10 mL of water. Air drying afforded 0.45 g (77% yield) of **7g** as a white powder, m.p. 203-204 °C: IR (ATR) cm^{-1} 3675.5, 2972.0, 1646.4, 1531.5, 1393.9, 1066.0; ^{1}H NMR (CF_3CO_2D) δ 11.69 (br s, 4H, *N*H), 3.77 (m, 2H), 1.97 (br s, 4H), 1.87 (br s, 4H), 1.72 (br d, *J* = 12.4 Hz, 2H), 1.35-1.50 (m, 8H), 1.26 (m, 2H); ^{13}C NMR (CF_3CO_2D) δ 162.6, 53.6, 34.6, 26.6, 26.5; HRMS (ESI) m/z [M+H]+ Calcd for $C_{14}H_{27}N_4O_2$ 283.21285; Found 283.21103.

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2.2.9 1,6-Dibenzylbisurea (7g). To a stirring solution of 0.5 g (1.83 mmol) of compound **8** in 20 mL of CH_3CN was added 1.17 g (6 eq) of benzyl amine dropwise via Pasteur pipette. After stirring overnight, the resulting white precipitate was isolated via vacuum filtration and washed with 10 mL of water. Air drying afforded 0.42 g (76% yield) of **7g** as a white powder, m.p. 245-246 °C: IR (ATR) cm^{-1} 3292.2, 1660.3, 1552.1, 1298.6, 1219.0; ^{1}H NMR (CF_3CO_2D) δ 11.68 (br s, 4H, *N*H), 7.26-7.34 (m, 10H), 4.53 (s, 4H); ^{13}C NMR (CF_3CO_2D) δ 163.6, 138.1, 130.89, 130.3, 129.5, 46.6; HRMS (ESI) m/z [M+H]+ Calcd for $C_{16}H_{19}N_4O_2$ 299.15025; Found 299.15007.

2.2.10 *N*-Methylurazole (1a). 100 mg (0.68 mmol) of finely powdered **7a** was heated in a vial to 260 °C over approximately a 10 min period. Visible fuming began to appear at a temperature of ~ 240 °C. As the sample was held at 260 °C it melted to provide a colorless oil. The melt was held at this temperature with occasional swirling to allow liberated methyl amine to escape. After 10 mins, fuming had ceased, and the vial was removed from the heat with swirling to aid in crystallization of the urazole product with cooling. The product was scraped from the vial to afford 62 mg of **1a** as a white crystalline product (80% yield), m.p. 237-238 °C (lit. 232-233 °C [12]): ^{1}H NMR (DMSO-d_6) δ 9.59 (br s, 2H, *N*H), 2.84 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 155.3, 24.3. The spectra were consistent with those reported in the literature [13].

Repeating this process on a larger scale starting with 0.50 g of **7a** afforded 0.39 g (85% yield) of **1a**.

2.2.11 *N*-Ethylurazole (1b). 100 mg (0.68 mmol) of finely powdered **7b** was heated in a vial to 260 °C over approximately a 10 min period. Visible fuming began to appear at a temperature of ~ 240 °C. As the sample was held at 260 °C it melted to provide a colorless oil. The melt was held at this temperature with occasional swirling to allow liberated ethyl amine to escape. After 10 mins, fuming had ceased, and the vial was removed from the heat with swirling to aid in crystallization of the urazole product with cooling. The product was scraped from the vial to afford 68 mg of **1b** as a white crystalline product (80% yield), m.p. 193-194 °C (lit. 195-196 °C [12]): ^{1}H NMR (DMSO-d_6) δ 9.90 (br s, 2H, *N*H), 3.37 (q, *J* = 7.3 ppm, 2H), 1.09 (t, *J* = 7.3 ppm, 3H); ^{13}C NMR (DMSO-d_6) δ 154.9, 32.9, 13.3. The spectra were consistent with those reported in the literature [14].

