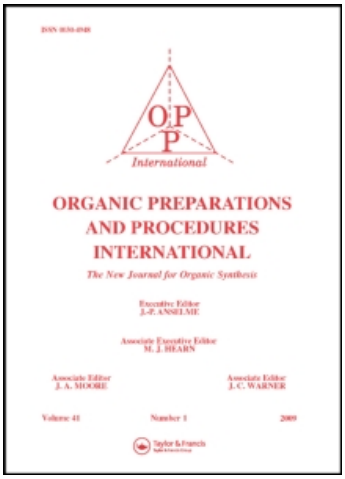

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SYNTHESIS OF 2-ALKOXY-5-NITROBENZAMIDES BY PHASE-TRANSFER CATALYZED NUCLEOPHILIC SUBSTITUTION OF 2-CHLORO-5-NITROBENZAMIDES

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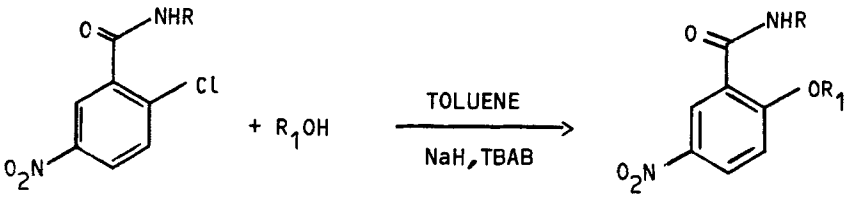
A new application of liquid-liquid PTC (LL-PTC) for the synthesis of ethers of primary alcohols by nucleophilic substitution of 2-chloro-5-nitrobenzamides was previously reported;[1] we also demonstrated that all other alcohols and phenols failed to give any product with acceptable yields even under forcing conditions. This could be explained in terms of steric hindrance of the ion-pair extracted together with water of solvation into the organic phase.[2] In order to test this hypothesis and to provide a generalized application of the proposed reaction for ether preparation, we decided to investigate a heterogeneous solid-liquid (SL) system where the nucleophilicity of the ion pair is strongly enhanced.[3,4]



1 2 3

We report our results of the conversion of 2-chloro-5-nitrobenzamides 1

into the corresponding ethers 3 by reaction with primary or secondary alcohols, or phenols 2 in toluene in the presence of a catalytic amount of tetrabutylammonium bromide (TBAB), using sodium hydride as base. As shown in Table 1, the uncatalyzed reactions for the preparation of 3a, 3c and 3i proceed smoothly with lower yields or at higher temperatures than the catalyzed ones. The reactivity of the system is greatly enhanced in the presence of TBAB so that secondary alcohols and phenols react in good yields under mild conditions. The low yield for benzhydrol (entry e) is explained by the concurrent formation of benzophenone whereas the arylation of 2,6-di(tert-butyl)phenol with 1 (R = n-C_4H_9) gave the quinone[5] as the sole reaction product;[6] 2,4,6-trichlorophenol did not react at all (entry 3q) and the lack of reactivity was probably due to steric hindrance of the ortho-substituents [(2,5-dichlorophenol did react, (entry 3l)]. All efforts to prepare ethers of tertiary alcohols failed under all the experimental PTC conditions. The reactivity of the system is also influenced by the nature of the amide group in 1; thus, secondary amides react faster than primary ones probably because of their greater solubility in toluene. Tertiary amides do not react at all and this result would suggest the absence of anchimeric assistance of amide proton or a sterically congested transition state. Furthermore NaH could be successfully replaced by anhydrous powdered KOH; the yield for the preparation of 3a was 90% (1 hr at room temperature). In the synthesis of 3c, 3d and 3i with KOH as the base, complete disappearance of the starting materials occurred after 1 hr at 40°, 6 hrs for 3i, (monitored by TLC, 80:20 cyclohexane-ethyl acetate as eluent). The ready accessibility of a large number of these compounds under the mild conditions employed makes this method particularly suitable for the preparation of these intermediates on both laboratory and industrial scale.

