..., 379 (1) and 381 (0.7) ($M^{\cdot+} - C_7H_6Cl^{\cdot}$), 504 (0.5) and 506 (0.4) ($M^{\cdot+}$).

Anal. Calcd for $C_{26}H_{23}Cl_3O_4$: C, 61.72; H, 4.55; Cl, 21.07. Found: C, 61.71; H, 4.66; Cl, 21.02.

2,3,5-Tri-*O*-(4-chlorobenzyl)-α- and -β-L-arabinofuranose (12): recrystallized from ether–hexane; mp 87–88 °C; $[\alpha]^{22}_D$ −3.3° (*c* 1.8, $CHCl_3$); R_f 0.25 (solvent F); IR (CCl_4) 3450 (OH), 3020, 2910, 2860, 1600, 1550, 1490, 1410, 1360, 1250, 1210, 1090, 1060, 1020, 970, 800 (br) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, α/β ~1:1) δ 3.51 and 3.57 (2 m, 2 H, $J_{4\alpha,5A\alpha} = J_{4\alpha,5B\alpha} = 4.7$ Hz, $J_{4\beta,5A\beta} = J_{4\beta,5B\beta} = 4.0$ Hz, $J_{5A,5B} = 10.1$ Hz, H-5Aα,β, H-5Bα,β), 3.87 (dd, 0.5 H, $J_{2\alpha,3\alpha}$ ~ 1.5 Hz, $J_{3\alpha,4\alpha} = 4.0$ Hz, H-3α), 3.95 (d, 0.5 H, H-2α), 3.99 (t, 0.5 H, $J_{1\beta,2\beta} = 4.0$ Hz, $J_{2\beta,3\beta}$ ~ 5 Hz, H-2β), 4.08 (m, 0.5 H, H-4β), 4.10 (q, 0.5 H, H-4α), ~4.42 (m, 0.5 H, H-3β), 4.40–4.55 (m, 5.5 H) and 4.63 (d, 0.5 H) (3 OCH_2Ar), 5.33 (d, 0.5 H, H-1β), 5.39 (s, 0.5 H, H-1α), 7.18–7.35 (m, 12 H, 3 C_6H_4); MS, *m/z* 125 (100) and 127 (32) ($C_7H_6Cl^+$), 126 (8), 69 (8), 115 (7), 89 (7), 141 (4), 77 (3), 90 (3), 128 (3), ..., 397 (2) and 399 (1) ($M^{\cdot+} - C_7H_6Cl^{\cdot}$).

Anal. Calcd for $C_{26}H_{25}Cl_3O_5$: C, 59.59; H, 4.77. Found: C, 59.71; H, 4.83.

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Registry No. 3, 108008-65-7; 4, 108008-66-8; 5, 108008-67-9; 6, 108008-68-0; 7, 108008-69-1; 8, 108008-70-4; 9, 52706-45-3; 10, 108008-71-5; 11, 108008-72-6; 12, 108008-73-7; methyl β-D-ribofuranoside, 7473-45-2; methyl α-D-ribofuranoside, 52485-92-4; methyl α-L-arabinofuranoside, 3795-68-4.

Tetrahedral Intermediates Formed by Nitrogen and Oxygen Attack of Aromatic Hydroxylamines on Acetyl Cyanide

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Aromatic hydroxylamines **1** have been postulated as intermediates in the carcinogenic process induced by some aromatic amines. The necessary chemical activation of **1** for the latter stages of this process can subsequently be achieved by O-acylation, rendering the N–O bond labile for cleavage and reaction with DNA bases.[2] We have discovered that aromatic hydroxylamines react with aroyl cyanides at room temperature to afford in almost quantitative yield the O-aroylated derivatives,[3] of obvious interest in carcinogenesis. More recently it became possible to observed directly,[4] by using ^1H and ^{13}C NMR spectroscopy, an O-tetrahedral intermediate **3a** formed in the reaction between *N*-phenylhydroxylamine (**1a**) and acetyl cyanide (**2**) (Scheme I) and to demonstrate its base-catalyzed decomposition to the *O*-acyl derivative **5a**. We present in this paper evidence that O-tetrahedral intermediates such as **3** result from thermodynamic control and that under kinetic control N-tetrahedral intermediates such as **4** are formed instead.

