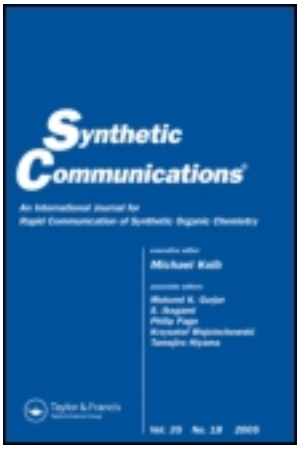

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Expeditious Method for Synthesis of Symmetrical 1,3-Disubstituted Ureas and Thioureas

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Abstract: Symmetrical 1,3-disubstituted ureas and symmetrical thioureas have been synthesized from corresponding isocyanates, diisocyanates, and isothiocyanates by a new versatile, simple, and quick method in the presence of tertiary amines at room temperature. The method under discussion has several advantages over the existing techniques, as it is simple to carry out, does not require complicated equipment, has a simple workup, and does not use expensive chemicals. Moreover, the yields are almost quantitative. This method has potential in commercial applications.

Keywords: 1,3-Disubstituted ureas, diisocynates, isocyanates, tertiary amines, thioisocyanates

INTRODUCTION

During recent years much attention has been paid to the synthesis and application of symmetrical substituted ureas. These are essential components of drug candidates including HIV protease inhibitors, CCK-B receptor antagonists,

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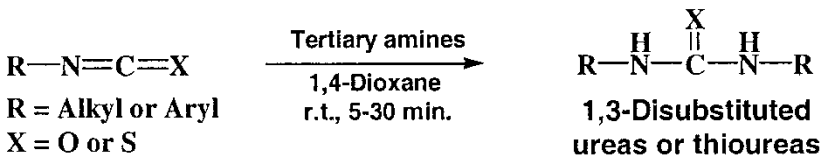
and endothelin antagonists.[1] Recently oligoureas have also been introduced as scaffolds for the creation of artificial β sheets[2] and as peptide backbone mimetics.[3] The symmetrical substituted ureas are found in natural products[4] and act as useful intermediates in the synthesis of different chemicals.[5,6] The traditional synthetic approaches to symmetrical ureas are well documented and standard procedures involve the reactions of amines with phosgene and its derivatives,[7] isocyanates,[8] or carbamates.[8,3b] A report describes synthesis by phenyl diisocyanate in hot pyridine without indicating its mechanism and conversion into urea.[9] A synthesis of 1,3-disubstituted ureas is reported through a reaction of carbonic acid ester with an amine in the presence of catalyst.[10] Several homogenous Pd,[11,12] Ru,[13] Co,[14] Mn,[15] Se,[16,17] and W[18,19] catalysts were also used for the oxidative carbonylation of amine into ureas. Very recently, two procedures have appeared in print: one is by oxidative carbonylation in the presence[20] of $Pd/ZrO_4\text{-}SO_4^{-2}$, but in a majority of cases the actual product was accompanied with a measurable amount of undesired by-products and results are quoted by GC-MS, whereas the other report is a two-step synthesis of disubstituted ureas through reaction of substituted carbamates with an amine.[21]

During the total synthesis of a natural product, we discovered that tertiary amines could promote the reaction of isocyanate to symmetrical ureas without generating intermediate primary amines. Thus, we used three amines as reaction promoters including triethyl amine, pyridine, and 2,6-lutidine for synthesis of different ureas. Herein we describe a general one-step procedure for the preparation of symmetrical substituted ureas and thioureas from the corresponding isocyanates and isothiocyanates in almost quantitative yields.

RESULTS AND DISCUSSION

Reaction of phenylisocyanate in 1,4-dioxane/water or pyridine/water gives 1,3-diphenylurea,[21] but the reaction is very slow and takes about 12 to 16 h. In this communication, we report a simple, economical, efficient, high-yielding, one-pot synthesis of symmetrical disubstituted ureas, cyclic ureas, and thioureas from the corresponding isocyanates, diisocyanates, and isothiocyanates in 1,4-dioxane in the presence of different tertiary amines. It was found that excellent yields for the synthesis of symmetrical disubstituted ureas and thioureas were obtained in the presence of triethyl amine (Scheme 1).



