Halogenation Using Quaternary Ammonium Polyhalides. IX.[1] One-Step Syntheses of Acylureas and Carbamates from Amides by Use of Tetrabutylammonium Tribromide and DBU

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(Received June 15, 1987)

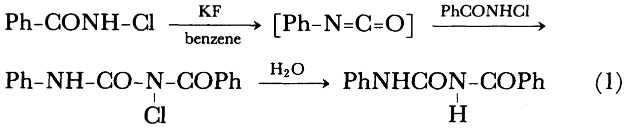
Synopsis. The reaction of amides with tetrabutylammonium tribromide (TBA Br_3) (0.5 equiv) and DBU (one equiv) in dichloromethane at room temperature gave *N*-substituted acylureas in fairly good yields. In the presence of alcohols, the reaction of amides with TBA Br_3 (one equiv) and DBU (two equiv) gave *N*-substituted carbamates.

Tetraalkylammonium polyhalides have recently been reported to act as useful, selective halogenating reagents.[2] In this paper, we wish to report on a one-step synthesis of *N*-substituted acylureas and carbamates from amides by the use of tetrabutylammonium tribromide[2a] (TBA Br_3) in the presence of a base, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

Results and Discussion

Recently, it has been noted that acylureas reveal the physiological actitivities of insects. That is, derivatives of *N*-benzoyl-*N'*-phenylurea are known to inhibit a formation of the epidermis of insects during their ecdyses.[3]

Rand et al. have already reported that a treatment of *N*-chlorobenzamide with potassium fluoride gave *N*-benzoyl-*N'*-phenylurea. In this case, they showed that an initial proton abstraction by the fluoride followed by a Hofmann-type rearrangement gave intermadiate phenyl isocyanate; then, the addition of residual *N*-chlorobenzamide to the isocyanate with a subsequent hydrolysis yielded the product.[4]



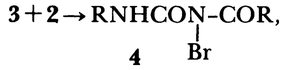
$$\text{Ph-CONH-Cl} \xrightarrow[\text{benzene}]{\text{KF}} [\text{Ph-N=C=O}] \xrightarrow{\text{PhCONHCl}}$$
$$\text{Ph-NH-CO-}\underset{\text{Cl}}{\text{N}}\text{-COPh} \xrightarrow{H_2O} \text{PhNHCO}\underset{\text{H}}{\text{N}}\text{-COPh} \qquad (1)$$

The reaction of amides with TBA Br_3 (half equiv) and DBU (one equiv) in commercially available dichloromethane (contained a catalytic amount of methanol) gave *N*-substituted acylureas in fairly good yields. In these cases, isocyanates should also be produced as reaction intermadiates. Since the presence of methanol considerably promotes the reaction,[5] it is assumed that the main active species is probably methyl hypobromite produced from the reaction of TBA Br_3 with methanol.[2b] Therefore, the reaction which affords acylureas can be presented in the following equations:

$$(C_4H_9)_4NBr_3 + CH_3OH + DBU$$
$$\rightarrow CH_3OBr + (C_4H_9)_4N^+Br^- + DBU(HBr), \qquad (2)$$

$$\underset{\mathbf{1}}{RCONH_2} + CH_3OBr \rightarrow \underset{\mathbf{2}}{RCONH\text{-}Br} + CH_3OH, \qquad (3)$$

$$\mathbf{2} + DBU \rightarrow \underset{\mathbf{3}}{R\text{-}N{=}C{=}O} + DBU(HBr), \qquad (4)$$



$$\mathbf{3}+\mathbf{2} \rightarrow \underset{\mathbf{4}}{\text{RNHCO}\underset{\text{Br}}{\text{N}}\text{-COR}}, \qquad (5)$$

and

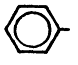
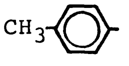
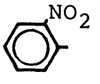
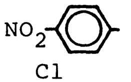
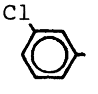
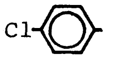
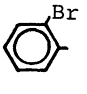
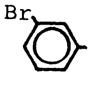
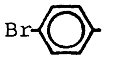
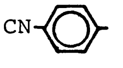
$$\mathbf{4}+\mathbf{1} \rightarrow \underset{\mathbf{5}}{\text{RNHCONH-COR}} + \mathbf{2}. \qquad (6)$$

Equation 7 can be derived from Eqs. 2—6.

