Alkylation of Thioureas and Related Compounds by Use of Alcohols, Diethyl Azodicarboxylate, and Triphenylphosphine

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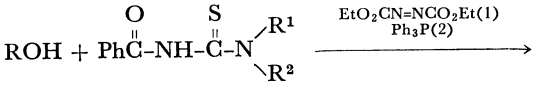
Synopsis. The alkylation of ambident nucleophiles having a thiocarbonyl group by use of alcohols, diethyl azodicarboxylate, and triphenylphosphine was studied. Selective *S*-alkylation took place in the cases of *N*-benzoyl-*N'*-mono- and -disubstituted thioureas, while selective *N*-alkylation occurred in the reaction of *N*-phenyl-*N',N'*-diethylthiourea. 1-Methoxymethyl-2-thiouracil afforded both *N*-alkylated and *S*-alkylated products.

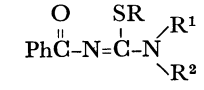
The reaction of either *N*-benzyloxycarbonylbenzamide[1] or ethyl acetoacetate[2] with an alcohol, diethyl azodicarboxylate (**1**), and triphenylphosphine (**2**) mainly gives *O*-alkylated products. The results indicate that the triphenylalkoxyphosphonium salt formed as a key intermediate of the present reaction[3] is a harder alkylating reagent than alkyl halides or alkyl tosylates.[4]

In order to examine the present alkylating system, we studied the alkylation of other ambident nucleophiles, *N*-acylthioureas and 1-methoxymethyl-2-thiouracile, ambident at N, S, and O, being chosen as reagents.

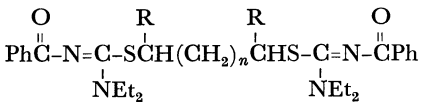
A series of *N*-benzoylthioureas, PhCO–NH–CS–NR^1R^2 with R^1=H, R^2=*t*-butyl (**3**), R^1=H, R^2=cyclohexyl (**4**), and R^1=R^2=ethyl (**5**) was prepared by the reaction of benzoyl isothiocyanate with amines. The reaction of 2-phenylethanol with **3**, **4**, and **5** in the presence of 1.5 molar equivalents each of **1** and **2** proceeded smoothly at room temperature giving the corresponding *S*-alkylated products (**6a**, **7a**, and **8a**) in good to excellent yields (Table 1).[5] The structure was confirmed by the reaction of the products with ammonia at room temperature, the corresponding *N*-benzoylguanidines and bis(2-phenylethyl) disulfide being isolated (Table 2). The reaction of **5** with **1**, **2**, and 2-phenoxyethanol also gave *S*-alkylated product (**8b**) almost quantitatively.



3: R^1=H, R^2=*t*-Bu
4: R^1=H, R^2=cyclo-C_6H_{11}
5: R^1=R^2=Et



6: R^1=H, R^2=*t*-Bu
7: R^1=H, R^2=cyclo-C_6H_{11}
8: R^1=R^2=Et
a: R=$PhCH_2CH_2$–
b: R=$PhOCH_2CH_2$–
c: R=$CH_3CH(OH)CH_2CH_2$–
d: R=$PhCH(OH)CH_2CH_2$–
e: R=$CH_3CH(OH)CH_2CH_2CHCH_3$



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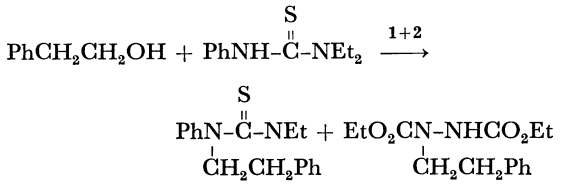
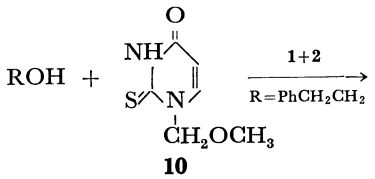
Selective *S*-alkylation also took place when sodium salt of **5** was treated with 2-phenylethyl bromide in tetrahydrofuran. Compound **8a** was obtained in 38% yield and 59% of **5** was recovered.

When primary, secondary-diol was allowed to react with **1**, **2**, and **5**, the primary hydroxyl group predominantly reacted to give 2-(hydroxylakyl)isothiourea (**8c**, **8d**). 2,5-Hexanediol also gave 2-(1-methyl-4-hydroxypentyl)isothiourea (**8e**). No detectable amount of bis(amidinothio) derivatives (**9**) could be obtained by preparative layer chromatography.