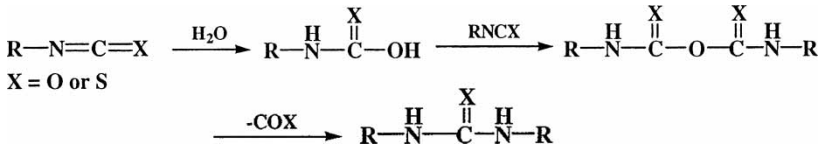
Scheme 1.

Other amines used in this investigation were pyridine and 2,6-lutidine, but they were found to be less effective (Table 1). When the reaction was carried out in 1,4-dioxane, the tertiary amines acted as promoters; the reaction proceeded very vigorously and was completed in 5–30 min. Isocyanates react more rapidly than isothiocyanates and the reaction was completed in 1–3 min. In a typical reaction, 0.3 mol of isocyanate/diisocyanate or isothiocyanate is treated with 2 mol of tertiary amines in the presence or absence of 1,4-dioxane at room temperature, and progress of the reactions was monitored through TLC. After the completion of the reactions, the reaction mixture was poured into ice-cold water with continuous stirring. The solid was filtered, which afforded pure desired product.

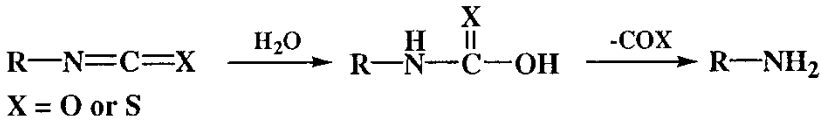
The rate enhancement of the reactions indicated that the reactions are promoted by tertiary amines (see the mechanism in Scheme 4). The same type of reactions are also observed when isocyanates are treated with tertiary amines in the absence of 1,4-dioxane. The latter result gave very strong evidence that the tertiary amines are acting as reaction promoters. Reagent-grade tertiary amines were used, which contain moisture that was responsible for the transformation. Under anhydrous conditions, cyclic diamide was formed. If we look at our proposed mechanisms, it seems that the final product, that is, the urea derivatives, cannot be obtained without some moisture and in the end the intermediate will be easily converted to the product during aqueous workup. A report[22] describes the synthesis of several aromatic and carbohydrate-based ureas and thioureas. According to their mechanism (Scheme 2), the reaction was initiated by water and an anhydride-type intermediate was formed. This anhydride was then converted into substituted symmetrical disubstituted urea. Interestingly, this report does not show the role of tertiary amine in the proposed mechanism. If the reaction was initiated by water, then the amine was formed (Scheme 3) instead of symmetrical disubstituted ureas. Schemes 2 and 3 indicated that these were amine-free mechanisms. In our case, the requirement of tertiary amines and presence of inherent moisture supports our proposed mechanism (Scheme 4).

CONCLUSION

The described procedure serves as an excellent method for preparing symmetrical 1,3-disubstituted ureas and thioureas. It is an efficient, one-step



Scheme 2.



Scheme 3.

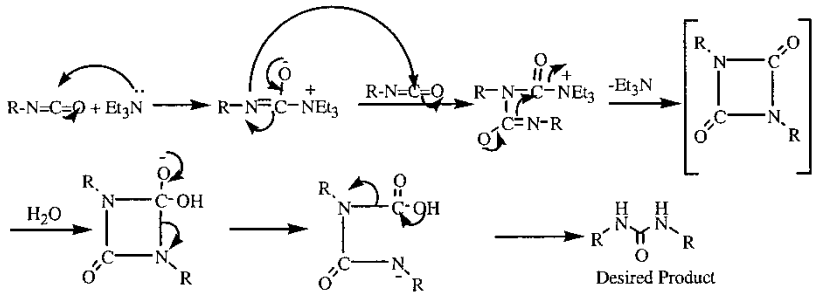
method. The requirement of moisture supports the proposed mechanism for the transformation.

EXPERIMENTAL

^{1}H NMR spectra were recorded in CD_3OD, $CDCl_3$, and DMSO-d_6 on a Bruker Aspect AM-300 operating at 300 MHz using TMS as an internal standard. The solvent was CD_3OD unless otherwise mentioned. 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-1 12 instrument. High-resolution EIMS were recorded in Jeol JMS HX-110 spectrometer.

