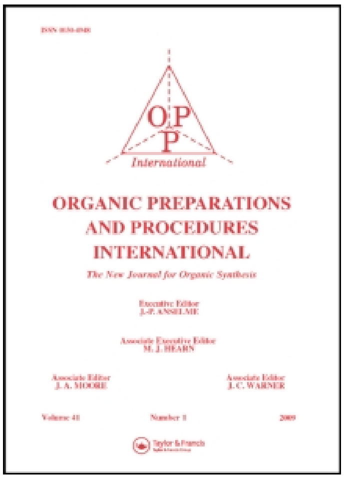

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OPPI BRIEFS

SUBSTITUTION REACTION OF N,N'-DIPHENYLUREA BY AMINES TO UNSYMMETRIC PHENYLUREAS

Submitted by
(4/20/99)

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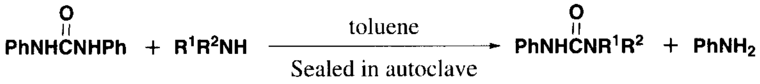
The disclosure that 3-(4-chlorophenyl)-1,1-dimethylurea (*monuron*) possesses herbicidal activity led to studies of the synthesis of unsymmetric phenylureas.[1] The most common method for their preparation is the addition of amines to isocyanates, whose synthesis involves the use of highly toxic phosgene which can be difficult to purchase. In 1967, it was reported that a tertiary amine-catalyzed condensation reaction of diphenylurea with primary amines in dioxane gave unsymmetric phenylureas, a process which required prolonged periods (20 h) and gave poor yields.[2] In 1993, a reinvestigation of the triethylamine-catalyzed reaction of diphenylurea and primary amines in DMF was reported to give the expected products in 77-92% yields.[3] However, the authors reported that the reaction of sterically hindered secondary amines and gaseous amines available as aqueous solutions did not seem to proceed. In the course of our study, we found that in a sealed autoclave, not only primary but also secondary aliphatic amines reacted very well with diphenylurea in toluene to give unsymmetric phenylureas in good yields. No catalyst was required and the reactions were complete in a short time (2 h), which providing a very simple and practical route to unsymmetric phenylureas.



$$\mathrm{PhNH\overset{O}{\overset{\|}{C}}NHPh} + \mathrm{R^1R^2NH} \xrightarrow[\text{Sealed in autoclave}]{\text{toluene}} \mathrm{PhNH\overset{O}{\overset{\|}{C}}NR^1R^2} + \mathrm{PhNH_2}$$

EXPERIMENTAL SECTION

All reagents were used as purchased. Melting points were determined on a Taike X-4 apparatus (Beijing, China) and were uncorrected. IR spectra (KBr) were measured on a Perkin Elmer 683 spectrophotometer. ^{13}C and ^{1}H NMR spectra were recorded on a Bruker DRX 400 spectrometer with

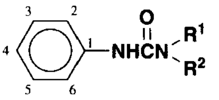
$CDCl_3$ as solvent and Me_4Si as internal standard. Elemental analyses were performed on a Italy 1106 type Micro-organic Elemental Analysis Instrument. The purity of products were determined by a Waters HPLC with $MeOH\text{-}H_2O$ mixed solvent as eluent.

Typical Procedure.- The reactions were carried out in a 70 mL stainless steel autoclave. All components (amine, 25 mmol; *N,N'*-diphenylurea, 5 mmol; toluene, 10.0 g) were charged into the vessel, sealed and put into an oil bath maintained at 150-160° with magnetic stirring for 2.0 h. After the reaction, the autoclave was cooled to room temperature. The collected solid was combined with that obtained from concentration of the filtrate, recrystallized and characterized by HPLC, IR, ^1H NMR, ^{13}C NMR and melting points.

TABLE. Unsymmetric Phenylureas from Diphenylurea and Amines

Compd	R^1	R^2	mp. (°C) (lit.)	Yield (%)
1a	morpholinyl		162-163(161.5-162)[4]	85
1b	piperidinyl		168-170(171-172)[4]	90
1c	pyrrolidinyl		128-130(133-134)[4]	80
1d	H	i-propyl	152-154(151-153)[5]	87
1e	H	n-butyl	127-129(130)[2]	85
1f	H	t-butyl	163-164 (168)[2]	90
1g	H	benzyl	169-170(169-173)[3]	93
1h	H	cyclohexyl	183-185(180-183)[3]	89
1i	methyl	methyl	129-130(127.5-128)[6]	75
1j	ethyl	ethyl	88-90(85-87)[5]	54
1k	*n*-propyl	*n*-propyl	68-70	85
1l	*i*-propyl	*i*-propyl	108	35
1m	*n*-butyl	*n*-butyl	83-84	92
1n	*i*-butyl	*i*-butyl	105-107	65
1o	*n*-pentyl	*n*-pentyl	61-64	66

Spectral data and elemental analysis:



Compound 1k.- ^1H NMR ($CDCl_3$): δ 0.91 (t, 6H, $N\text{-}CH_2CH_2C\underline{H}_3$); 1.61(m, 4H, $N\text{-}CH_2C\underline{H}_2CH_3$); 3.23 (t, 4H, $N\text{-}C\underline{H}_2CH_2CH_3$); 6.55 (br, 1H, $N\underline{H}$); 6.98 (m, 1H, one H of phenyl); 7.21-7.39 (m, 4H, rest Hs of phenyl); ^{13}C NMR: δ 11.16 ($\text{-}CH_2CH_2\underline{C}H_3$); 21.61 ($\text{-}CH_2\underline{C}H_2CH_3$); 49.10 ($\text{-}\underline{C}H_2CH_2CH_3$); 119.72 (phenyl 2, 6); 122.43 (phenyl 4); 128.48 (phenyl 3, 5); 139.27 (phenyl 1); 154.92 (C=O); IR (KBr): 3330 cm^{-1} (N-H)), 1630 cm^{-1} (C=O)).

