An Unplanned Synthesis of Symmetrical 1,3-Disubstituted Ureas

[1]SHAHNAZ PERVEEN*, [2]SANA MUSTAFA AND [3]KHALID MOHAMMED KHAN
[1]*PCSIR Laboratories Complex, Shahrah-e-Dr. Salim-uz-zaman Siddiqui, Karachi-75280, Pakistan*
[2]*Department of Chemistry, University of Karachi, Karachi-75270, Pakistan*
[3]*H. E. J. Research Institute of Chemistry, International Center for Chemical and Biological Sciences, University of Karachi, Karachi-75270, Pakistan*

(Received on 26th August 2009, accepted in revised form 22nd December 2009)

Summary: When urea derivatives (*N*-aryl-*N'*,*N'*-dialkyl urea) or (*N*-aryl-*N'*-alkyl/aryl urea) **1a-1u** react with diethylcarbamyl chloride at 50-60 °C symmetrical 1,3-disubstituted ureas **2a-2f** were formed as major products instead of forming ployureas.

Introduction

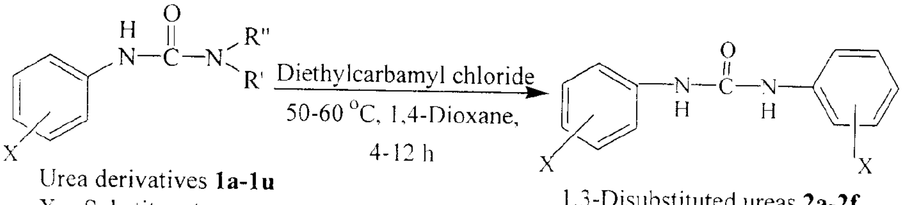
Polyureas are of tremendous biological significance as they are used as anti-HIV agents [1]. They are used as bed liners to form durable coatings to protect against rust and corrosion, as a multipurpose joint fillers, caulking and sealant material. They have significant application in race car body parts, mold making and artificial rock. They are resistant to many fuels and chemicals.

Due to great application of symmetrical 1,3-disubstituted ureas, much attention has been paid to their synthesis. Disubstituted ureas are essential components of drug candidates including HIV protease inhibitor, CCK-B receptor antagonists, and endothelin antagonists [2]. Recently oligoureas have also been introduced as scaffolds for the creation of artificial β-sheets [3] and as peptide backbone mimetics [4]. The symmetrical substituted ureas are found in natural products [5] and act as useful intermediates in synthesis of different chemicals [6, 7]. The traditional synthetic approaches to symmetrical ureas are well known [8, 9]. Unsymmetrical and symmetrical *N*,*N'*-substituted ureas or thioureas are prepared by refluxing carbamyl or thiocarbamyl halide in the presences of an alkaline material and water [10].

The references cited in literature indicated that aliphatic and aromatic amines react with carbamyl or thiocarbamyl chloride [11] to form substituted ureas. In an attempt to synthesize polyurea by reacting *N*-aryl-*N'*, *N'*-dialkyl or *N*-aryl-*N'*-alkyl/aryl ureas (**1a-1u**) with diethylcarbamyl chloride at 50-60 °C considering weak nucleophilicity of NH functional group, surprisingly we isolated symmetrical 1,3-disubstituted ureas as major product. To the best of our knowledge no reaction is reported for the synthesis of symmetrical 1,3-disubstituted ureas in these conditions. In the course of our study to expanded the scope of this reaction, we found that reaction of urea (**1a-1u**) in the above-mentioned conditions afforded 1,3-disubstituted ureas (**2a-2f**). No reaction was observed when reaction was performed without using diethylcarbamyl chloride.