$$\underset{\mathbf{1}}{2RCONH_2} + (C_4H_9)_4NBr_3 + 2DBU$$
$$\rightarrow \underset{\mathbf{5}}{RNHCONHCOR} + 2DBU(HBr) + (C_4H_9)_4NBr. \qquad (7)$$

Table 1. Acylureas from Amides by Use of TBA Br_3 and DBU

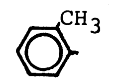
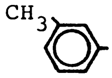
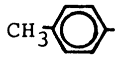
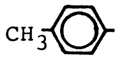
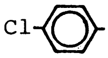
$$\underset{\mathbf{1}}{2\text{R-CONH}_2} \xrightarrow[CH_2Cl_2{}^{a)}\ \ rt]{(C_4H_9)_4N^+Br_3^-\ ,\ DBU} \underset{\mathbf{5}}{\text{R-NHCONHCO-R}}$$

	R	Reaction time/h	Yield[b]	Mp θ_m/°C	
			%	Found	Reported
a		0.5	70	206—207	206—208[4]
b		0.5	73	230—232	216.2—219.8[8]
c		0.5	77	213—215	—
d		0.5	70	261—263	—
e		0.5	65	208—211	—
f		0.5	87	253—254	—
g		1.0	93	211—212	—
h		1.0	50	214—216	—
i		1.0	50	264—266	—
j		1.0	83	270—273	—
k	CH_3CH_2-	0.5	87	100—102	—
l	$CH_3(CH_2)_4$-	0.5	45	99—101	—

a) Commercially available dichloromethane (containing methanol (0.5 vol%) as a stabilizer) was used. b) Yield of isolated product.

Table 2. Carbamates from Amides by Use of TBA Br_3 and DBU

$$\underset{\mathbf{1}}{\text{R-CONH}_2} \xrightarrow[\text{CH}_2\text{Cl}_2{}^{\text{a)}}\ \text{rt}]{(\text{C}_4\text{H}_9)_4\text{N}^+\text{Br}_3^-\text{, DBU, R'-OH}} \underset{\mathbf{7}}{\text{R-NHCO}_2\text{-R}'}$$

	R	R′	Reaction time/h	Yield[b)]	Mp θ_m/°C	
				%	Found	Reported
a		CH_3-	1.0	65	47—48.5	48[9)]
b		CH_3CH_2-	1.5	69	49—50.5	51[10)]
c		$CH_3CH_2CH_2$-	1.5	80	54—55	57—59[11)]
d		$CH_3(CH_2)_3$-	1.5	77	62	65.5[12)]
e		CH_3-	1.5	97	61—62	60—61[13)]
f		CH_3-	1.5	88	70—72	67.5—69[13)]
g		CH_3-	1.5	79	99—101	98.5—99.5[13)]
h		CH_3CH_2-	1.5	78	49—51	51—52[13)]
i		CH_3-	1.5	76	115—117	115[14)]
j	CH_3CH_2-	CH_3CH_2-	1.5	54	Bp 174—176	Bp 175[15)]

a) Purified dichloromethane was used. b) Yield of isolated product.

The results are summarized in Table 1.

In the presence of a large excess of alcohols ($\gg$20 equiv), the reaction of amides with TBA Br_3 (one equiv) and DBU (two equiv) in dichloromethane gave carbamates as main products.[6)] That is, as shown in the following Eq. 8, intermediary isocyanates react with alcohols to afford carbamates:[7)]

$$\underset{\mathbf{3}}{\text{R-N=C=O}} + \underset{\mathbf{6}}{\text{R}'\text{-OH}} \rightarrow \underset{\mathbf{7}}{\text{RNH-CO}_2\text{R}'}. \tag{8}$$

Equation 9 can be obtained from Eqs. 2—4 and 8.

$$\underset{\mathbf{1}}{\text{RCONH}_2} + (\text{C}_4\text{H}_9)_4\text{NBr}_3 + \underset{\mathbf{6}}{\text{R}'\text{OH}} + 2\text{DBU}$$
$$\rightarrow \underset{\mathbf{7}}{\text{RNHCO}_2\text{R}'} + (\text{C}_4\text{H}_9)_4\text{NBr} + 2\text{DBU(HBr)}. \tag{9}$$

The results are summarized in Table 2.

These methods would be useful in the preparation of **5** or **7** from the readily available starting materials **1** and TBA Br_3 by one-step under mild conditions.