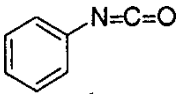
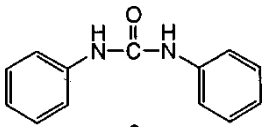
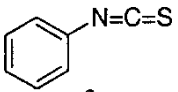
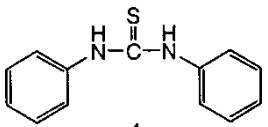
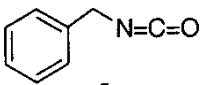
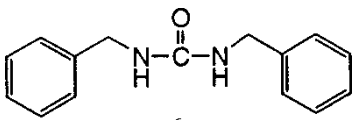
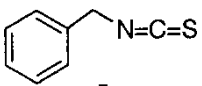
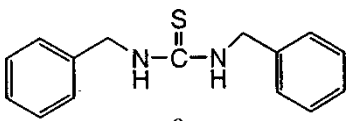
General Procedure for the Synthesis of Ureas and Thioureas

To a mixture of 0.3 mol of isocyanate/diisocyanate or isothiocyanate in 20 to 25 mL of 1,4-dioxane was added 2 mol of tertiary amines at room temperature and progress of reaction was monitored via TLC. After completion of reaction (times for individual reactions are shown in Table 1), the reaction mixture was poured into ice-cold water with continuous stirring, and the solid was filtered and crystallized by appropriate solvent to afford the desired product. Elemental analyses were performed by a Perkin Elmer analyzer.



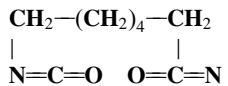
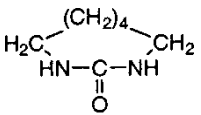
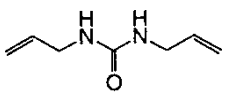
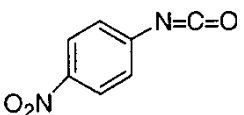
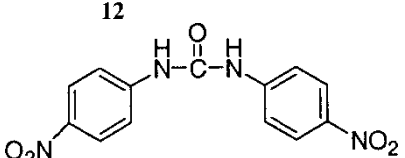
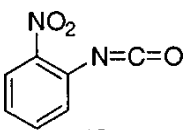
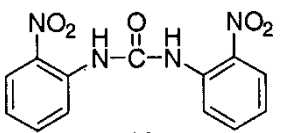
Scheme 4.

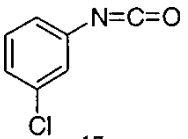
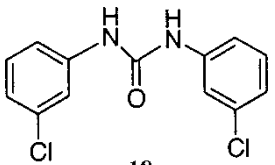
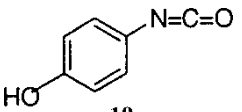
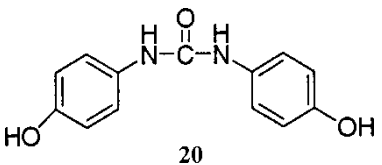
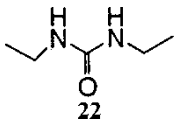
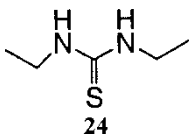
Table 1. Results of syntheses of symmetrical 1,3-disubstituted ureas and thioureas

Substrates	Products	%Yield TEA	%Yield Py.	%Yield Lut.	M.P. (°C)
 **1**	 **2**	98[a]	85[c]	80[c]	240
 **3**	 **4**	97[b]	80[d]	80[d]	152–153
 **5**	 **6**	99[a]	83[c]	82[c]	166–168
 **7**	 **8**	98[b]	84[d]	80[d]	147–148

(*continued*)

Table 1. Continued

Substrates	Products	%Yield TEA	Py.	Lut.	M.P. (°C)
	 **10**	96[a]	85[c]	84[c]	252–253
 **11**	 **12**	98.5[a]	90[c]	86[c]	91–93
 **13**	 **14**	99[a]	80[c]	80[c]	310
 **15**	 **16**	97[a]	80[c]	70[c]	225–227

 **17**	 **18**	98[a]	88[c]	84[c]	245–248
 **19**	 **20**	99[a]	88[c]	78[c]	286–288
$H_3C-CH_2-N=C=O$ 21	 **22**	98.5[a]	82[c]	78[c]	112–113
$H_3C-CH_2-N=C=S$ 23	 **24**	99[b]	85[d]	80[d]	142–143

TEA = triethylamine, Py. = pyridine, lut. = 2,6-Lutidine.
[a]∼3 min.
[b]∼10 min.
[c]∼15–20 min.
[d]∼25–30 min.