TABLE 1. 2-Alkoxy-5-nitrobenzamides 3[a]

3	R	R_1	T(°C)	t(hrs)	Yield(%)[b]
a	butyl	butyl	20	20	25[c]
a	butyl	butyl	20	0.5	89
b	butyl	$H_5C_6CONH(CH_2)_2$	20	1	75
c	butyl	sec-butyl	80	4	40[c]
c	butyl	sec-butyl	40	0.5	88
d	butyl	cyclohexyl	40	3	80
e	butyl	benzhydryl	40	1	50
f	butyl	1-isopropyl-2-methylpropyl	25	24	75
g	H	isopropyl	25	24	63
h	H	1-isopropyl-2-methylpropyl	40	6	55
i	butyl	phenyl	40	24	70[c]
i	butyl	phenyl	40	4	90
k	butyl	2,6-di(tert-butyl)phenyl	40	5	0
l	butyl	2,5-dichlorophenyl	25	8	95
m	butyl	2-tert-butylphenyl	25	6	95
n	H	2-tert-butylphenyl	25	12	72
o	butyl	1-naphthyl	80	4	75
p	butyl	2-naphthyl	80	4	70
q	butyl	2,4,6-trichlorophenyl	50	6	0

a) Reaction conditions: benzamide 1 (100 mmol), alcohol 2 (100 mmol), 50: NaH (100 mmol), toluene (100 ml); catalyst TBAB (1 mmol).
b) Yields of recrystallized product or silica chromatography purified product.
c) No catalyst.

EXPERIMENTAL SECTION

2-Alkoxy-5-nitrobenzamides (3). General Procedure.- To a suspension of sodium hydride (50% in mineral oil, 115 mmol) in anhydrous toluene (100 ml), was added the alcohol or phenol 2 (115 mmol). The mixture was stirred at room temperature or at 60-80° until the evolution of hydrogen ceased. The catalyst (TBAB) (1.15 mmol) and benzamide 1 (115 mmol) were then sequentially added at room temperature. The reaction was stirred at

TABLE 2. mp. and ^{1}H-nmr Data of Compounds 3

Product[a]	mp.(°C)	^{1}H nmr[c](δ)
3a	85-86[b]	lit.[2] mp. 85-86°
3b	185-188[e]	DMSO-d_6: 0.7-0.9(m+t,3H),1.0-1.7(m,4H),3.1-3.5(m-q,2H), 3.6-4.0(m-q,2H),4.3-4.6(m-t,2H),7.2-8.8(H + 2H exch).
3c	40-42[d]	DMSO-d_6: 0.6-1.1(m,6H),1.1-2.0(m,9H),3.2-3.4(m,2H),4.5-5.0(m-sext,1H),7.36(d,1H,J=9Hz),8.1(m,1H,exch), 8.27(dd,1H,J_1=9Hz,J_2=3Hz),8.49(d,1H,J=3Hz).
3d	64-66[e]	DMSO-d_6: 0.8-1.0(m+t,3H),1.0-2.1(m,14H),3.2-3.5(m,2H), 4.6-5.0(m,1H),7.42(d,1H,J=9Hz),8.1(m,1H,exch), 8.30(dd,1H,J_1=9Hz,J_2=3Hz),8.49(d,1H,J=3Hz).
3e	99-102[b]	DMSO-d_6: 0.7-0.9(m+t,3H),1.0-1.6(m,4H),3.2-3.4(m,2H), 6.82(s,1H),7.2-7.7(m,11H),8.1-8.4(m,3H).
3f	69-71[f]	$CDCl_3$: 1.0(d,12H,J=6Hz),0.8-1.1(m,3H),1.2-1.9(m,4H),2.15 (d sept,2H,J_1=J_2=6-7Hz),3.49(m,2H),4.33(t,1H,J=6 Hz),7.13(d,1H,J=9Hz),7.83(br s,1H,exch),8.26(dd, 1H,J_1=9Hz,J_2=3Hz),9.11(d,1H,J=3Hz).
3g	186-188[e]	$CDCl_3$: 1.50(d,6H,J=6Hz),4.89(sept,1H,J=6Hz),6.3(br s,1H, exch),7.07(d,1H,J=9Hz),7.67(br s,1H,exch),8.33(dd, 1H,J_1=9Hz,J_2=3Hz),9.10(d,1H,J=3Hz).
3h	134-135[g]	$CDCl_3$: 1.00(d,12H,J=7Hz),2.16(d sept,2H,J_1=J_2=6-7Hz), 4.35(t,1H,J=6Hz),6.3(br s,1H,exch),7.15(d,1H,J=9 Hz),7.7(br s,1H,exch),8.30(dd,1H,J_1=9Hz,J_2=3Hz), 9.11(d,1H,J=3Hz).
3i	oil	DMSO-d_6: 0.6-0.9(m+t,3H),1.0-1.6(m,4H),3.1-3.5(m,2H), 6.98(d,1H,J=9Hz),7.1-7.7(m,5H),8.30(dd,1H,J_1=9 Hz,J_2=3Hz),8.48(d,1H,J=3Hz),8.5(m,1H,exch).
3l	oil	$CDCl_3$: 0.8-1.1(m+t,3H),1.2-1.8(m,4H),3.5(m,2H),6.70(d,1H, J=9Hz),6.9-7.3(m,3H),7.8(br s,1H,exch),8.14(dd,1H, J_1=9Hz,J_2=3Hz),9.13(d,1H,J=3Hz).
3m	100-103[h]	$CDCl_3$: 0,8-1.1(m+t,3H),1.2-1.8(m,4H),1.38(s,9H),3.3-3.7 (m,2H),6.79(d,1H,J=9Hz),6.8-7.7(m,4H),7.6(br s,1H, exch),8.15(dd,1H,J_1=9Hz,J_2=3Hz),9.12(d,1H,J=3Hz).

