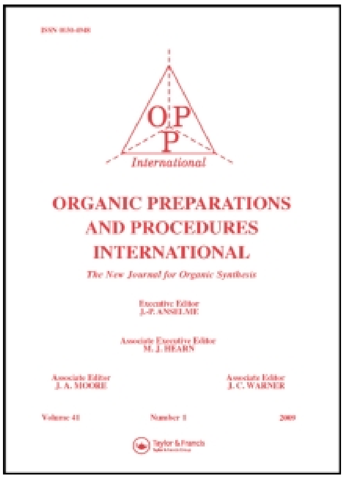

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CYCLIC CARBONATE ESTER OF 4-NITROCATECHOL. REACTIONS WITH AMINES

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CYCLIC CARBONATE ESTER OF 4-NITROCATECHOL. REACTIONS WITH AMINES

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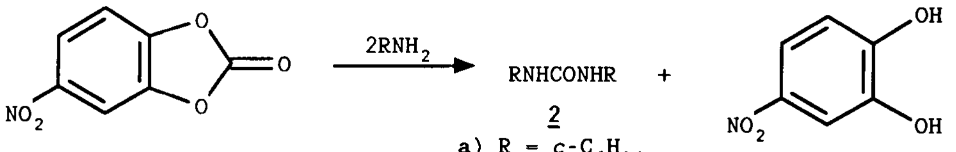
o-(4-Nitrophenylene) carbonate (5-nitrobenz-1,3-dioxol-2-one, **1**, NPC) was reported as a substrate for kinetic studies of carbonate ester hydrolysis.[1] Its preparation from 4-nitrocatechol and phosgene was described as the same as that utilized for bis-(4-nitrophenyl) carbonate, but few specific details regarding workup and yield were provided.[1,2] This procedure was not entirely successful in our hands, perhaps due to the prescribed exposure of the product to aqueous hydroxide in the course of reaction. Engaged in the development of new activated esters of carbonic acid as selective diacylating reagents, we set out to improve the procedure for preparing NPC and to study its reactions with several amines. The results indicate that NPC is a suitable reagent for the preparation of N,N'-disubstituted ureas.

Treatment of equimolar amounts of 4-nitrocatechol and 4-dimethylaminopyridine (DMAP) in tetrahydrofuran (THF) with excess phosgene (20% in toluene) consistently produced o-(4-nitrophenylene) carbonate (**1**, NPC) as pale yellow needles in 40-45% yields. Doubling the amount of DMAP did not significantly alter the yield of NPC, but replacing phosgene with 2/3 mol triphosgene[3] per mol 4-nitrocatechol and raising the temperature to 50-60^0 improved the yield of NPC to 81%. The melting



(1)

1

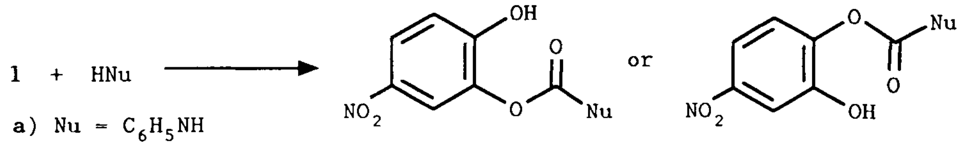
2

a) R = *c*-C_6H_{11}

b) R = C_6H_5

point of the product (100-101^0) was in good agreement with that reported by Fife and McMahon (99-100^0),[1] and the assigned structure **1** was confirmed by MS, IR, ^{13}C NMR and elemental analysis.

While the reaction of NPC (1 mol) with excess primary aliphatic amine (cyclohexylamine, 2.4 mol) in acetone at room temperature gave N,N'-dicyclohexylurea in 78% yield overnight, precipitation of product was observed about 1.5 hr following mixing. The weaker nucleophile (aniline, 2.7 mol), required overnight reflux with NPC (1 mol) in acetone to produce N,N'-diphenylurea in 87% yield. These reactions indicate that primary amines react with NPC to form symmetric N,N'-disubstituted ureas in accord with Eq. 1. On the other hand, addition of one equivalent of aniline in benzene led to a single adduct in 78% yield following overnight stirring at room temperature. Although infrared and elemental analyses are consistent with two possible structures (Eq. 2), product **3a** is the more likely alternative because the 4-nitro group would be expected to stabilize a transient negative charge at the 1-phenoxy site more effectively than at the 2-phenoxy by *para* resonance interaction. Reaction 2 may compete with 1, but since neither N,N'-diphenylurea nor 4-nitrocatechol are detected, its rate is substantially higher. The harsher conditions necessary for the preparation of N,N'-diphenylurea confirm that the second addition of amine nucleophile is more difficult than the first for the same reasons mentioned above, *i.e.* the *less* favorable process mounts a transition state with negative charge on the oxygen atom *meta* to the nitro group. This regiospecificity suggests a general procedure for the synthesis of asymmetric ureas RNHCONHR' by stepwise addition of RNH_2 (1 equiv) at room temperature followed by a small excess of $R'NH_2$ with or without isolation of intermediates. The preparation of N,N'-allylphenylurea from **3a** and allylamine is a promising example.