Contrary to the case of *N*-benzoylthioureas, the reaction of *N*-phenyl-*N',N'*-diethylthiourea with 2-phenylethanol, **1**, and **2** resulted in the formation of *N*-alkylated product in 48% yield rather than *S*-alkylated product. Diethyl 1-phenethyl-1,2-hydrazinedicarboxylate was isolated in 26% yield.



The alkylation of 1-methoxymethyl-2-thiouracil (**10**),[6] a cyclic analogue of **5**, with 2-phenylethanol in the presence of **1** and **2** resulted in the formation of *N*-alkylated (**11**) and *S*-alkylated (**12**) products in 64% and 18% yields, respectively.[7] The change in solvent scarcely affected the product ratio.



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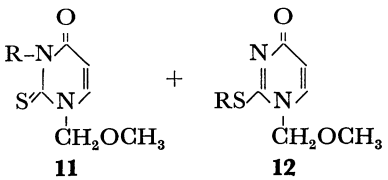

11 **12**

THF	64%	18%
DMF	64%	19%
THF-DMF(4:1)	60%	17%
Benzene-DMF(4:1)	66%	18%

Table 1. Alkylation of *N*-benzoylthioureas

	SR BzN=C-NR¹R²			Yield %	TLC[a]	NMR ($CDCl_3$), 60 MHz, δ/ppm from TMS[b]
	R	R¹	R²			
6a	$PhCH_2CH_2$	H	*t*-Bu	82	C-EA 20:1	1.45 (s, *t*-Bu), 2.75—3.65 (A_2B_2, $PhCH_2CH_2S$), 7.15 (s, Ph), 7.2—8.3 (m, Bz)
7a	$PhCH_2CH_2$	H	cyclo-C_6H_{11}	90	C-EA 20:1	0.8—2.2 (m, C_6H_{11}), 2.7—3.6 (A_2B_2, $PhCH_2CH_2S$), 7.1 (s, Ph), 7.1—8.3 (m, Bz)
8a	$PhCH_2CH_2$	Et	Et	94	E	1.15 (t, CH_3), 2.5—3.25 (A_2B_2, $PhCH_2CH_2S$), 3.45 (q, CH_3CH_2), 6.65—7.1 (m, Ph), 7.1—8.2 (m, Bz)
8b	$PhOCH_2CH_2$	Et	Et	97	B-EA 1:1	1.19 (t,CH_3), 3.15 (t, CH_2S), 3.48 (q, CH_3CH_2), 4.0 (t, CH_2O), 6.55—7.15 (m, Ph), 7.1—8.3 (m, Bz)
8c	$CH_3CHCH_2CH_2$ OH	Et	Et	78	B-EA 1:1	1.0 (d, $CH_3CH(OH)$), 1.2 (t, CH_3CH_2), 1.6 (br. q, $CH_2CH_2CH(OH)$), 2.85 (t, SCH_2), 3.5 (q, CH_3CH_2), 3—4.1 (m, $CH(OH)$), 7.05—8.25 (m, Bz))
8d	$PhCHCH_2CH_2$ OH	Et	Et	36	B-EA 1:1 then E	1.2 (t, CH_3CH_2), 1.95 (br. $CH_2CH_2CH(OH)$), 2.85 (br. t, SCH_2), 3.5 (q, CH_3CH_2), 4.5 (t, $CH_2CH(OH)$), 7.25 (s, Ph), 7—8.1 (m, Bz)
8e	$CH_3CHCH_2CH_2CH$ OH CH_3	Et	Et	31	B-EA 1:5	1—1.19 (m, CH_3CH_2, $CH_3CH(OH)CH_2CH_2CH(CH_3)S$), 2.8—4 (m, $CH(OH)$, $CH(CH_3)S$), 3.5 (q, CH_3CH_2), 7.05—8.1 (m, Bz)

a) Solvent systems used for isolation of products; C=CCl_4, EA=AcOEt, E=ether, B=benzene. b) NMR spectra of **6a** and **7a** were measured in CCl_4.

