Table 1. Preparation of Ketones from N-Methyl-N-(2-Pyridinyl)-N'-Propylene Urea and Grignard/Organolithium Reagents

Step 1[a] RMgBr, R	Step 2 R'Li or R'MgBr	Reaction conditions[b] temp. °C	time, h	Isolated yield, %[c]
CH_3	$CH_3(CH_2)_4C=CLi$	0 → r.t.	1	50
$C_6H_5(CH_2)_3$	EtMgBr	r.t.	1	63
	n-BuLi	0	0.3	86
$CH_3(CH_2)_4C=C$	t-BuLi	0	1	48
c-C_6H_{11}	n-BuLi	0	0.3	77
	sec-BuLi	r.t.	0.5	43
C_6H_5	$CH_2=CHCH_2MgBr$	r.t.	0.5	71
	C_6H_5MgBr	0 → r.t.	2	93
	n-BuLi	0	0.2	93
	n-BuLi (2 eq)	0	0.2	78
4-Cl-C_6H_4	CH_3Li	0 → r.t.	0.5	76
	C_6H_5MgBr	0 → r.t.	2	80
	C_6H_5Li	0 → r.t.	0.5	74
4-Me-C_6H_4	CH_3Li	0 → r.t.	0.5	78
	sec-BuLi	0	0.5	79
	t-BuLi	0	1	71
4-MeO-C_6H_4	$CH_3(CH_2)_4MgBr$	r.t.	2	77
	n-BuLi	0	0.2	90
	t-BuLi	0	1	74

[a] The Grignard reagent was added over a period of 15–20 min at 0 °C. [b] Reaction conditions indicate step 2. [c] The numbers indicate overall yield of two steps and all the products, purified by Kugelrohr distillation, were identified by comparison of their physical and spectral properties with reported data.

nificantly, the reaction was not limited to primary organolithium reagents and the N-acylaziridine intermediates react effectively with secondary and tertiary organolithiums. However, the steric hindrance of aliphatic Grignard reagents in the first step has fairly influenced the yield, and thus sequential reaction of cyclohexyl-magnesium bromide and sec-butyl lithium gave the corresponding ketone in 43% yield.

A representative experimental procedure is as follows. To the solution of N-methyl-N-(2-pyridinyl)-N'-propylene urea (306 mg, 1.6 mmol) in dry THF (3 ml) was added 6.4 ml of phenylmagnesium bromide (0.25 M in THF, 1.6 mmol) dropwise over a period of 15–20 min at 0 °C. After completion of the addition, stirring was continued for an additional 5–10 min at the same temperature, and then 1 ml of n-butyl lithium (1.6 M in hexane, 1.6 mmol) was added to the reaction mixture at 0 °C. After being stirred for 0.3 h, reaction mixture was quenched with 3% aqueous HCl and extracted with methylene chloride (30 ml) three times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under vacuum. The crude product was purified by Kugelrohr distillation (95–100 °C/5 mm, lit.[3c] 90–91 °C/2.8 mm) to give 259.3 mg (93%) of valerophenone: ^{1}H NMR (CDCl$_3$) 1.01 (t, 3H, J = 7 Hz), 1.15–2.08 (m, 4H), 2.98 (t, 2H, J = 7 Hz), 7.35–7.67 (m, 3H), 7.85–8.15 (m, 2H); IR (neat) 1680 cm^{-1} (C = O).

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5. ^{1}H NMR (CDCl$_3$) 1.12 (d, J = 6 Hz, 3H), 1.86–2.00 (m, 1H), 2.35–2.55 (m, 2H), 3.54 (s, 3H), 6.94–7.20 (m, 1H), 7.54–7.83 (m, 2H), 8.35–8.55 (m, 1H); IR (neat) 1665 (C = O), 3060 cm^{-1} (aromatic CH); MS (70 eV), m/z 191 (M$^+$, 15.0), 135 (CO-N(CH$_3$)-2-Py$^+$, 76.3), 107 (N(CH$_3$)-2-Py$^+$, 65.0), 78 (2-Py$^+$, 100). Anal. Calcd. for $C_{10}H_{13}N_3O$: C, 62.81; H, 6.85; N, 21.97. Found: C, 61.45; H, 6.75; N, 21.79.
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Convenient Synthesis of Carboxylic Anhydrides Using N-Methyl-2-Pyridinecarbamoyl Chloride