(2)

a) Nu = C_6H_5NH
b) Nu = Et_2N
c) Nu = c-$C_6H_{11}NH$

3

4

Similar results were obtained with diethylamine, a representative secondary amine. One equivalent of diethylamine was added to NPC in chloroform and following an overnight reaction at room temperature, a single product (mp. 149-151^{0}) was isolated in 61% yield. Its IR spectrum included characteristic nitro and carbamate bands consistent with **3b**. On the other hand, addition of one equivalent of cyclohexylamine to NPC in benzene gave a mixture of two adducts in 81% total yield on overnight reaction at room temperature. The major fraction (denoted **P1**, ~2/3), yellow plates, mp. 108-109^{0}, was obtained as a precipitate from the benzene solution. The minor fraction (**P2**, ~1/3), white flakes, mp. 124-126^{0}, was isolated from partial evaporation of the filtrate. The IR spectra of these two products included diagnostic NH, nitro and carbamate bands and differed in the fingerprint region. ^{13}C NMR comparison of **P1** and **P2** (Table I) indicates nearly identical cyclohexyl resonances but the chemical shifts of the 4-nitrophenylene groups did not match quite as well. Both these products, when reacted further with cyclohexylamine at room temperature, produced dicyclohexylurea and 4-nitrocatechol. This evidence suggests that fractions **P1** (yellow) and **P2** (white) correspond to structural isomers **3c** and **4c**, respectively. Although this reaction is not regioselective in the sense that both carbamate isomers are formed with one equivalent of cyclohexylamine, it is nevertheless suitable for the preparation of asymmetric ureas, since no contamination by DCU was detected following the first addition and the second addition led to N,N'-dicyclohexylurea exclusively. Results of all amine reactions with NPC are summarized in Table II.

Table I. ^{13}C NMR Chemical Shifts of Cyclohexyl Carbamates

chemical shifts, ppm[a]			
P1	**P2**	**P1**	**P2**
CO and aryl		cyclohexyl	
156.51	154.45	50.86	50.87
153.63	153.44	32.94	32.90
139.75	140.73	25.29	25.26
139.08	138.66	24.68	24.63
122.98	122.60		
119.14	119.00		
118.28	117.95		

a)Relative to $CDCl_3$ solvent triplet @ 77.00 ppm.

Table II. Reactions of NPC with Amines

Amine	mol/mol NPC	Conditions	Product	mp.(°C)	Yield(%)
$C_6H_5NH_2$	1.0	a	**3a**	162-163	78
$C_6H_5NH_2$	2.7	b	**2b**	240-241	87
$C_6H_{11}NH_2$	1.0	a	**P1**	108-109	56
			P2	124-126	25
$C_6H_{11}NH_2$	2.4	c	**2a**	230-231	78
$(CH_3CH_2)_2NH$	1.0	d	**3b**	149-151	61

a)Benzene, overnight RT. b)Acetone, overnight reflux. c)Acetone, overnight RT. d)Chloroform, overnight RT.

EXPERIMENTAL SECTION

Mps were determined on a Hoover oil-immersion unit and are uncorrected. ^{13}C NMR spectra were recorded on a Bruker HX-270 spectrometer operating at 67.89 MHz. IR spectra were obtained with a Beckman Acculab 2 spectrophotometer. Elemental analyses were performed at the Microanalysis Laboratory, University of Massachusetts at Amherst. Mass spectra were recorded on a Finnegan 4510B quadrupole mass spectrometer. Solvent evaporations were carried out with a Buchi Rotovapor apparatus. All reagents were supplied by the Aldrich Chemical Co. (except for the phosgene solution which was obtained from Fluka Industries) and were used as supplied. THF was distilled from CaH_2 and stored over 4A molecular sieves.

o-(4-Nitrophenylene) Carbonate (NPC, 1).- To a solution of 4-nitrocatechol (3.10 g, 20 mmol) in THF (250 mL) was added a solution of DMAP (2.44 g, 20 mmol) in THF (100 mL) in one portion with stirring. To this mixture was added dropwise with stirring a phosgene solution (84 mmol, 50 mL, 20% in toluene) over a period of 2 hrs. and the reaction mixture was further stirred at RT for 2 hrs. A white precipitate began to form on addition of the phosgene solution. Nitrogen was bubbled through the suspension for 15 min and the precipitate was removed by filtration. The solvent was evaporated and the residue was crystallized from hexane to yield product **1** (1.49 g, 41%) as pale yellow needles, mp. 100-101°. Dropwise addition of triphosgene[3] (3.96 g, 13.3 mmol) in THF (150 mL over 4 hrs. at RT), instead of excess phosgene, followed by 2-hr. stirring at 50-60° and the same workup gave 2.92 g (81%) of **1**. IR (KBr disc): 1830 (cyclic carbonate) and 1530, 1340 cm^{-1} (NO_2); ^{13}C NMR (ppm relative to $CDCl_3$ solvent triplet at 77.00 ppm) 149.77, 147.29, 144.87, 142.93, 121.62, 110.53, 106.87; MS, m/z 181 (M), 135 ($M-NO_2$), 107 ($M-CNO_3$).