Experimental

All melting points are uncorrected. The ^{1}H NMR spectra were recorded on a JMN-MH-100 spectrometer with tetramethylsilane as an internal standard. The IR spectra were obtained on a JASCO IRA-1 spectrometer.

***N*-Benzoyl-*N*′-phenylurea (5a). Typical Procedure.** To a solution of benzamide (0.48 g, 4.0 mmol) and TBA Br_3 (1.00 g, 2.07 mmol) in commercially available dichloromethane (contained a catalytic amount of methanol) (20 ml) was added DBU (0.64 g, 4.2 mmol) in dichloromethane (5 ml) at room temperature. After the mixture was stirred for 30 min the solvent was distilled in vacuo. To the residue was added a small amount of ether and water; then the precipitate obtained was filtered and washed with ether and water to give **5a** as colorless crystals; yield 0.33 g (70%); mp 206—207 °C (lit,[3)] mp 206—208 °C).

***N*-(2-Nitrobenzoyl)-*N*′-(2-nitrophenyl)urea (5c).** Compound **5c** was prepared similarly: Yield 77%; pale yellow crystals; mp 213—215 °C; IR (KBr) 3210 (ArN-H), 3100 (N-H), 1700 (ArC=O), and 1680 cm^{-1} (C=O); ^{1}H NMR (DMSO-d_6) δ=7.38—8.68 (8H, m, 2Aromatics), and 11.60—12.00 (2H, m, 2NH). Found: C, 50.66; H, 3.25; N, 17.06%. Calcd for $C_{14}H_{10}O_6N_4$: C, 50.91; H, 3.05; N 16.97%.

***N*-(4-Nitrobenzoyl)-*N*′-(4-nitrophenyl)urea (5d).** Yield 70%; pale yellow crystals; mp 261—263 °C; IR (KBr) 3220 (ArN-H), 3100 (N-H), 1690 (ArC=O), and 1670 cm^{-1} (C=O). Found: C, 50.68; H, 3.20; N, 16.90%. Calcd for $C_{14}H_{10}O_6N_4$: C, 50.91; H, 3.05; N, 16.97%.

***N*-(3-Chlorobenzoyl)-*N*′-(3-chlorophenyl)urea (5e).** Yield 65%; colorless crystals; mp 208—211 °C; IR (KBr) 3200 (ArN-H), 3110 (N-H), 1700 (ArC=O), and 1660 cm^{-1} (C=O); ^{1}H NMR (DMSO-d_6) δ=7.20—8.27 (8H, m, 2Aromatics), 10.88 (1H, br.s, Ar-N$\underline{\text{H}}$-), and 11.28 (1H, br.s, -NH-). Found: C, 54.52; H, 3.38; N, 9.15%. Calcd for $C_{14}H_{10}O_2N_2Cl_2$: C, 54.39;

H, 3.26; N, 9.06%.

N-(4-Chlorobenzoyl)-N′-(4-chlorophenyl)urea (5f). Yield 87%; colorless crystals; mp 253—254 °C; IR (KBr) 3100 (N-H), 1680 (ArC=O), and 1650 cm^{-1} (C=O); ^{1}H NMR (DMSO-d_6) δ=7.40—8.18 (8H, m, 2Aromatics), 10.90 (1H, br.s, Ar-N$\underline{H}$-), and 11.23 (1H, br.s, -NH-). Found: C, 54.35; H, 3.35; N, 9.06%. Calcd for $C_{14}H_{10}O_2N_2Cl_2$: C, 54.39; H, 3.26; N, 9.06%.

N-(2-Bromobenzoyl)-N′-(2-bromophenyl)urea (5g). Yield 93%; colorless crystals; mp 211—212 °C; IR (KBr) 3230 (ArN-H), 3130 (N-H), and 1710 cm^{-1} (C=O); ^{1}H NMR (DMSO-d_6) δ=6.92—8.40 (8H, m, 2Aromatics), 10.93 (1H, br.s, ArN$\underline{H}$-), and 11.42 (1H, br.s, -NH-). Found: C, 42.15; H, 2.45; N, 7.12%. Calcd for $C_{14}H_{10}O_2N_2Br_2$: C, 42.24; H, 2.53; N, 7.04%.