Jin Hee Kim and Jae In Lee*

Department of Chemistry, Duksung Women's University, Seoul 132-714

One-step synthesis of carboxylic anhydrides from the corresponding acids is usually accomplished by dehydration. This can be generally carried out with various dehydrating agents. They include N,N'-carbonyldiimidazole,[1] N,N'-dicyclohexylcarbodiimide,[2] tetracyanoethylene,[3] or thionyl chloride.[4] It has also been reported that triethylamine salts of carboxylic acids can be converted to anhydrides by reaction with phosgene,[5] N,N-diphenylcarbamoyl chloride,[6] organophosphorus reagents,[7] chlorosulfonyl isocyanate,[8] N,N,N',N'-tetramethylchloroformamidinium chloride,[9] mesyl chloride,[10] or phosphonium anhydride.[11] The advantage of these

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Table 1. Preparation of Carboxylic Anhydrides from Carboxylic Acids and N-Methyl-2-Pyridinecarbamoyl Chloride[a]

$$2 \ RCOOH + Cl-CO-N(CH_3)-2-Py + Et_3N \xrightarrow[THF, r.t.]{0.01 \ equiv \ DMAP} (RCO)_2O$$

RCOOH R	Isolated yield, %[b]	M.p. or b.p., °C/torr	
		Found	Lit.
$CH_3(CH_2)_5$	90	90–95/1.0	170–173/15[7]
c-C_6H_{11}	87	180–188/0.35	200/0.3[9]
$(CH_3)_3C$	96	80–85/13	78/12[7]
1-Adamantane	92	139–141	140–142[13]
$C_6H_5CH = CH$	91	134–137	135–136[8]
C_6H_5	94	40–41	40–42[7]
4-CH_3-C_6H_4	94	94–96	94[8]
4-Cl-C_6H_4	92	192–194	193–194.5[7]
4-CH_3O-C_6H_4	95	96–97	98–99[8]
$2,4,6$-$(CH_3)_3$-C_6H_2	94	103–104	103–104[7]
Nicotinic	78	120–122	122–123[5]

[a]The reaction was normally completed within 1.5 h at room temperature. [b]The numbers indicate purified yield after crystallization or distillation (Kugelrohr) and all products had identical spectral properties with reported data.

methods is direct conversion of the acids to the anhydrides, however some methods suffer from the disadvantage of separation of side products, heating conditions, and unstableness of dehydrating agents.

We now report that carboxylic anhydrides can be conveniently prepared from their corresponding acids by using N-methyl-2-pyridinecarbamoyl chloride in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP). The reagent was prepared by a modification of a known method[12] and thus by addition of an equimolar solution of 2-(methyl-

amino)pyridine and triethylamine in methylene chloride to a toluene solution of 2 equiv of a phosgene at 0°C over period of 15 min. Since the reagent was decomposed during aqueous work-up in ca. 5%, it was separated by dissolving in n-hexane after evaporation of methylene chloride and excess phosgene, followed by filtering off triethylamine hydrochloride. N-Methyl-2-pyridinecarbamoyl chloride was obtained in 92% yield after vacuum distillation and could be stored in a refrigerator for several weeks without any decomposition.
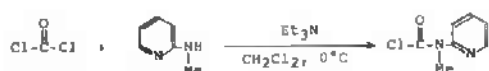
The effect of solvents and bases was examined for the dehydration of benzoic acid with N-methyl-2-pyridinecarbamoyl chloride and triethylamine to find out optimum conditions. When tetrahydrofuran, methylene chloride, diethyl ether, and acetonitrile were employed as a solvent in the presence of 0.01 equiv of DMAP, reaction was completed in 1.5 h, 8 h, 12 h, and 14 h, respectively. Furthermore, the use of 0.1 equiv of DMAP in tetrahydrofuran required 0.3 h for

the completion of the reaction, whereas the use of 0.5 equiv of pyridine, 0.5 equiv of 1,8-diazabicyclo[5,4,0]undec-7-ene, and 0.1 equiv of tetramethylguanidine required 2 h, 1.5 h, and 7 h, respectively. However, reaction of benzoic acid with N-methyl-2-pyridinecarbamoyl chloride in the presence of 0.1 equiv of DMAP without triethylamine did not give benzoic anhydride to an observable extent, even after 24 h at room temperature.