Anal. Calcd. for $C_7H_3NO_5$: C, 46.42; H, 1.67; N, 7.74
Found: C, 46.24; H, 1.79; N, 7.61

N,N'-Dicyclohexylurea (**2a**).- A solution of NPC (0.91 g, 5.0 mmol) in acetone (50 mL) was treated with cyclohexylamine (1.20 g, 12 mmol) in acetone (20 mL) with stirring. Cloudiness was observed after *ca.* 1.5 hr and stirring was continued overnight at RT. The precipitate was collected, washed with acetone and dried to yield 0.87 g (78%) of **2a** as a white powder, mp. 230-231°, lit.[4] 232-233°; IR (KBr disc) 3330 (NH) and 1635 cm^{-1} (urea CO).

N,N'-Diphenylurea (**2b**).- NPC (0.91 g, 5.0 mmol) in acetone (100 mL) was mixed with an acetone solution (25 mL) of aniline (1.25 g, 13.4 mmol) and the mixture was refluxed overnight. Pouring into ice-water precipitated 0.92 g (87%) of an amorphous white solid following washing with water and drying, mp. 240°, lit.[5] 237-237.5°.

N-Phenyl-2-(1-hydroxy-4-nitrophenyl) Carbamate (**3a**). To a solution of NPC (0.91 g, 5.0 mmol) in benzene (50 mL) was added a solution of aniline (0.47 g, 5.0 mmol) in benzene (20 mL) dropwise with stirring. Following overnight stirring at RT, a white precipitate formed which was filtered and crystallized from benzene to yield 1.07 g (78%) of a product, mp. 162-163°; IR (KBr disc) 3370 (NH), 1700 (carbamate) and 1530, 1340, 740 cm^{-1} (NO_2).

Anal. Calcd. for $C_{13}H_{10}N_2O_5$: C, 56.93; H, 3.68; N, 10.22
Found: C, 56.92; H, 3.88; N, 10.24

1-Allyl-3-phenylurea.- Carbamate **3a** (0.51 g, 1.9 mmol) in THF (30 mL) was mixed with allylamine (0.11 g, 1.9 mmol) in THF (25 mL) and stirred overnight at RT. The volume of the solution was reduced by half, the residue was treated with saturated aqueous Na_2CO_3 and extracted with ether. The ether extracts were dried over $MgSO_4$ and evaporated to yield an oily residue which upon crystallization from hexane and recrystallization from benzene yielded 0.12 g (35%) of a white-flaky powder, mp. 115°, lit.[6] 115°.

N,N'-Diethyl-2-(1-hydroxy-4-nitrophenyl) Carbamate (**3b**).- A solution of NPC (0.91 g, 5.0 mmol) in chloroform (100 mL) was treated with diethylamine (0.37 g, 5.0 mmol) in chloroform (25 mL) in one portion and the reaction mixture was stirred overnight at RT. The solvent was removed in vacuum to yield an oil which was washed with boiling hexane (2x50 mL) leaving a brown residue. This was crystallized from EtOAc/hexane giving yellow needles which were dried at 80^0 in vacuum to yield 0.78 g (61%) of the product, mp. 149-151^0, IR (KBr disc) 1690 (carbamate) and 1535, 1340, 740 cm^{-1} (NO_2).

Anal. Calcd. for $C_{11}H_{14}N_2O_5$: C, 51.96; H, 5.56; N, 11.02
Found: C, 51.93; H, 5.71; N, 11.02

Reaction of NPC with Cyclohexylamine, P1 and P2.- A solution of cyclohexylamine (0.50 g, 5.0 mmol) in benzene (15 mL) was dripped into NPC (0.91 g, 5.0 mmol) in benzene (50 mL) with stirring. Cloudiness was observed after 5 min and stirring was continued overnight at RT. The precipitate was filtered and dried to obtain 0.79 g (56%) of **P1**, which was crystallized from benzene as yellow plates: mp 108-109^0; IR (KBr disc) 3330 (NH), 1710, 1680 (carbamate) and 1520, 1340, 740 cm^{-1} (NO_2). The volume of the filtrate was reduced, the precipitate was collected and dried to yield 0.35 g (25%) of **P2** which was crystallized from benzene as white flakes, mp. 124-126^0; IR (KBr disc): 3330 (NH), 1710, 1680 (carbamate) and 1530, 1345, 745 cm^{-1} (NO_2). ^{13}C NMR of **P1** and **P2**, Table I.

Anal. Calcd. for $C_{13}H_{16}N_2O_5$: C, 55.70; H, 5.77; N, 10.00
Found: C, 55.66; H, 5.67; N, 9.85 for **P1**
C, 55.60; H, 5.68; N, 9.86 for **P2**

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