Table 2. Ammonolysis of **6a**, **7a**, and **8a**

Isothiourea	Reaction time h	Products/% $BzN=C(NH_2)-NR^1R^2$ R¹	R²		$(PhCH_2CH_2S)_2$	Recovered isothiourea %
6a	20	H	*t*-Bu	29	38	47
7a	90	H	cyclo-C_6H_{11}	77	78	6
8a	72	Et	Et	51	81	17

Experimental

Alkylation of Thiocarbonyl Compounds. A solution of **1** (259 mg, 1.5 mmol) in tetrahydrofuran (THF, 2 ml) was added dropwise over a period of 15 min to a solution of a thiocarbonyl compound (1 mmol), an alcohol (1 mmol) and **2** (392 mg, 1.5 mmol) in THF (5 ml) at room temperature. After the solution had been stirred for 18 h, the solvent was removed and products were isolated by preparative layer chromatography (Merck PF_{254} 20 cm×30 cm). The results are summarized in Table 1.

*Ammonolysis of **8a**.* Compound **8a** (215 mg, 0.6 mmol) was treated with ammonia saturated in methanol (10 ml) at room temperature for 72 h. After evaporation, *N*-benzoyl-*N'*,*N'*-diethylguanidine and diphenethyl disulfide were isolated by preparative layer chromatography in 51% and 81% yields, respectively.

*Alkylation of **10**.* A solution of **1** (519 mg, 3 mmol) in THF was added dropwise over a period of 30 min to a solution of **10** (345 mg, 2 mmol), 2-phenylethanol (243 mg, 2 mmol) and **2** (785 mg, 3 mmol) in a mixture of THF (6 ml) and DMF (2 ml) at room temperature. After the solution had been stirred at room temperature for 16 h, **11** and **12** were obtained by preparative layer chromatography (benzene–AcOEt=1:1) in 60% and 17% yield, respectively.

Compound **11** was recrystallized from petroleum ether (bp 30—60 °C); mp 73—75 °C. UV_{max} (MeOH) 282 nm. NMR ($CDCl_3$, 60 MHz) δ 2.75—3.2 (m, $PhCH_2$), 3.35 (s, CH_3), 4.4—4.85 (m, CH_2CH_2N), 5.5 (s, OCH_2), 5.95 (d, N–CH=), 7.1—7.5 ppm (d, O=C–CH= and m, Ph).

Compound **12** was recrystallized from CCl_4; mp 110—113 °C. UV_{max} (MeOH) 238 nm. NMR ($CDCl_3$) δ 2.75—3.2 (m, $PhCH_2$), 3.2—3.7 (s, CH_3, superimposed on m, SCH_2), 5.97 (d, N–CH=), 7.25 (s, Ph), 7.35 ppm (d, O=C–CH=).

References

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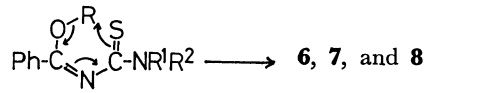
2) T. Kurihara, M. Sugizaki, I. Kime, M. Wada, and O. Mitsunobu, *Bull. Chem. Soc. Jpn.*, **54**, 2107 (1981).

3) O. Mitsunobu and M. Eguchi, *Bull. Chem. Soc. Jpn.*, **44**, 3427 (1971).

4) For reviews of alkylation of ambident nucleophiles, see a) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin Inc., Menlo Park ,California (1972), pp. 492—628; b) R. Gompper and H. -U. Wagner, *Angew. Chem. Int. Ed. Engl.*, **15**, 321 (1976); c) T. -L. Ho, "Hard and Soft Acids and Bases Principle in Organic Chemistry," Academic Press, New York, N. Y. (1977), pp. 26—54; d) M. Ono, *Yuki Gosei Kagaku Kyokai Shi*, **38**, 836 (1980).

5) Two routes are possible for the formation of **6**—**8**, direct *S*-alkylation and one involving alkyl group rearrangement of initially formed *O*-alkylated product *via* six membered transition state. The latter process seems unlikely since alkylation proceeds under mild neutral conditions.



6) H. Vorbrüggen and P. Strehlke, *Chem. Ber.*, **106**, 3039 (1973).

7) 1-Methyl-2-methylthio-4(1*H*)-pyrimidinone exhibits UV_{max}(MeOH) 231 nm.[6] Thus the alkylated product which absorbs light at 238 nm was assigned to be **12**.