Anal. Calcd. for $C_{13}H_{20}N_2O$: C, 70.91; H, 9.09; N, 12.73.Found: C, 70.78; H, 9.18; N, 12.75

Compound 1l.- ^1H NMR ($CDCl_3$): δ 1.31 (d, 6H, $2\text{-}CH(C\underline{H}_3)_2$); 3.96 (m, 1H, $2\text{-}C\underline{H}(CH_3)_2$); 6.32 (br, 1H, NH); 6.98 (m, one H of phenyl); 7.23-7.37 (m, 4H, rest Hs of phenyl); ^{13}C NMR: δ 21.75

(-CH($\underline{C}H_3)_2$); 45.36 (-$\underline{C}H(CH_3)_2$); 119.69 (phenyl 2, 6); 122.50 (phenyl 4); 128.59 (phenyl 3, 5); 139.18 (phenyl 1); 154.56 (C=O); IR (KBr): 3275 cm^{-1} (N-H)), 1625 cm^{-1} (C=O)).

Anal. Calcd. for $C_{13}H_{20}N_2O$: C, 70.91; H, 9.09; N, 12.73. Found: C, 70.62; H, 8.94; N, 12.79

Compound 1m.- ^{1}H NMR ($CDCl_3$): δ 0.95 (t, 6H, N-$CH_2CH_2CH_2C\underline{H}_3$); 1.35 (m, 4H, N-$CH_2CH_2C\underline{H}_2CH_3$); 1.57 (m, 4H, N-$CH_2C\underline{H}_2CH_2CH_3$); 3.27 (t, 4H, N-$C\underline{H}_2CH_2CH_2CH_3$); 6.37 (br, 1H, N$\underline{H}$); 7.00 (m, one H of phenyl); 7.24-7.39 (m, 4H, rest Hs of phenyl); ^{13}C NMR: δ 13.82 (-$CH_2CH_2CH_2\underline{C}H_3$); 20.13 (-$CH_2CH_2\underline{C}H_2CH_3$); 30.71 (-$CH_2\underline{C}H_2CH_2CH_3$); 47.31 ($\underline{C}H_2CH_2CH_2CH_3$); 119.66 (phenyl 2, 6); 122.60 (phenyl 4); 128.68 (phenyl 3, 5); 139.29 (phenyl 1); 154.85 (C=O); IR (KBr): 3275 cm^{-1} (N-H)), 1625 cm^{-1} (C=O)).

Anal. Calcd for $C_{15}H_{24}N_2O$: C, 72.58; H, 9.68; N, 11.29. Found: C, 72.56; H, 9.69; N, 11.43

Compound 1n.- ^{1}H NMR ($CDCl_3$): δ 0.94 (d, 12H, N-$CH_2CH(C\underline{H}_3)_2$); 2.03 (m, 2H, N-$CH_2C\underline{H}(CH_3)_2$); 3.15 (d, 4H, N-$C\underline{H}_2CH(CH_3)_2$); 6.38 (s, 1H, NH); 7.00 (m, 1H, one H of phenyl); 7.24-7.39 (m, 4H, rest Hs of phenyl); ^{13}C NMR: δ 20.22 (-$CH_2CH(\underline{C}H_3)_2$); 27.71 (-$CH_2\underline{C}H(CH_3)_2$); 55.89 (-$\underline{C}H_2CH(CH_3)_2$); 119.62 (phenyl 2, 6); 122.65 (phenyl 4); 128.72 (phenyl 3, 5); 139.22 (phenyl 1); 155.32 (C=O); IR (KBr): 3280 cm^{-1} (N-H)), 1630 cm^{-1} (C=O)).

Anal. Calcd for $C_{15}H_{24}N_2O$: C, 72.58; H, 9.68; N, 11.29. Found: C, 72.36; H, 9.71; N, 11.45

Compound 1o.- ^{1}H NMR ($CDCl_3$): δ 0.93 (t, 6H, N-$CH_2CH_2CH_2CH_2C\underline{H}_3$); 1.30-1.36 (m, 4H, N-$CH_2CH_2C\underline{H}_2C\underline{H}_2CH_3$); 1.61 (m, 2H, N-$CH_2C\underline{H}_2CH_2CH_2CH_3$); 3.27 (t, 2H, N-$C\underline{H}_2CH_2CH_2CH_2CH_3$); 6.40 (br, 1H, NH); 7.00 (m, 1H, one H of phenyl); 7.24-7.39 (m, 4H, rest Hs of phenyl); ^{13}C NMR: δ 13.94 (-$CH_2CH_2CH_2CH_2\underline{C}H_3$); 22.41 (-$CH_2CH_2CH_2\underline{C}H_2CH_3$); 27.91 (-$CH_2CH_2\underline{C}H_2CH_2CH_3$); 29.40 (-$CH_2\underline{C}H_2CH_2CH_2CH_3$); 47.55 (-$\underline{C}H_2CH_2CH_2CH_2CH_3$); 119.64 (phenyl 2, 6); 122.57 (phenyl 4); 128.65 (phenyl 3, 5); 139.25 (phenyl 1); 154.83 (C=O); IR (KBr): 3310 cm^{-1} (N-H)), 1630 cm^{-1} (C=O)).

Anal. Calcd for $C_{17}H_{28}N_2O$: C, 73.91; H, 10.14; N, 10.14. Found: C, 74.18; H, 10.20; N, 10.35

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