Results and Discussion

The symmetrical 1,3-disubstituted ureas **2a-2f** were synthesized by reacting *N*-aryl-*N'*,*N'*-dialkyl or *N*-aryl-*N'*-alkyl/aryl urea with diethylcarbamyl chloride at 50-60 °C (Scheme 1). The reaction afforded products as solids by only pouring them into ice-cold water with stirring. Recrystallization of the



Urea derivatives **1a-1u**
X = Substituent

1,3-Disubstituted ureas **2a-2f**

Scheme 1

---

*To whom all correspondence should be addressed.

Table-1: Results of Syntheses of Symmetrical 1,3-Disubstituted Ureas

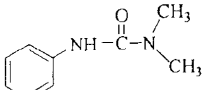
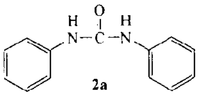
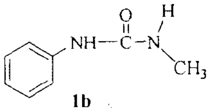
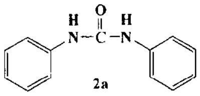
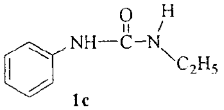
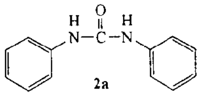
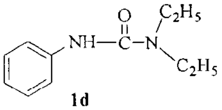
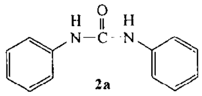
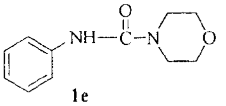
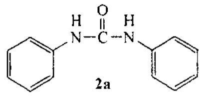
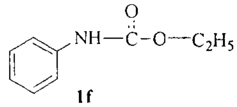
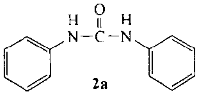
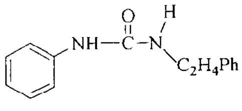
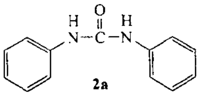
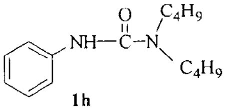
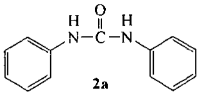
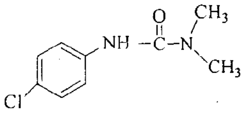
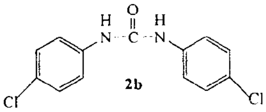
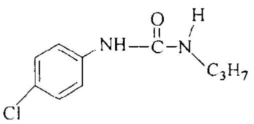
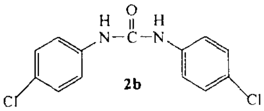
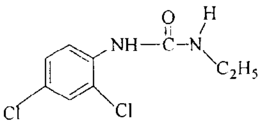
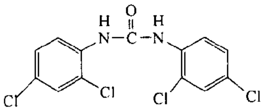
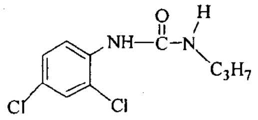
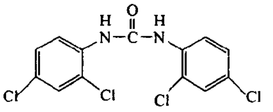
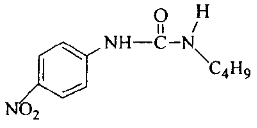
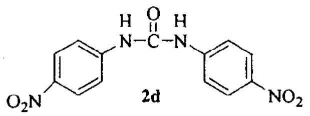
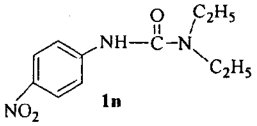
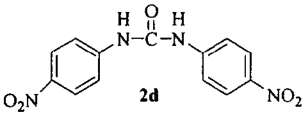
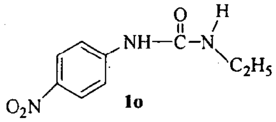
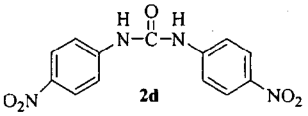
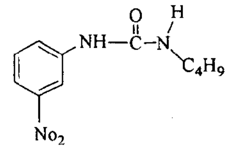
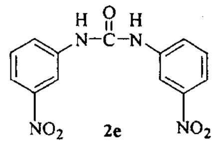
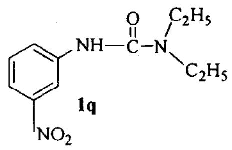
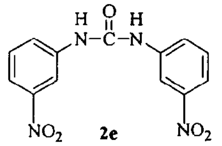
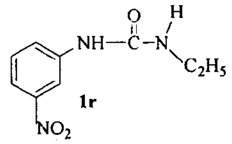
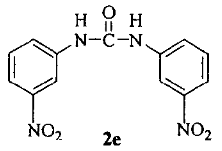
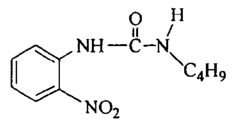
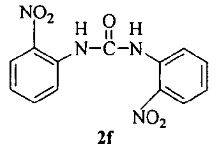
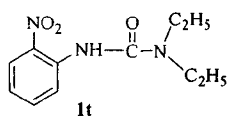
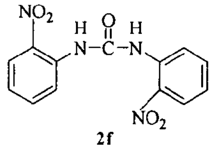
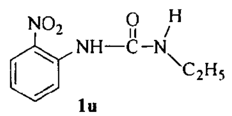
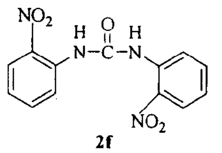
Entry	Subtract	Product	Yield (%)	Reaction Time (h)	M.P. (°C)
1	 1a	 2a	80	4-6	240
2	 1b	 2a	78	4-6	240
3	 1c	 2a	78	4-6	240
4	 1d	 2a	80	4-6	240
5	 1e	 2a	75	10	240
6	 1f	 2a	82	8-10	240
7	 1g	 2a	77	12 hr	240
8	 1h	 2a	74	8-10	240
9	 1i	 2b	81	8-10	306
10	 1j	 2b	80	8-10	306
11	 1k	 2c	79	10-12	Semi solid

