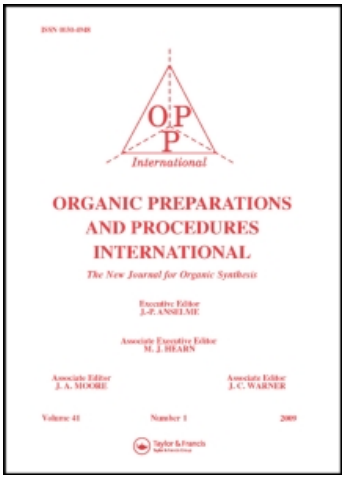

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ACYLATION AND ALKYLATION OF 2- AND 4-METHYLBENZONITRILE

Richard A. Bunce[a]; Lara B. Johnson[a]
[a] Department of Chemistry, Oklahoma State University, Stillwater, OK

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ACYLATION AND ALKYLATION OF 2- AND 4-METHYLBENZONITRILE

Richard A. Bunce* and Lara B. Johnson

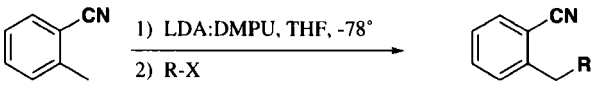
Department of Chemistry, Oklahoma State University
Stillwater, OK 74078-3071

A recent project required a convenient route to methyl (2-cyanophenyl)acetate (**2a**). Reference to the literature revealed that several syntheses of this compound (or the ethyl ester) have been published: 1) Sandmeyer reaction of (2-aminophenyl)acetic acid to give (2-cyanophenyl)acetic acid followed by treatment with diazomethane,[1] 2) $S_{RN}1$ arylation of the ethyl acetoacetate anion by 2-bromobenzonitrile,[2] 3) acylation of the 2-methylbenzonitrile anion with diethyl carbonate,[3] and 4) regioselective enzyme catalyzed hydrolysis of (2-cyanophenyl)acetonitrile followed by treatment with diazomethane.[4] These syntheses all have serious drawbacks, including multiple steps, low yields, or the use of expensive or hazardous reagents. We have modified the conditions used to acylate the anions of 2- and 4-methylbenzonitrile, and expanded the scope of the reaction to include a variety of acylation and alkylation reactions.[5]

The current work sought to utilize lithium diisopropylamide (LDA) for the deprotonation of the benzonitrile derivatives. One previous report[6] has appeared using LDA:HMPA to generate the anions of 2-, 3- and 4-methylbenzonitrile. Self-acylations were observed for the 3- and 4-methyl isomers when 2 eq. of the nitrile were treated with 1 eq. of base. Alkylations were also carried out, but these were largely restricted to studies on 3-methylbenzonitrile; only one other alkylation result was reported for the 4-methyl isomer. The current work refines this procedure by use of less hazardous LDA:DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone)[7] as the base. Alternative acylating agents are also employed which permit greater structural diversity in the products. Finally, acylation and alkylation of 2-methylbenzonitrile are described. While the compounds prepared here differ from those in the earlier paper, it appears that these modifications provide improved yields for both processes.

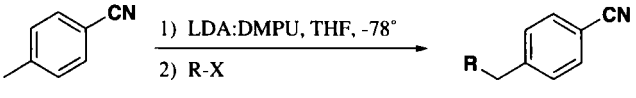
The results of our study are summarized in the Scheme. The procedure was initiated by deprotonation of 2-methylbenzonitrile using 1:1 LDA:DMPU in THF at -78°. Treatment of the anion with methyl chloroformate followed by protic workup gave **2a** in 76% yield after purification. Because the acylation product is considerably more acidic than the starting 2-methylbenzonitrile, 2.1 eq. of LDA:DMPU were used in the reaction to prevent quenching of the reacting anion by **2a**.[8] Similarly, acylation of 4-methylbenzonitrile afforded **4a** in 74% yield. Product purification, in both cases,

was readily accomplished by column chromatography.



1 **2**

R-X	eq. LDA:DMPU	Product	% Yield
MeOCO-Cl	2.1	**2a** (R = CO_2Me)	76
$PhCH_2$-Br	1.1	**2b** (R = CH_2Ph)	90
CH_2=$CHCH_2$-Br	1.1	**2c** (R = CH_2CH=CH_2)	86
n-C_6H_{13}-I	1.1	**2d** (R = n-C_6H_{13})	72
CH_3CO-$N(OCH_3)CH_3$	1.1	**2e** (R = CH_3CO)	81
$PhCO$-$N(OCH_3)CH_3$	1.1	**2f** (R = PhCO)	86



3 **4**

R-X	eq. LDA:DMPU	Product	% Yield
MeOCO-Cl	2.1	**4a** (R = CO_2Me)	74
CH_2=$CHCH_2$-Br	1.1	**4b** (R = CH_2CH=CH_2)	85
n-C_6H_{13}-I	1.1	**4c** (R = n-C_6H_{13})	88

Attempts to acylate the 2-methylbenzonitrile anion with simple acid chlorides gave poor yields of acylated material accompanied by larger amounts of the double addition product. This problem was overcome through the use of *N*-methoxy-*N*-methylamides[9] as the acylation reagents. Deprotonation using 1.1 eq. of LDA:DMPU at -78°, followed by addition of the amide, warming to -20°, and mild acid workup gave cyano ketones **2e** and **2f** in 81% and 86% yields, respectively. Since acylations using *N*-methoxy-*N*-methylamides proceed through a stable, non-enolizable, metal-chelated, tetrahedral intermediate, a second equivalent of base was not required.