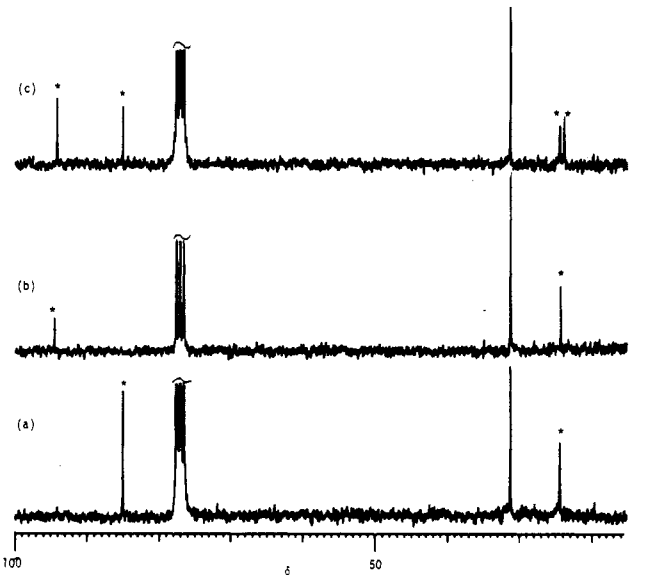
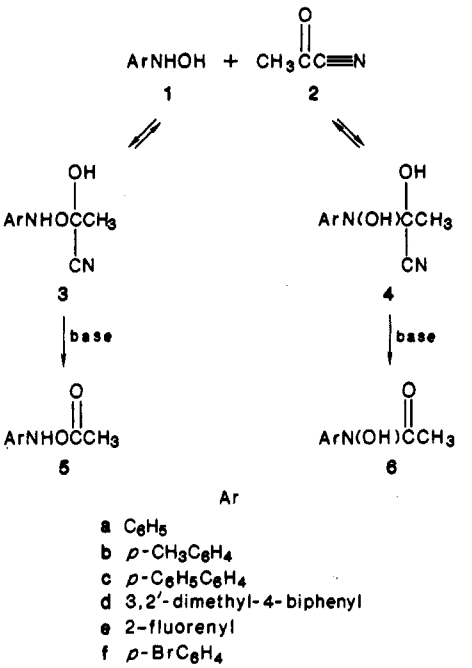


Figure 1. ^{13}C NMR spectra at 62.93 MHz for the reaction between **2** and **1c** in 50% (v/v) $CDCl_3/CD_3CN$: (a) at 215 K immediately after mixing, corresponding to formation of **4c**; (b) warming to 285 K, corresponding to **3c**; (c) recooling to 215 K, showing the presence of both **3c** and **4c**. Key carbon atoms referred to in the text are indicated with an asterisk. Peaks at δ 77.0 and 31.0 are due to *C*DCl_3 and *Me*COCN, respectively.

Scheme I



Results and Discussion

When ^{15}N-labeled **1a** is mixed with **2** at 215 K in acid-free solution[5] of 50% (v/v) $CDCl_3/CD_3CN$, the formation of a single new species can be observed with ^1H and ^{13}C NMR spectroscopy. This is attributed to **4a** on the following basis: The new sp^3 carbon resonance[4] appears as a doublet [δ 85.0 ($^1J_{^{15}N-^{13}C} = 1.3$ Hz)],[6] as does the new

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(5) Our previous study[4] was carried out in $CDCl_3$ solutions containing traces of DCl. Under these conditions, **3** was found to dcompose rapidly to **5** at room temperature. If rigorously purified $CDCl_3$ or mixtures of $CDCl_3/CD_3CN$ are used, no decomposition of the tetrahedral intermediate **3** is observed over a period of several hours at temperatures up to 290 K.

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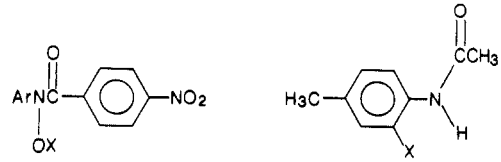
methyl resonance [δ 24.3 (^2J = 3.7 Hz)] and the nitrile resonance [δ 117.7 (^2J = 1.9 Hz)]. However, on warming to temperatures between 265 and 290 K, these peaks are almost entirely replaced by new ones at δ 94.3 (doublet, ^2J = 2.5 Hz), 24.0 (doublet, ^3J = 0.8 Hz), and 117.6 (singlet), attributed previously[4] to the formation of **3a**. The corresponding ^{1}H methyl resonances in **4a** and **3a** are observed at δ 1.52 and 1.76, respectively. The other aromatic hydroxylamines **1b–f** behave in essentially the same way (cf. Experimental Section).