1,3-Diphenylurea (2). Crystallization by diethyl ether or ethanol gave needle-like crystals. $R_f = 0.40$ ($CHCl_3$–MeOH; 9.5:0.5); mp 240°C. IR ν_{max} (KBr): 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 (CD_3OD): δ 7.1–7.75 (m, 10H), 7.43 (brs, 2H); 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 $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.54; H, 5.68; N, 13.18.

1,3-Diphenylthiourea (4). Recrystallization by hot ethanol gave leaflets. $R_f = 0.9$ ($CHCl_3$–MeOH; 9.5:0.5); mp 152–153°C. IR ν_{max} (KBr): 3206, 3011, 1595, 1549, 1342, 1238 cm^{-1}; UV λ_{max} 259.46 ($\in$ 327.6), 287.59 ($\in$ 430.5), 293.33 ($\in$ 457.6); ^{1}H NMR (CD_3OD): δ 8.99 (brs, 2H), 7.23–7.75 (m, 10H); HREIMS: m/z (rel. int.) = 228.0719 [M^+, $C_{13}H_{12}N_2S$ requires 228.3179] (100), 194 (100), 135 (84), 119 (37), 93 (100), 77 (100). Anal. calcd. for $C_{13}H_{12}N_2S$: C, 68.39; H, 5.30; N, 12.27. Found: C, 68.41; H, 5.32; N, 12.25.

1,3-Dibenzylurea (6). The compound on crystallization from ethanol gave needle-like crystals. $R_f = 0.40$ ($CHCl_3$–MeOH; 9.5:0.5); mp 166–168°C. IR ν_{max} (KBr): 3350, 3020, 1660, 1600, 1410 cm^{-1}; ^{1}H NMR (CD_3OD): δ 7.0 (m, 10H), 5.78 (brs, 2H), 3.90 (d, 4H, $J = 16.0$ Hz); HREIMS: m/z (rel. int.) = 240.1264 [M^+, $C_{15}H_{16}N_2O$ requires 240.3075] (30), 163 (20), 149 (100), 133 (65). Anal. calcd. for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.95; H, 6.72; N, 11.67.

1,3-Dibenzylthiourea (8). The solid was crystallized from ethanol and gave leaflets or plates. $R_f = 0.90$ ($CHCl_3$–MeOH; 9.5:0.5); mp 147–148°C. IR ν_{max} (KBr): 3110, 3010, 1610, 1550, 1340 cm^{-1}; ^{1}H NMR (CD_3OD): δ 7.10 (m, 10H), 5.69 (brs, 2H), 3.92 (d, 4H, $J = 16.1$ Hz); HREIMS: m/z (rel. int.) = 256.1036 [M^+, $C_{15}H_{16}N_2S$ requires 256.3721] (29), 179 (15), 165 (100), 149 (76). Anal. calcd. for $C_{15}H_{16}N_2S$: C, 70.28; H, 6.29; N, 10.93. Found: C, 70.23; H, 6.27; N, 10.99.

Octahydro-2*H*-1,3-diazonin-2-one (10). $R_f = 0.60$ ($CHCl_3$–MeOH; 9.5:0.5); mp 252–253°C. IR ν_{max} (KBr): 3335, 2932, 2856, 1626, 1574, 1477, 1254 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 5.74 (t, 2H, $J = 5.88$ Hz), 2.94 (q, 4H, $J = 5.88$ Hz), 1.33 (m, 4H), 1.22 (m, 4H); HREIMS: m/z (rel. int.) = 142.1106 [M^+, $C_7H_{14}N_2O$ requires 142.2023] (4), 113 (5), 100 (23), 99 (22), 86 (58), 85 (62), 83 (93), 70 (15). Anal. calcd. for $C_7H_{14}N_2O$: C, 59.13; H, 9.92; N, 19.70. Found: C, 59.16; H, 9.91; N, 19.69.

1,3-Diallylurea (12). Recrystallization from ethanol afforded crystals of compound 12. $R_f = 0.40$ ($CHCl_3$–MeOH; 9.5:0.5); mp 90–93°C. IR ν_{max} (KBr): 3200, 3015, 2930, 1620, 1540, 1330 cm^{-1}; ^{1}H NMR (CD_3OD): δ

9.68 (brs, 2H), 5.93 (ddd, 2H, $J = 16.2, 11.6, 5.0$ Hz), 5.76 (dd, 2H, $J = 16.2$, 1.3 Hz), 5.05 (dd, 2H, $J = 11.6$, 1.3 Hz), 4.16 (m, 4H); HREIMS: m/z (rel. int.) = 140.0945 [M^+, $C_7H_{12}N_2O$ requires 140.1864] (10), 99 (100), 83 (56). Anal. calcd. for $C_7H_{12}N_2O$: C, 59.98; H, 8.63; N, 19.98. Found: C, 60.00; H, 8.61; N, 19.86.