2.2.12 *N*-Propylurazole (1c). 100 mg (0.68 mmol) of finely powdered **7c** was heated in a vial to 260 °C over approximately a 10 min period. Visible fuming began to appear at a temperature of ~ 240 °C. As the sample was held at 260 °C it melted to provide a colorless oil. The melt was held at this temperature with occasional swirling to allow liberated propyl amine to escape. After 10 mins, fuming had ceased, and the temperature was dropped to 190 °C where it was held for 25 min, again with occasional swirling. After the heating period, the vial was removed from the heat with swirling to aid in crystallization of the urazole product with cooling. The product was scraped from the vial to afford 62 mg of **1c** as a white crystalline product (89% yield), m.p. 166-167 °C (lit. 168-169 °C [12]): ^{1}H NMR (DMSO-d_6) δ 9.90 (br s, 2H, *N*H), 3.30 (t, *J* = 7.4 ppm, 2H), 1.52 (h, *J* = 7.4 ppm, 2H), 0.81 (t, *J* = 7.5 ppm, 3H); ^{13}C NMR (DMSO-d_6) δ 155.2, 39.51, 21.0, 11.0. The spectra were consistent with those reported in the literature [15].

2.2.13 *N*-Butylurazole (1d). 100 mg (0.68 mmol) of finely powdered **7d** was heated in a vial to 260 °C over approximately a 10 min period. Visible fuming began to appear at a temperature of ~ 240 °C. As the sample was held at 260 °C it melted to provide a colorless oil. The melt was held at this temperature with occasional swirling to allow liberated butyl amine to escape. After 15 mins, fuming had ceased, and the temperature was dropped to 190 °C where it was held for 25 min, again with occasional swirling. After the heating period, the vial was removed from the heat with swirling to aid in crystallization of the urazole product with cooling. The product was scraped from the vial to afford 53 mg of **1d** as a white crystalline product (78% yield), m.p. 170-171 °C (lit. 167-168 °C [12]): ^{1}H NMR (DMSO-d_6) δ 10.00 (br s, 2H, *N*H), 3.34 (t, *J* = 7.4 ppm, 2H), 1.50 (p, *J* = 7.4 ppm, 2H), 1.04 (h, *J* = 7.4 ppm, 2H), 0.87 (t, *J* = 7.5 ppm, 3H); ^{13}C NMR (DMSO-d_6) δ 155.2, 37.6, 29.6, 19.4, 13.5. The spectra were consistent with those reported in the literature [13].

Repeating this process on a larger scale starting with 0.95 g of **7d** afforded 0.49 g (75% yield) of **1d**.

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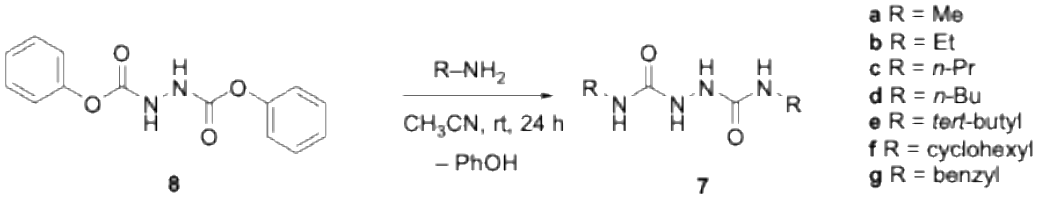
2.2.14 *N*-Cyclohexylurazole (1f). 100 mg (0.68 mmol) of finely powdered **7f** was heated in a vial to 260 °C over approximately a 10 min period. Visible fuming began to appear at a temperature of ~ 250 °C. As the sample was held at 260 °C it melted to provide a colorless oil. The melt was held at this temperature with occasional swirling to allow liberated butyl amine to escape. After 30 min, fuming had ceased, and the temperature was dropped to 190 °C where it was held for 25 min where it solidified. After the heating period, the vial was removed from the heat with swirling to aid in crystallization of the urazole product with cooling. The product was scraped from the vial to afford 55 mg of **1f** as a white crystalline product (85% yield), m.p. 242-243 °C (lit. 239-241 °C [16]): ^{1}H NMR (DMSO-d_6) δ 9.95 (br s, 2H, *NH*), 3.68 (dt, *J* = 12.4, 3.9 Hz, 1H), 2.02 (dg, *J* = 12.4, 3.9 Hz, 1H), 1.76 (br d, 2H), 1.55-1.65 (m, 3H), 1.25 (qt, *J* = 12.4, 3.3 Hz, 1H), 1.12 (dt, *J* = 12.4, 3.0 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 155.3, 50.6, 29.5, 25.8, 25.3. The spectra were consistent with those reported in the literature [16].