When these solutions are recooled to 215 K (Figure 1), the NMR peaks attributed to, e.g., **4c** reappear, in addition to the presence of peaks due to **3c**. We interpret these results as indicating that at 215 K formation of **4** is fast compared to that of **3**,[7] which is therefore not observed under nonequilibrium conditions. The relative ratio of the tetrahedral intermediates **3** and **4** and unreacted acetyl cyanide **2** present in solution were obtained from the ^{1}H NMR spectra, using the methyl resonance derived from the acetyl cyanide (at 243 K, solutions 100–150 mM, δ): **3b**, 1.75, **4b**, 1.48, **3b/4b/2** = 53:38:9 (CD_3CN); **3c**, 1.79, **4c**, 1.58, **3c/4c/2** = 28:7:65 (CD_3CN); **3d**, 1.81, **4d**, 1.51, **3d/4d/2** = 28:3:69 (CD_3CN); **3e**, 1.84, **4e**, 1.52, **3e/4e/2** $\approx$ 17:1:82 (CD_2Cl_2); **3f**, 1.79, **4f**, 1.56, **3f/4f/2** = 23:34:43 ($CDCl_3/CD_3CN$, 1:1). At higher temperatures, under equilibrium conditions, **3** is significantly favored over **4**. On recooling to 215 K, the concentration of **4** increases relative to **3**, although the latter still predominates.

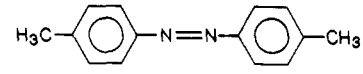
Addition of DABCO (1,4-diazabicyclo[2.2.2]octane) at 243 K to the reaction mixture of **1b** and **2** in acetonitrile, which was shown, by ^{1}H NMR, to contain at that temperature a relative ratio of **3b/4b** equal to 58:42, led to an extremely rapid appearance of hydroxamic acid **6b** and the *O*-acetyl derivative **5b** is essentially the same ratio. The structure of the *O*-acetyl compounds **5a** and **5f** was further ascertained by synthesis, isolation of the crystalline *N*-*p*-nitrobenzoyl derivatives **7a** and **7f**, and comparison with authentic samples synthesized independently via acylation of the corresponding hydroxamic acids **8a** and **8f**. Compound **5b** was too unstable for isolation and gave rise at room temperature to a complex mixture of products. Detailed analysis of the reaction mixture resulting from the reaction between **1b** and acetyl cyanide showed a marked dependence on the temperature. Thus while at 243 K the products *isolated* were the hydroxamic acid **6b** (42.5%) and the phenol amide **9** (25.5%), at room temperature the compounds *isolated* were **6b** (5%), **9** (34%), **10** (11%), **11** (15%), and **12** (10%), an observation which has precedent.[3]

Hydroxylamines **1c–e**, which are useful model carcinogens, led also to very unstable *O*-acetyl compounds **5**. Typically, a dichloromethane solution of **5e** containing DABCO decomposed entirely in less than 2 h at 243 K, affording, among other products, the corresponding hydroxamic acid **6e**, unlike **5a**, which remained unaltered under the same conditions. It is noteworthy that this instability closely parallels the known[8] carcinogenicity of the parent hydroxylamines.



7a, X = $COCH_3$
7f, X = $COCH_3$
8a, X = H
8f, X = H

9, X = OH
10, X = H



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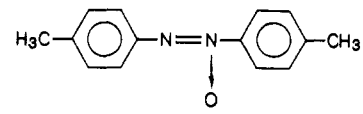