Table-1: Continue...

12	 1l	 2c	82	10-12	Semi solid
13	 1m	 2d	80	10-12	310
14	 1n	 2d	83	10-12	310
15	 1o	 2d	81	10-12	310
16	 1p	 2e	82	10-12	242
17	 1q	 2e	85	10-12	242
18	 1r	 2e	85	10-12	242
19	 1s	 2f	82	10-12	227
20	 1t	 2f	86	10-12	227
21	 1u	 2f	85	10-12	227

solid from appropriate solvents gave pure analytical samples.

It was observed that at room temperature the reaction was very slow while on heating at 50-60 °C the reaction was completed in 4-12 h (Scheme-1). In a typical reaction 0.2 mol of *N*-aryl-*N'*,*N'*-dialkyl or *N*-aryl-*N'*-alkyl/aryl urea was treated with 0.1 mol of diethylcarbamyl chloride in the presence of 1,4-dioxane at 50-60 °C and progress of reaction was monitored through TLC. After completion of reaction, the reaction mixture was poured into ice cold water with stirring. The solid was filtered to afford pure 1,3-disubstituted ureas Table-1.

In our proposed mechanism, when the reaction was carried out in 1,4-dioxane with diethylcarbamyl chloride initially weak nucleophilic nitrogen of *N*-aryl-*N'*,*N'*-dialkyl or *N*-aryl-*N'*-alkyl/aryl urea attacks diethylcarbamyl group to form protonated polyurea. The protonated polyurea so formed simultaneously attacked by another molecule of *N*-aryl-*N'*,*N'*-dialkyl or *N*-aryl-*N'*-alkyl/aryl urea which on rearrangement resulted in the formation of 1,3-disubstituted ureas as major products. To ensure the participation of diethylcarbamyl chloride in the reaction, several reactions were carried out without using diethylcarbamyl chloride. No reaction took place in the absence of diethylcarbamyl chloride which indicates the reaction is essentially initiated by diethylcarbamyl chloride to form polyurea first which then converted into 1,3-disubstituted ureas. A total of twenty one un-symmetrical ureas were reacted with diethylcarbamyl chloride which resulted in respective symmetrical ureas. In some cases the minor products were also characterized and found to be symmetrical urea of second part of the initial unsymmetrical urea.