2.2.15 *N*-Benzylurazole (1g). 100 mg (0.68 mmol) of finely powdered **7g** was heated in a vial to 260 °C over approximately a 10 min period. Visible fuming began to appear at a temperature of ~ 250 °C. As the sample was held at 260 °C it melted to provide a colorless oil. The melt was held at this temperature with occasional swirling to allow liberated butyl amine to escape. After 1 hr, fuming had ceased, and the temperature dropped to 190 °C where it was held for 25 min, again with occasional swirling. After the heating period, the vial was removed from the heat with swirling to aid in crystallization of the urazole product with cooling. The product was scraped from the vial to afford 60 mg of **1g** as a white crystalline product (94% yield), m.p. 181-182 °C (lit. 182-183 °C [12]): ^{1}H NMR (DMSO-d_6) δ 10.21 (br s, 2H, *NH*), 7.26-7.35 (m, 5H), 4.54 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 154.8, 136.8, 128.6, 127.6, 127.5, 41.3. The spectra were consistent with those reported in the literature [13].

3. Results and Discussion

3.1. Improved Synthesis of 1,6-Dialkylbisureas

Based upon our earlier described success substituting phenol with amines from semicarbazide **6** (see Scheme 4) [6], we considered the possibility of forming the required 1,6-dialkylbisureas **7** via reaction of diphenyl hydrazine-1,2-dicarboxylate **8** (Scheme 7). Compound **8**, itself, is easily synthesized in high yield and purity from the reaction of hydrazine hydrate with two equivalents of phenyl chloroformate in THF [see Materials and Methods section], and isolated via vacuum filtration of the crude reaction mixture without the need for any further purification.



Scheme 7. Synthesis of 1,6-dialkylbisureas **7**.

Addition of amines to **8** successfully and cleanly afforded the desired bisureas **7**. While 2 equivalents of amine at first glance seems adequate for the reaction, we soon realized that the progress of the reaction was quickly stifled by release of the acidic phenol which ties up unreacted amine. Therefore, at least 4 equivalents of amine are necessary to complete the reaction, but we observed that 6 equivalents of amine (i.e., 3 equivalents per carboxylate group) were optimal to afford the corresponding bisureas in good-to-high yield in reasonable time and in a reproducible manner without the need to heat the reaction. Given that the amines used are inexpensive, this did not prove to be a disadvantage. CH_3CN proved to be the optimal solvent for the reaction although THF could be used with only slightly lower yields. Other than the di-*tert*-butyl derivative, the bisurea products are nearly insoluble in either solvent and can be isolated by simple filtration followed by washing with water (to remove phenol byproduct and excess amine) to afford compounds **7** as powdery white solids. The reaction yields are summarized in Table 1. The di-*tert*-butyl derivative **7e** was soluble

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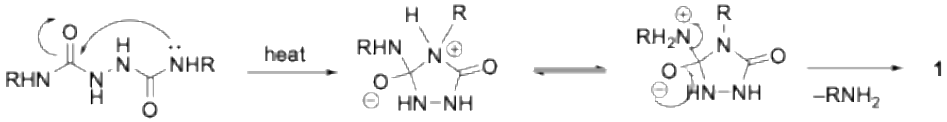
in both organic solvents, however, and necessitated removal of solvent for product isolation. The generally low solubility of the bisureas in typical organic solvents (even in DMSO) necessitated the use of deuterated trifluoroacetic acid as solvent for ^{1}H and ^{13}C NMR spectral analysis, in which they were all readily soluble. The NMR spectra of the isolated solids revealed essentially pure compounds free of any significant phenol contamination (see Supplementary Materials for the ^{1}H and ^{13}C NMR spectra).