N-(3-Bromobenzoyl)-N′-(3-bromophenyl)urea (5h). Yield 50%; colorless crystals; mp 214—216 °C; IR (KBr) 3220 (ArN-H), 3140 (N-H), and 1720 cm^{-1} (C=O); ^{1}H NMR (DMSO-d_6) δ=7.36—8.44 (8H, m, 2Aromatics), 10.87 (1H, br.s, ArN$\underline{H}$-), and 11.28 (1H, br.s, -NH-). Found: C, 42.03; H, 2.43; N, 7.12%. Calcd for $C_{14}H_{10}O_2N_2Br_2$: C, 42.24; H, 2.53; N, 7.04%.

N-(4-Bromobenzoyl)-N′-(4-bromophenyl)urea (5i). Yield 50%; colorless crystals; mp 264—266 °C; IR (KBr) 3200 (ArN-H), 3120 (N-H), 1700 (PhC=O), and 1660 cm^{-1} (C=O); ^{1}H NMR (DMSO-d_6) δ=7.68—8.10 (8H, m, 2Aromatics), 10.90 (1H, br.s, ArN$\underline{H}$-), and 11.26 (1H, br.s, -NH-). Found: C, 42.07; H, 2.45; N, 7.15%. Calcd for $C_{14}H_{10}O_2N_2Br_2$: C, 42.24; H, 2.53; N, 7.04%.

N-(4-Cyanobenzoyl)-N′-(4-cyanophenyl)urea (5j). Yield 83%; colorless crystals; mp 270—273 °C; IR (KBr) 3200 (ArN-H), 2200 (C≡N), 1680 (PhC=O), and 1660 cm^{-1} (C=O); ^{1}H NMR (CF_3CO_2H) δ=7.92—8.34 (8H, m, 2Aromatics). Found: C, 65.87; H, 3.65; N, 19.48%. Calcd for $C_{16}H_{10}O_2N_4$: C, 66.20; H, 3.47; N, 19.30%.

N-Ethyl-N′-propionylurea (5k). Yield 87%; colorless crystals; mp 100—102 °C; IR (KBr) 3200 (N-H), and 1680 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ=1.10—1.34 (6H, m, $2CH_3$), 2.44 (2H, q, $COCH_2$-), 3.40 (2H, m, -NHC$\underline{H}_2$-), 8.58 (1H, br.s, $CH_2N\underline{H}CO$), and 9.92 (1H, br.s, $CON\underline{H}CO$). Found: C, 49.99; H, 8.37; N, 19.49%. Calcd for $C_6H_{12}O_2N_2$: C, 49.98; H, 8.36; N, 19.43%.

N-Hexanoyl-N′-pentylurea (5l). Yield 45%; colorless crystals, mp 99—101 °C; IR (KBr) 3200 (N-H), and 1660 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ=0.80—1.10 (6H, m, $2CH_3$), 1.28—2.00 (12H, m, $2(CH_2)_3$), 2.40 (2H, br.t, $COCH_2$), 3.38 (2H, m, NHC$\underline{H}_2$-), 8.68 (1H, br.s, -$CH_2N\underline{H}CO$), and 9.94 (1H, br.s, $CON\underline{H}CO$). Found: C, 62.97; H, 10.72; N, 12.41%. Calcd for $C_{12}H_{24}O_2N_2$: C, 63.12; H, 10.60; N, 12.27%.

Methyl Phenylcarbamate (7a). Typical Procedure. To a solution of benzamide (0.61 g, 5.0 mmol) and TBA Br_3 (2.50 g, 5.18 mmol) in dichloromethane (15 ml)-methanol (40 ml, 1 mol) was added DBU (1.70 g, 11.2 mmol) in dichloromethane (5 ml) at room temperature. After the mixture was stirred for 1 h the solvent was distilled in vacuo and the obtained precipitate was extracted with ether. The ether layer was dried with magnesium sulfate and evaporated. A crude product was purified by column chromatography on silica gel (3:1 hexane-benzene) to afford **7a** as colorless crystals; yield 0.49 g (65%); mp 47—48.5 °C (lit,[9] mp 48 °C).

The authors wish to thank Professor Masashi Tashiro, Institute of Advanced Material Study, Kyushu University, for the elemental analyses.

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5) In the case of the absence of methanol, the reaction of benzamide (**1a**) with half equiv of TBA Br_3 and one equiv of DBU in dichloromethane for 0.5 h at room temperature gave **5a** in only 35% yield.

6) When about 10—15 equiv of methanol was previously added to the reaction mixtures, the resultant acylureas were obtained in equally good yields. In these cases, methyl carbamates expected were hardly obtained.

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