12

Experimental Section

General Methods. Melting points were determined with a Kofler hot-stage melting point apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer 457 spectrometer. ^{1}H and ^{13}C NMR spectra were obtained in 50–150 mM solutions of deuteriated solvents on Bruker CXP300 and WM250 spectrometers with tetramethylsilane as a reference. The sample temperatures were calibrated by using standard methanol samples together with the chemical shift data of Van Geet.[9] Thin-layer chromatography (TLC) was carried out on silica gel (GF_{254}) (0.5 mm thick for preparative work, PTLC). Microanalyses were performed at the Microanalytical Laboratory in Centro de Química Estrutural, INIC, Lisbon. Acetyl cyanide was commercially available from Fluka. Compounds **1a**, **1b**, and **1f** were obtained by reduction of the corresponding nitro compounds by standard methods[10] and have melting points respectively of 80–81 (lit.[10] mp 81 °C), 91–92 (lit.[11] mp 93–94 °C), and 86–88 °C (lit.[12] mp 90 °C). Compounds **1c** and **1e** were kindly supplied by Dr. F. Beland, and compound **1d** was supplied by Dr. T. J. Flammang (National Center for Toxicological Research, Jefferson, AR).

Reaction between 1b and 2. At 243 K. To a solution of *N*-(4-methylphenyl)hydroxylamine (**1b**) (0.25 M) in dry acetonitrile, cooled to 243 K, under nitrogen, was added acetyl cyanide (1 equiv) and left to react for 45 min. Monitoring of the ^{1}H NMR peaks at δ 1.73 and 1.48 due to the methyl group attached to the sp^3 central carbon atoms revealed an equilibrium ratio of **3b/4b** of 58:42. Addition of DABCO (2 equiv) at 243 K to the reaction mixture caused the immediate disappearance of **3b** and **4b** and appearance of **5b** [δ (CD_3CN) 2.22 (s, CH_3CO)] and **6b** [δ (CD_3CN) 2.14 (s, CH_3CO)] in essentially the same ratio (NMR). Removal of the solvent under reduced pressure at temperatures not exceding 313 K and redissolution of the oily residue obtained in dichloromethane was followed by extraction of the organic phase with an aqueous HCl, 1 N (solution A), and then with aqueous solution of 1 N NaOH (solution B). From solution B, after careful neutralization with dilute HCl, extraction with dichloromethane, drying of the organic phase with anhydrous sodium sulfate, filtration, and solvent removal, *N*-(4-methylphenyl)acetohydroxamic acid (**6b**) (34% yield) was obtained [mp 71–73 °C (dichloromethane–petroleum ether); IR (KBr) 3120 and 1625 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.14 (s, 3 H), 2.27 (s, 3 H), 7.19 (d, J = 8.8 Hz, 2 H), 7.41 (d, J = 8.8 Hz, 2 H)], identical in all respects with an authentic sample. From the aqueous solution A, after neutralization, extraction with ethyl acetate, and PTLC purification (SiO_2; eluent, CH_2Cl_2/ethyl acetate, 2:1), more hydroxamic acid **6b** (8.5%) was recovered. The remaining organic phase of dichloromethane, upon partial removal of the solvent and PTLC (SiO_2; eluent CH_2Cl_2/ethyl acetate, 5:1) crystals of 2-hydroxy-

(6) The relative small one-bond coupling found between ^{15}N and the new sp^3 carbon in **4a** has been previously encountered (cf.: Schulman, J. M.; Venanzi, T. *J. Am. Chem. Soc.* **1976**, *98*, 6739) and attributed to the extremely large perturbation created by the nitrogen lone pair character.

(7) This kinetic effect can be expected by extrapolation of the work of Jencks (cf.: Palling, D. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 4869), where the rate constants for N- and O-acetylation of hydroxylamine with acetyl chloride are found to be 28000 and 8900 M^{-1} s^{-1}, respectively.

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4-methyl acetanilide (9) (25.5% yield), mp 167-169 °C (CH_2Cl_2/petroleum ether) (lit.[13] mp 169-170 °C).