Table 1. Synthesis of 1,6-dialkylbisureas **7**.

R	Yield (%)
methyl	96
ethyl	88
n-propyl	87
n-butyl	90
tert-butyl	57
cyclohexyl	77
benzyl	76

3.2. Thermal Cyclization of 1,6-Dialkylbisureas ***7*** *to N-Alkyl Urazoles* ***1****.*

The bisureas **7** all had high melting points (> 180 °C) with most in the range of 230 – 250 °C. Conversion to the urazoles (100 mg samples) occurred readily upon heating neat samples of **7** [9]. At temperatures of ~230-250 °C, amine was released and could be observed to escape via either visible fuming and/or condensation of the amine near the top of the reaction vial. A reasonable mechanism for the conversion is provided in Scheme 8. All of the powders were heated to a final pot temperature of 260 °C to induce the cyclization reaction.



Scheme 8. Proposed mechanism for formation of urazoles **1** from bisalkylureas **7**.

The urazole products **1** all have melting points lower than 260 °C. Therefore, as the cyclization reaction took place, a melt was formed. The melt was occasionally swirled to aid in removal of liberated amine. For bisureas **7a** and **7b**, once fuming stopped, the mixture could be cooled immediately to afford crystalline urazoles **1a** and **1b**. However, for bisureas derived from medium sized amines (i.e., **7c,d**), after fuming ceased, the sample temperature was dropped to 190 °C with continued heating for 25 min to allow time for the amine to completely escape. Cooling of the melt then afforded crystalline products. Longer heating times were generally required for bisureas derived from higher boiling amines (e.g., benzyl and cyclohexyl). Larger scale reactions were also conducted starting with bisureas **7a** (0.5 g) and **7d** (1 g) to afford the corresponding urazole products with comparable yields (see Materials and Methods section).

The identities of the known urazole products were confirmed by ^{1}H and ^{13}C NMR spectroscopy (spectra are provided in the Supporting Information) and melting point comparison with literature data. Specific heating protocols for each of the bisureas are provided in the Materials and Methods section. The yields for the urazole products are provided in Table 2 (column 2) which are generally good to high.

Unfortunately, the *tert*-butyl derivative **7e** failed to provide the corresponding urazole cleanly despite many efforts to optimize the heating protocol. In addition to formation of urazole **1e** as a major product, other unknown products were also formed. The reluctance of **1e** to cleanly cyclize can likely be traced to the sterically bulky *tert*-butyl group that inhibits initial nucleophilic attack of the nitrogen atom on the neighboring carbonyl group in the cyclization process (see Scheme 8).

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Table 2. Yields from thermal cyclization of 1,6-dialkylbisureas **7** to afford *N*-alkyl urazoles **1**.

R =	% Yield
methyl	80
ethyl	92
n-propyl	89
n-butyl	78
cyclohexyl	85
benzyl	94

4. Conclusion

The literature synthesis of urazoles via thermal cyclization of 1,6-dialkylbisureas **7** was a largely forgotten synthetic method [1,9]. The reason for its neglect is presumably due to the poor experimental procedures that were provided at the time which led many to the conclusion that the results were difficult to reproduce. Furthermore, the dependence of the method on toxic reagents such as isocyanates for the synthesis of the bisureas made it unattractive. We have now provided a high yielding and convenient method for the synthesis of the bisurea precursors that not only eliminates the use of isocyanates, but also allows for their isolation via a simple filtration process. Finally, experimental details for the thermal conversion of the bisureas to the desired urazoles have been provided that allow for good-to-high yields of the urazoles in a reproduceable manner.

Supplementary Materials: The following supporting information can be downloaded at: Preprints.org, ^{1}H and ^{13}C NMR spectra and IR spectra for compounds **7a-g**, and ^{1}H and ^{13}C NMR spectra for compounds **8** and **1a-d**, **1f-g**.

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