As shown in the Table 1, various structurally different carboxylic anhydrides can be conveniently prepared without side products in high yield by this method. The reaction works well with both aliphatic and aromatic carboxylic acids, including the hindered acids such as pivalic, 1-adamantanecarboxylic, and mesitoic acid. Significantly, reaction of carboxylic acids with N-methyl-2-pyridinecarbamoyl chloride did not give the corresponding N-methyl-N-(2-pyridyl)-carboxamides to an observable extent in contrast to the results obtained from the reaction of acids with N,N'-carbonyldiimidazole, di-2-pyridyl carbonate, or di-2-pyridyl sulfite, where the corresponding N-acylimidazoles or 2-pyridyl esters are produced as by-products. Furthermore, the presence of electron-withdrawing or electron-donating group in substituted benzoic acid does not affect the efficiency of the reaction under the present reaction conditions.

The typical experimental procedure is as follows. To a solution of 4-chlorobenzoic acid (313.1 mg, 2 mmol) and triethylamine (139.4 μl, 1 mmol) in tetrahydrofuran (2 ml) at room temperature was added N-methyl-2-pyridinecarbamoyl chloride (170.6 mg, 1 mmol) in tetrahydrofuran (3 ml), and then DMAP (1.2 mg, 0.01 mmol). After being stirred for 1.5 h at room temperature, the reaction mixture was diluted with methylene chloride, washed with 5% $NaHCO_3$, 0.025 M oxalic acid, and saturated NH_4Cl. The organic phase was dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness under vacuum. The crude prduct could be crystallized from acetonitrile to afford 4-chlorobenzoic anhydride in 92% yield. M.p. 192–194 °C [lit.[7] 193–194.5 °C]; ^{1}H NMR ($CDCl_3$) 7.52 (d, 2H, J = 8.4 Hz), 8.12 (d, 2H, J = 8.4 Hz); IR (KBr) 1715, 1780 cm^{-1} (C = O).

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Kinetic Isotope Effects in Bimolecular Nucleophilic Displacement of Ethyl and Phenacyl Derivatives by Deuterated Aniline Nucleophiles. Evidence for Resonance Shunt Phenomenon

Ikchoon Lee*, Han Joong Koh, and Hai Whang Lee

Department of Chemistry, Inha University, Inchon 402-751

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Kinetic isotope effects (KIE) observed with deuterated aniline nucleophiles in S_N2 reactions can be a versatile tool in the elucidation of the transition state (TS) structure.[1] We report here the KIE determined for the associative S_A2 reactions of ethyl (EBS) and phenacyl benzenesulfonates (PAB) with deuterated aniline nucleophiles in acetonitrile, presenting evidence for the TS variation predicted by cross-interaction constants, ρ_{ij} and β_{ij} in eqs. (1).[2]

$$\log (k_{ij}/k_{HH}) = \rho_i \sigma_i + \rho_j \sigma_j + \rho_{ij} \sigma_i \sigma_j \quad (1a)$$

$$= \beta_i \Delta pK_i + \beta_j \Delta pK_j + \beta_{ij} \Delta pK_i \Delta pK_j \quad (1b)$$

where i, j and k represent the substituents in the nucleophile, substrate or leaving group (LG).

The sign and magnitude of the cross-interaction constant, ρ_{XZ} (and β_{XZ}), between substituents X in the nucleophile and Z in the leaving group have indicated that the reactions of EBS[3] and PAB[1a] with anilines are very similar; they proceed by an associative S_A2 mechanism with large positive ρ_{XZ} (and β_{XZ}) reflecting relatively tight TS compared to a dissociative S_N2 reaction e.g., the reaction of benzyl benzenesulfonates (BBS) with anilines[2a,4] for which ρ_{XZ} (β_{XZ}) is not only negative but also is smaller in magnitude (Table 1). The dissociative and associative nature of the S_A2 TS, for the reactions of BBS and EBS, respectively, are indeed evidenced by the magnitude of the inverse secondary α-deuterium KIE observed (Table 1) with deuterated aniline nucleophiles. Reference to Table 1 reveals that the inverse secondary KIE are greater, i.e., the k_H/k_D values are smaller, for the reactions of EBS than for those of BBS correctly reflecting the greater degree of bond formation for EBS. Moreover, for a stronger nucleophile ($X = p-CH_3O$) and a better LG ($Z = p-NO_2$) the k_H/k_D values