At Room Temperature. Repetition of the previous reaction at ca. 22 °C gave rise to a complex mixture, which was purified by PTLC (SiO_2; CH_2Cl_2), yielding 4,4'-dimethylazobenzene (11) [10% yield; mp 142-144 °C (MeOH) (lit.[14] mp 143 °C], 4,4'-dimethylazoxybenzene (12) [15% yield; mp 67-69 °C (MeOH) (lit.[15] mp 68 °C)], 4-methylacetanilide (10) [11% yield; mp 146-148 °C (CH_2Cl_2/petroleum ether) (lit.[16] mp 146-146.5 °C; IR (KBr) 3280 and 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.16 (s, 3 H)], 2-hydroxy-4-methylacetanilide (9) [34% yield; mp 168-169 °C (CH_2Cl_2/petroleum ether) (lit.[13] mp 169-170 °C); IR (KBr) 3260, 3100, and 1640 cm^{-1}, ^{1} H NMR ($CDCl_3$) δ 2.26 (s, 3 H)], and *N*-acetyl-*N*-(4-methylphenyl)hydroxylamine (**6b**) [5% yield; mp 71-73 °C (CH_2Cl_2/petroleum ether)] identical with an authentic sample.

Reaction between 5a,f and 4-Nitrobenzoyl Chloride. To a solution of **1a** (0.1 M) in dry benzene at room temperature was added **2** (1 equiv) and the reaction monitored by TLC (SiO_2; CH_2Cl_2) until completion (ca. 2 h). TLC showed the mixture to contain essentially **5a** [IR (neat) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.22 (s, 3 H)], contaminated with a small amount (≤15%) of **6a**, which was removed by shaking the organic phase with a cold (0-5 °C) aqueous solution of NaOH, 1 N, until the organic phase no longer gave a positive test with ferric chloride (absence of hydroxamic acid). To the benzene solution, after washing with water, drying with anhydrous Na_2SO_4, and filtering, were added solid sodium bicarbonate (1 equiv) and 4-nitrobenzoyl chloride (1 equiv) dissolved in dry benzene. The reaction was left to react at room temperature for 24 h, and after filtration, evaporation of the solvent, and crystallization of the residue from dichloromethane/petroleum ether, **7a** was obtained (18.5% yield): mp 146.5-148 °C; IR (KBr) 1780 and 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.21 (s, 3 H), 7.33 (s, 5 H), 7.68 (d, J = 9 Hz, 2 H), 8.13 (d, J = 9 Hz, 2 H). Anal. Calcd for $C_{15}H_{12}N_2O_5$: C, 60.00; H, 4.03; N, 9.33. Found: C, 60.29; H, 4.08; N, 9.35.

Similarly, **7f** was obtained (29% yield): mp 162-163 °C (dichloromethane/petroleum ether); IR (KBr) 1770 and 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.17 (s, 3 H), 7.22 (d, J = 7.5 Hz, 2 H), 7.48 (d, J = 7.5 Hz, 2 H), 7.70 (d, J = 8.7 Hz, 2H), 8.18 (d, J = 8.7 Hz, 2 H). Anal. Calcd for $C_{15}H_{11}BrN_2O_5$: C, 47.52; H, 2.92; N, 7.39. Found: C, 47.58; H, 3.15; N, 7.52.

General Method for the Preparation of Hydroxamic Acids. To a cooled (0-5 °C) solution of *N*-arylhydroxylamine (ca. 0.2 M) in dry benzene or diethyl ether containing in suspension sodium bicarbonate (1.1 equiv) was added acyl chloride (1.1 equiv). The reaction was monitored by TLC (SiO_2; CH_2Cl_2/MeOH, 100:1; red color upon spray with an aqueous solution of ferric chloride). The hydroxamic acid was isolated after filtration of the reaction mixture, evaporation of the solvent, and crystallization of the residue.

***N*-Acetyl-*N*-phenylhydroxylamine (6a)**: 86% yield; mp 64-66 °C (ethyl acetate/petroleum ether) (lit.[17] mp 65-66 °C); IR (KBr) 3020 and 1630 cm^{-1}; ^1H NMR (CD_3CN) δ 2.18 (s, 3 H), 7.27-7.60 (m, 5 H), 8.42 (br s, 1 H, OH).

***N*-Acetyl-*N*-(4-methylphenyl)hydroxylamine (6b)**: 80% yield; mp 71-72.5 °C (dichloromethane/petroleum ether) (lit.[18] mp 72-73 °C); IR (KBr) 3120 and 1625 cm^{-1}; ^1H NMR (CD_3CN) δ 2.14 (s, 3 H), 2.27 (s, 3 H), 7.19 (d, J = 8.8 Hz, 2 H), 7.41 (d, J = 8.8 Hz, 2 H).