Experimental

^{1}H NMR spectra were recorded in CD_3OD and $CDCl_3$ on a Bruker Aspect AM-300 and 400 MHz using TMS as an internal standard. Chemical shifts are given in ppm. IR spectra were recorded in KBr on a SHIMADZU IR-460 and Bruker vector 22 spectrometer (wave numbers in cm^{-1}). Mass spectra (EIMS) were measured on Finnigan MAT-112 instrument. High resolution EIMS were recorded in Jeol JMS HX-110 spectrometer.

General Procedure for the Synthesis of Ureas

To mixture of 0.2 mol of *N*-aryl-*N'*,*N'*-dialkyl or *N*-aryl-*N'*-alkyl urea in 20 to 25 mL of 1,4-dioxane was added 0.1 mol of diethylcarbamyl chloride initially at room temperature and then at 50-60 °C progress of reaction was monitored *via* TLC. After completion of reaction, the reaction mixture was poured into ice cold water with continuous stirring, solid was filtered and crystallized by appropriate solvent to afford desired product. Elemental analyses were performed on Perkin Elmer analyzer.

1,3-Diphenylurea (2a)

Crystallization by diethyl ether or ethanol gave needle like crystals. R_f = 0.40 ($CHCl_3$; 10.0); mp 240 °C. IR (KBr): ν_{max} 3285, 3194, 3036, 1647, 1597, 1555, 1312 cm^{-1}; UV λ_{max} 254.3 ($\in$ 289.7), 262.9 ($\in$ 285), 275.5 ($\in$ 314.7), 283.57 ($\in$ 333.6); ^{1}H NMR (300 MHz, CD_3OD): δ 7.1-7.75 (m, 10H, Ar. H), 7.43 (brs, 2H, NH); HREIMS: m/z (rel. int.) = 212.0947 [M^+, $C_{13}H_{12}N_2O$ requires 212.2533] (22), 120 (2), 119 (5), 93 (100), 77 (11), 66 (10), 65 (13); Anal. calcd. for: C, 73.56; H, 5.70; N, 13.20. $C_{13}H_{12}N_2O$ requires C, 73.54; H, 5.68; N, 13.18.

4, 4'-Dichlorocarbanilide (2b)

Recrystallization from ethanol gave needle like crystals. mp 306-7 °C. ^{1}H NMR (400 MHz, CD_3OD): δ 9.62 (brs, 2H), 7.94 (dd, 4H, J = 9.0, 2.7 Hz), 7.25 (dd, 4H, J = 9.0, 2.7 Hz); HREIMS: m/z (rel. int.) = 281.247 [M^+, $C_{13}H_{10}N_2OCl_2$ requires 281.137] (15), 245.5 (50), 153.5 (100), 126.5 (80). Anal. calcd. for $C_{13}H_{10}N_2OCl_2$: C, 55.54; H, 3.59; N, 9.96. Found: C, 55.83; H, 3.38; N, 9.78.

2,2', 4,4'-Tetrachlorocarbanilide (2c)

Yield: 79%. ^{1}H NMR (400 MHz, CD_3OD): δ 10.58 (brs, 2H), 8.42 (d, J = 8.8 Hz, 2H), 7.43 (d, J = 2.2 Hz, 2H), 7.24 (dd, J = 8.8, 2.2 Hz, 2H); HREIMS: m/z (rel. int.) = 350.064 [M^+, $C_{13}H_8N_2OCl_4$ requires 350.026] (7), 314.5 (10), 279 (45), 188 (100), 161(37); Anal. calcd. for $C_{13}H_8N_2OCl_4$: C, 44.61; H, 2.30; N, 8.00. Found: C, 44.72; H, 2.80; N, 8.21.