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(1) $^lXC_6H_4NH_2(D_2) + YC_6H_4CH_2OSO_2C_6H_4Z \xrightarrow[\ 30.0\ ^\circ C\ ]{MeCN}$

(2) $XC_6H_4NH_2(D_2) + C_2H_5OSO_2C_6H_4Z \xrightarrow[\ 65.0\ ^\circ C\ ]{MeCN}$

(3) $XC_6H_4NH_2(D_2) + YC_6H_4COCH_2OSO_2C_6H_4Z \xrightarrow[\ 45.0\ ^\circ C\ ]{MeCN}$

Substituents[a]		Reactions		
		(1)[1]	(2)	(3)
X	Z	k_H/k_D		
$p-CH_3O$	$p-NO_2$	$0.89_8 \pm 0.007$[*]	$0.86_9 \pm 0.009$	$1.02_9 \pm 0.008$
$p-CH_3O$	$p-CH_3$	$0.95_5 \pm 0.007$	$0.86_2 \pm 0.008$	$1.03_4 \pm 0.009$
$m-NO_2$	$p-NO_2$	$0.95_1 \pm 0.007$	$0.85_8 \pm 0.006$	$1.05_7 \pm 0.008$
$m-NO_2$	$p-CH_3$	$0.97_3 \pm 0.005$	$0.85_1 \pm 0.010$	$1.07_8 \pm 0.008$
		$\rho_{XZ}(\beta_{XZ})^{[2a,3]}$		
		$-0.10(-0.06)$	$0.33(0.19)$	$0.32(0.19)$

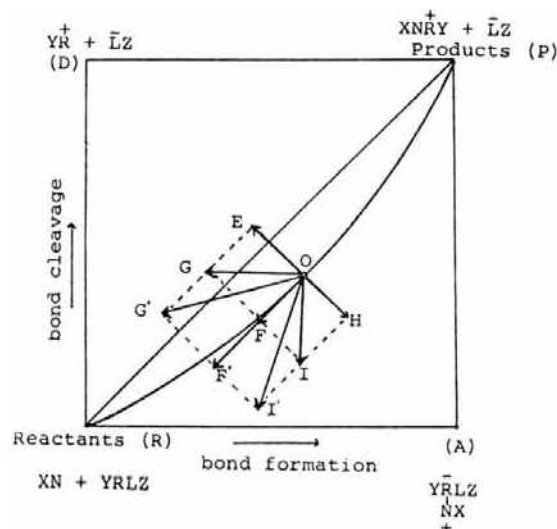[a] Y = H for reactions 1 and 3. [*] Standard error.

Figure 1. The potential energy surface diagram for an associative S_A2 reactions. X, Y and Z are the substituents in the nucleophile N, substrate R and leaving group L; $OF = OE = OH$, $OF' > OE$ or OH.

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are smaller with BBS but are greater with EBS as the opposite sign of ρ_{XZ} requires; a negative ρ_{XZ} in eq. (2) indicates that a more electron-withdrawing substituent in the LG i.e., a better LG, ($d\sigma_Z > 0$) leads to a greater negative ρ_X ($d\rho_X < 0$) i.e., to a later TS with a greater degree of bond formation as

$$\rho_{XZ} = \frac{\partial^2 \log k_{XZ}}{\partial \sigma_X \partial \sigma_Z} = \frac{\partial \rho_X}{\partial \sigma_Z} \left(= \frac{\partial \rho_Z}{\partial \sigma_X} \right) \quad (2)$$

required by the TS variation predicted by the quantum mechanical (QM) model,[4a,5] whereas if the ρ_{XZ} value is positive, a better LG leads to an earlier TS with a less degree of bond formation in accordance with the TS variation predicted by the potential energy surface (PES) diagrams.[6] Figure 1. In this PES model an electron-withdrawing substituent in the LG ($Z = p-NO_2$) stabilizes the upper corners, P and D, so that the TS shifts to G, i.e., bond formation is less, if the Hammond and anti-Hammond (or Thornton) effets are