4,4′-Dinitrocarbanilide (14). Recrystallization from ethanol gave yellow needle-like crystals. $R_f = 0.45$ ($CHCl_3$–MeOH; 9.5:0 5); mp 310°C. IR ν_{max} (KBr): 3286, 3190, 1649, 1600, 1556, 1312 cm^{-1}; ^1H NMR (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.

2,2′-Dinitrocarbanilide (16). Recrystallization from benzene gave pale yellow crystals. $R_f = 0.69$ ($CHCl_3$–MeOH; 9.5:0.5); mp 225–227°C. IR ν_{max} (KBr): 3285, 3194, 1647, 1597, 1555, 1443, 1312 cm^{-1}; ^1H NMR ($CDCl_3$): 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.

3,3′-Dichlorocarbanilide (18). Recrystallization by hot EtOH or hot AcOH afforded needles of compound 18. mp 245–248°C. IR ν_{max} (KBr): 3350, 3105, 1920, 1820, 1635, 1600, 1540, 1170 cm^{-1}; ^1H NMR (CD_3OD): δ 7.08 (ddd, 4H, $J = 8.0, 2.1, 1.9$ Hz), 7.03 (ddd, 2H, $J = 8.0, 2.2, 1.9$ Hz), 6.94 (dd, 2H, $J = 2.2$, 2.1 Hz); HREIMS: m/z (rel. int.) = 281.0170 [M^+, $C_{13}H_{10}Cl_2N_2O$ requires 281.1434] (15), 245 (50), 154 (100), 127 (80). Anal. calcd. for $C_{13}H_{10}Cl_2N_2O$: C, 55.54; H, 3.59; N, 9.96. Found: C, 55.57; H, 3.54; N, 9.92.

4,4′Dihydroxycarbanilide (20). Recrystallization from hot water gave fine needles. mp 286–288°C. IR ν_{max} (KBr): 3600, 3287, 3040, 1645, 1602, 1320 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.19 (brs, 4H), 6.91 (dd, 4H, $J = 8.2$, 0.3 Hz), 6.65 (dd, 4H, $J = 8.2$, 0.3 Hz); HREIMS: m/z (rel. int.) = 244.0849 [M^+, $C_{13}H_{12}N_2O_3$ requires 244.2521] (21), 277 (5), 151 (80), 136 (100), 93 (44). Anal. calcd. for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 63.90; H, 4.90; N, 11.54.

1,3-Diethylurea (22). Crystallization was carried out with ethanol, which gave needle-like crystals. $R_f = 0.54$ ($CHCl_3$-MeOH; 9.5:0.5), mp 112–113°C. IR ν_{max} (KBr): 3050, 2930, 1650, 1350 cm^{-1}; ^1H NMR (CD_3OD): δ 3.95 (brs, 2H), 3.22 (9, 4H, $J = 7.1$ Hz), 1.01 (t, 6H, $J = 7.1$ Hz); HREIMS: m/z (rel. int.) = 116.0953 [M^+, $C_5H_{12}N_2O$ requires 116.1641] (44), 101

(100), 87 (60), 71 (26). Anal. calcd. for $C_5H_{12}N_2O$: C, 51.70; H, 10.41; N, 24.12. Found: C, 51.73; H, 10.38; N, 24.09.

1,3-Diethylthiourea (24). Crystallization with ethanol gave crystals. $R_f = 0.95$ ($CHCl_3$–MeOH; 9.5:0.5), mp 142–143°C. IR ν_{max} (KBr): 3035, 2935, 1530, 1320 cm^{-1}; ^1H NMR (CD_3OD): δ 3.90 (brs, 2H), 3.10 (q, 4H, $J = 7.05$ Hz), 1.00 (t, 6H, $J = 7.05$ Hz); HREIMS: m/z (rel. int.) = 132.0725 [M^+, $C_5H_{12}N_2S$ requires 132.2287] (34), 117 (100), 103 (51), 88 (80), 87 (65). Anal. calcd. for $C_5H_{12}N_2S$: C, 45.42; H, 9.15; N, 21.19. Found: C, 45.44; H, 9.11; N, 21.21.

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