3n	150-153[i]	$CDCl_3$	: 1.4(s,9H),6.3(br s,1H,exch),6.79(d,1H,J=9Hz),6.8-7.8(m,5H,exch),8.21(dd,1H,J_1=9Hz,J_2=3Hz),9.16(d,1H,J=3Hz).
3o	oil	DMSO-d_6	: 0.8-0.9(m+t,3H),1.0-1.6(m,4H),3.1-3.4(m,2H),7.08(d,1H,J=9Hz),7.2-8.1(m,7H),8.29(dd,1H,J_1=9Hz,J_2=3Hz),8.49(d,1H,J=3Hz),8.5(m,1H,exch).
3p	90-92[d]	DMSO-d_6	: 0.8 -0.9(m+t,3H),1.0-1.6(m,4H),3.1-3.4(m,2H),6.81(d,1H,J=9Hz),7.0-8.1(m,7H),8.18(dd,1H,J_1=9Hz,J_2=3Hz),8.45(d,1H,J=3Hz),8.6(m-t,1H,exch).

a) Amide band occurs in the range 1630-1650 cm^{-1} (Bruker WP - 80 CW).
b) From 2-propanol. c) From ethanol. d) From Et_2O. e) From EtOAc.
f) From hexane. g) From Et_2O-EtOAc. h) From Hexane-Et_2O. i) From $(Me_2CHO)_2O$-EtOAc.

TABLE 3. Microanalytical and Mass Spectral Data

3	Molecular Formula	Calculated (Found) C	H	N
b	$C_{20}H_{23}N_3O_5$	62.33 (62.40)	6.02 (6.01)	10.90 (10.88)
c	$C_{15}H_{22}N_2O_4$	61.21 (61.28)	7.53 (7.52)	9.52 (9.53)
d	$C_{17}H_{24}N_2O_4$	63.73 (63.69)	7.55 (7.55)	8.74 (8.73)
e	$C_{24}H_{24}N_2O_4$	71.27 (71.15)	5.98 (5.99)	6.93 (6.93)
f	$C_{18}H_{28}N_2O_4$	64.26 (64.18)	8.39 (8.39)	8.33 (8.34)
g	$C_{10}H_{12}N_2O_4$	53.57 (53.50)	5.39 (5.39)	12.49 (12.46)
h	$C_{14}H_{20}N_2O_4$	62.22 (62.40)	3.73 (3.73)	10.37 (10.35)
m	$C_{21}H_{26}N_2O_4$	68.09 (68.26)	7.07 (7.06)	7.56 (7.56)
n	$C_{17}H_{18}N_2O_4$	64.96 (64.86)	5.77 (5.76)	8.91 (8.90)
o	$C_{21}H_{20}N_2O_4$	69.22 (69.18)	5.53 (5.53)	7.69 (7.69)

High-resolution Molecular Peak for Compounds 3i, 3l and 3p

i	$C_{17}H_{18}N_2O_4$	Calc. $M^{+\cdot}$ 314.1266	(314.1269)
l	$C_{17}H_{16}Cl_2N_2O_4$	Calc. $M^{+\cdot}$ 308.0487($^{35}Cl_2$)	(308.0479)
p	$C_{21}H_{20}N_2O_4$	Calc. $M^{+\cdot}$ 364.1423	(364.1419)

the temperature indicated in Table 1, until complete disappearance of 1 occurred (TLC, silica gel, 60:40 hexane-tetrahydrofuran as eluent). Diethyl ether (600 ml) and water (200 ml) were added and after stirring (10 min), the organic layer was separated and evaporated in vacuo. The residue was then crystallized from a suitable solvent or purified by silica chromatography.

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A PREPARATIVE AVICEL-CELITE TLC

Submitted by Nobutaka Suzuki*† and Toshio Goto
(12/29/81)

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The reproducibility of R_f values is excellent on cellulose paper chromatograms (PC) but spots are apt to enlarge and only a very small