4,4'-Dinitrocarbanilide (2d)

Recrystallization from ethanol gave yellow needle like crystals. R_f = 0.45 ($CHCl_3$: MeOH; 9.7 : 0.3); mp 310 °C. IR ν_{max} (KBr): 3286, 3190, 1649, 1600, 1556, 1312 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD): δ 9.62 (brs, 2H), 8.13 (dd, 4H, J = 8.1, 0.2

Hz), 8.22 (dd, 4H, J = 8.1, 0.2 Hz); HREIMS: m/z (rel. int.) = 302.0650 [M^+, $C_{13}H_{10}N_4O_5$ requires 302.2484] (6), 257 (15), 181 (20), 162 (100), 123 (55). Anal. calcd. for $C_{13}H_{10}N_4O_5$: C, 51.66; H, 3.33; N, 18.54. Found: C, 51.64; H, 3.35; N, 18.58.

3,3'-Dinitrocarbanilide (2e)

Recrystallization from ethanol gave yellow needle like crystals. R_f = 0.42 ($CHCl_3$ 10.0); mp 242 °C. IR ν_{max} (KBr): 3386, 3070, 1720, 1691, 1524, 1417, 1352 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD): δ 9.09 (dd, 2H, J = 7.7, 2.0 Hz), 8.83 (d, 2H, J = 1.5 Hz), 8.03 (dd, 2H, J = 7.7, 2.0 Hz), 7.7 (d, 2H, J = 7.7 Hz); HREIMS: m/z (rel. int.)=302.0650 [M^+, $C_{13}H_{10}N_4O_5$ requires 302.242] (6), 257 (15), 181 (20), 162 (100), 123 (55). Anal. calcd. for $C_{13}H_{10}N_4O_5$: C, 51.66; H, 3.33; N, 18.54. Found: C, 51.54; H, 3.38; N, 18.58.

2,2'-Dinitrocarbanilide (2f)

Recrystallization from benzene gave pale yellow crystals. R_f = 0.69 ($CHCl_3$: MeOH; 9.3 : 0.7); mp 225-227 °C. IR ν_{max} (KBr): 3285, 3194, 1647, 1597, 1555, 1443, 1312 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.82 (dd, 2H, J = 8.0, 1.4 Hz), 8.33 (dd, 2H, J = 8.2, 1.4 Hz), 7.66 (ddd, 2H, J = 8.0, 7.3, 1.4 Hz), 7.38 (ddd, 2H, J = 8.2, 7.3, 1.4 Hz); HREIMS: m/z (rel. int.) = 302.0655 [M^+, $C_{13}H_{10}N_4O_5$ requires 302.2484] (4), 257 (10), 181 (24), 164 (100), 123 (35). Anal. calcd. for $C_{13}H_{10}N_4O_5$: C, 51.66; H, 3.33; N, 18.54. Found: C, 51.63; H, 3.29; N, 18.58.