***N*-Acetyl-*N*-(4-bromophenyl)hydroxylamine (6f)**: 80% yield; mp 129-130 °C (dichloromethane/petroleum ether) (lit.[19] mp 130-132 °C); IR (KBr) 3140 and 1615 cm^{-1}; ^1H NMR (CD_3CN) δ 2.09 (s, 3 H), 7.71 (d, J = 9 Hz, 2 H), 8.18 (d, J = 9 Hz, 2 H), 8.54 (br s, 1 H, OH).

***N*-(4-Nitrobenzoyl)-*N*-phenylhydroxylamine (8a)**: 66% yield; mp 157-159 °C (dichloromethane/petroleum ether) (lit.[20] mp 163 °C); IR (KBr) 3170 and 1610 cm^{-1}; ^1H NMR [$(CD_3)_2CO$] δ 7.25 (t, J = 7.5 Hz, 1 H), 7.42 (t, J = 7.5 Hz, 2 H), 7.67 (d, J = 8.7 Hz, 2 H), 7.92 (d, J = 8.7 Hz, 2 H), 8.29 (d, J = 7.5 Hz, 2 H).

***N*-(4-Nitrobenzoyl)-*N*-(4-bromophenyl)hydroxylamine (8f)**: 73% yield; mp 140-141.5 °C (dichloromethane/petroleum ether); IR (KBr) 3100 and 1590 cm^{-1}; ^1H NMR [$(CD_3)_2CO$] δ 7.59 (d, J = 8.7 Hz, 2 H), 7.70 (d, J = 7.5 Hz, 2 H), 7.95 (d, J = 7.5 Hz, 2 H), 8.31 (d, J = 8.7 Hz, 2 H), 10.08 (br s, 1 H, OH). Anal. Calcd for $C_{13}H_9BrN_2O_4$: C, 46.31; H, 2.69; N, 8.31. Found: C, 46.15; H, 2.81; N, 8.24.

Acetylation of 8a and 8f. To a solution at room temperature of the hydroxamic acid (0.25 M) in dry benzene containing sodium bicarbonate (1.1 equiv) was added acetyl chloride (1.1 equiv). The reaction mixture after standing for ca. 24 h (until no more hydroxamic acid was detected by TLC) was filtered, the solvent distilled under reduced pressure, and the residue crystallized from dichloromethane/petroleum ether. *O*-Acetyl-*N*-(4-nitrobenzoyl)-*N*-phenylhydroxylamine (**7a**) and *O*-acetyl-*N*-(4-nitrobenzoyl)-*N*-(4-bromophenyl)hydroxylamine (**7f**) were obtained with melting points, mixed melting points, and spectroscopic properties identical with those of compounds isolated from the reaction between **5a** or **5f** and 4-nitrobenzoyl chloride.

Acknowledgment. We are pleased to acknowledge Junta Nacional de Investigação Científica e Tecnológica, Calouste Gulbenkian Foundation, NATO, and Instituto Nacional de Investigação Científica (Portugal) for financial support.

Registry No. **1a**, 100-65-2; **1b**, 623-10-9; **2**, 631-57-2; **1f**, 10468-46-9; **6a**, 1795-83-1; **6b**, 27451-21-4; **6f**, 67274-48-0; **7a**, 19958-60-2; **7f**, 108009-19-4; **8a**, 2029-61-0; **8f**, 108009-20-7; **9**, 13429-10-2; **10**, 103-89-9; **11**, 501-60-0; **12**, 955-98-6.

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One-Pot Preparation of Tertiary Alkyl Carboxylates and Sulfonates from Ketones

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Received December 10, 1986

Carboxylic and sulfonic acid esters are important categories of organic compounds useful in both synthetic applications and mechanistic studies. The commonly employed preparation method is the reaction of alcohols and acid chlorides in basic media.[1,2] For reactive tertiary alkyl esters the use of the corresponding metal alcoholates under neutral conditions becomes necessary.[3] Since tertiary alcohols are frequently synthesized by the addition of Grignard reagents to the appropriate carbonyl compounds, the drawbacks of such reactions, e.g., steric hindrance to additions, intolerance of labile groups, and the possibility of elimination in isolation steps, make the two-step preparation inconvenient. An improved method, using organolithium reagents followed by esterification, has been used for preparing highly hindered tertiary *p*-nitrobenzoates.[4]

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