References

1. J. M. Michael, E. D. Ray, D. C. Alan, P. P. Norton, *United State Patent No.* 5,728,874 (1984).
2. a) P. Y. S. Lam, P. K. Jadhav, C. J. Eyermann, C. N. Hodge, Y. Ru, L. T. Bacheler, J. L. Meek, M. J. Otto, M. M. Rayner, Y. N. Wong, C.-H. Chang, P. C. Weber, D. A. Jackson, T. R. Sharpe, S. Erickson-Viitanen, *Science*, **263**, 380 (1994); b) J. L. Castro, R. G. Ball, H. B. Broughton, M. G. N. Russell, D. Rathbone, A. P. Watt, R. Baker, K. L. Chapman, A. E. Fletcher, S. Patel, A. J. Smith, G. R. Marshall, W. Ryecroft, V. G. Matassa, *Journal Medicinal Chemistry,* **39**, 842 (1996); c) T. W. von Geldern, J. A. Kester, R. Bal, R. J. Wu-Wong, W. Chiou, D. B. Dixon, T. J. Opgenorth, *Journal of Medicinal Chemistry*, **39**, 968 (1996).
3. a) J. S. Nowick, E. M. Smith and G. Noronha, *Journal of Organic Chemistry*, **60**, 7386 (1995); b) J. S. Nowick, S. Mahrus, E. M. Smith and J. W. Ziller, *Journal of the American Chemical Society*, **118**, 1066 (1996); c) J. S. Nowick, D. L. Holmes, G. Mackin, G. Noronha, A. J. Shaka and E. M. Smith, *Journal of the American Chemical Society,* **118**, 2764 (1996); d) D. H. Holmes, E. M. Smith, J. S. Nowick, *Journal of the American Chemical Society*, **119**, 7665 (1997).
4. a) K. Burgess, D. S. Linthicum and H. Shin, *Angewandte Chemie International Edition*, **34**, 907 (1995); b) K. Burgess, J. Ibarzo, D. S. Linthicum, D. H. Russell, H. Shin, A. Shitangkoon, R. Totani and A. J. Zhang, *Journal of the American Chemical Society*, **119**, 1556 (1997); c) J.-M. Kim, Y. Bi, S. J. Paikoff and P. G. Schultz, *Tetrahedron Letters*, **37**, 5305 (1996); d) J.-M. Kim, T. E. Wilson, T. C. Norman and P. G. Schultz, *Tetrahedron Letters*, **37**, 5309 (1996); e) J. A. W. Kruijtzer, D. J. Lefeber and R. M. J. Liskamp, *Tetrahedron Letters,* **38**, 5335 (1997); f) M. E. Wilson and J. S. Nowick. *Tetrahedron Letters*, **39**. 6613 (1998).
5. a) A. Tsopmo, D. Ngnokam, D. Ngamga, J. F. Ayafor and O. Sterner, *Journal Natural Product*, **62**, 1435 (1999); b) Y. Funabashi, S. Tsubotani, K. Koyama, N. Katayama and S. Harada, *Tetrahedron,* **49**, 13 (1993).
6. D. P. Getman, G. A. Decrescenzo, R. M. Heintz, K. L. Reed, J. J. Talley, M. L. Bryant, M. Clare, K. A. Houseman, J. J. Marr, R. A. Mueller, M. L. Vazquez, H. S. Shieh, W. C. Stallings and R. A. Stegeman, *Journal of Medicinal Chemistry,* **36**, 288 (1993).
7. P. Y. S. Lam, Y. Ru, P. K. Jadhav, P. E. Aldrich, G. V. Delucca, C. J. Eyermann, C. H. Chang, G. Emmett, E. R. Holler, W. F. Daneker, L. Z. Li, P. N. Confalone, R. J. McHugh, Q. Han, R. H. Li, J. A. Markwalder, S. P. Seitz, T. R. Sharpe, L. T. Bacheler, M. M. Rayner, R. M. Klabe, L. Y. Shum, D. L. Winslow, D. M. Kornhauser, D. A. Jackson, S. Erickson-Viitanen, C. N. Hodge, *Journal of Medicinal Chemistry,* **39**, 3514 (1996).
8. S. M. A. Hai, S. Perveen, R. A. Khan, K. M. Khan, N. Afza, *Natural Product Research*, **17**, 351 (2003).

9. S. Perveen, S. M. A. Hai, R. A. Khan, K. M. Khan, N. Afza and T. B. Sarfaraz, *Synthetic Communications,* **35**, 1663 (2005), and references therein.
10. S. Charles, Schollenberger, Cuyahoga, Falls, Ohio, *United State Patent No.* 2,722,550 (1955).
11. C. Ivan, Popoff, Ambler, Pa. *United State No.* 3,138,571 (1964).