For simple alkylations, 1.1 eq. of LDA:DMPU was used to generate the anion at -78°. Addition of the alkyl halide, warming to -20°, and protic workup gave the products (**2b-d** and **4b-c**) in 72-90% yield. Alkylations proceeded smoothly for allylic and benzylic bromides as well as alkyl iodides.[5,6]

In summary, we have developed a simple synthetic route to methyl (2-cyanophenyl)acetate (**2a**) as well as several acylated and alkylated derivatives of 2- and 4-methylbenzonitrile. The current procedure is less hazardous, and provides yields comparable or superior to those reported using $NaNH_2$ in NH_3 or LDA:HMPA. It also avoids the use of multistep schemes or expensive reagents.

EXPERIMENTAL SECTION

THF was distilled from $LiAlH_4$ immediately prior to use; diisopropylamine was distilled from CaH_2 and stored over 4Å molecular sieves under N_2; DMPU was stored over 4Å molecular sieves under N_2. Other commercial reagents were used as received. Low temperature (-78°) conditions were achieved using a dry ice-acetone bath. The 5% NH_4Cl, 1 M HCl, and 5% NaCl used in workup procedures refer to aqueous solutions. Reactions were monitored by capillary GC with FI detection (SE-30 column, 6 m x 0.25 mm i.d., 0.25 μm film thickness) programmed between 50-300°. Preparative separations were performed using flash column chromatography[10] on silica gel (Grace, grade 62, 60-200 mesh) mixed with Sylvania no. 2282 UV-active phosphor; band elution was monitored using a hand-held UV lamp. IR spectra were run as thin films on NaCl disks and were referenced to polystyrene. ^1H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ at 300 MHz and 75 MHz, respectively, and were referenced to internal $(CH_3)_4Si$. High resolution mass spectra (HRMS, EI/DP) were obtained at 70 eV.

Representative Procedure for Acylation of 2-Methylbenzonitrile: Methyl (2-Cyanophenyl)-acetate (2a).- An oven-dried 500-mL three-necked round-bottomed flask equipped with a rubber septum, an addition funnel, an N_2 inlet, and a magnetic stirrer was charged with a solution of 5.30 g (7.34 mL, 52.5 mmol) of diisopropylamine in 30 mL of THF. The flask was cooled to -78° and 21.0 mL of 2.5 M *n*-butyllithium in hexanes (52.5 mmol) was added dropwise via syringe during 10 min. The solution was stirred at -78° for 10 min and 6.72 g (6.34 mL, 52.5 mmol) of DMPU was added by syringe. The solution was stirred for 15 min at -78° and a solution of 2.93 g (2.96 mL, 25.0 mmol) of 2-methylbenzonitrile in 10 mL of THF was added dropwise from the addition funnel during 10 min. The reaction was stirred for 15 min at -78° and a solution of 2.38 g (1.95 mL, 25.2 mmol) of methyl chloroformate in 10 mL of THF was added all at once from the addition funnel. The reaction was stirred for 15 min at -78°, then quenched by addition of 25 mL of 5% NH_4Cl and warmed to rt. The mixture was transferred to a separatory funnel using ether, the layers were separated, and the aqueous layer was extracted with ether (2x). The combined organic extracts were washed with 5% NaCl (1x), dried ($MgSO_4$), and concentrated under vacuum. The resulting oil was flash chromatographed on a 50-cm x 2-cm silica gel column eluted with 10-20% ether in hexanes to give 3.32 g (19.0 mmol, 76%) of **2a** as a light yellow oil.

IR 3075, 3040, 2228, 1744, 1602, 1495, 769 cm^{-1}; ^1H NMR δ 7.70 (d, 1 H, J = 7.8 Hz), 7.57 (t, 1 H, J = 7.8 Hz), 7.41 (m, 2 H), 3.90 (s, 2 H), 3.74 (s, 3 H); ^{13}C NMR δ 170.2, 137.6, 132.8, 130.6, 127.8, 117.5, 113.4, 52.4, 39.3; HRMS *m/z*: Calcd for $C_9H_9NO_2$: 163.0633. Found: 163.0632.

Anal. Calcd for $C_9H_9NO_2$: C, 66.25; H, 5.52. Found: 66.36; H, 5.60

Methyl (4-Cyanophenyl)acetate (4a): 1.30 g (7.42 mmol, 74%) as a yellow oil which crystallized upon standing, mp. 42-43°; IR 3010, 2232, 1744, 1609, 1509, 826 cm^{-1}; ^1H NMR δ 7.63 (d, 2 H, J = 8.4 Hz), 7.40 (d, 2 H, J = 8.4 Hz), 3.72 (s, 3 H), 3.70 (s, 2 H); ^{13}C NMR δ 170.7, 139.2, 132.3, 130.1, 118.7, 111.2, 52.3, 41.0; HRMS *m/z*: Calcd for $C_9H_9NO_2$: 163.0633. Found: 163.0630.

Anal. Calcd for $C_9H_9NO_2$: C, 66.25; H, 5.52. Found: 66.29; H, 5.57

Representative Procedure for Alkylation of 2-Methylbenzonitrile: 2-(2-Phenethyl)benzonitrile (2b).- An oven-dried 250-mL three-necked round-bottomed flask equipped with a rubber septum, an

addition funnel, an N_2 inlet, and a magnetic stirrer was charged with a solution of 1.11 g (1.54 mL, 11.0 mmol) of diisopropylamine in 15 mL of THF. The flask was cooled to -78 and 4.40 mL of 2.5M *n*-butyllithium in hexanes (11.0 mmol) was added dropwise via syringe during 10 min. The solution was stirred at -78° for 10 min and 1.41 g (1.33 mL, 11.0 mmol) of DMPU was added by syringe. The solution was stirred for 15 min at -78° and a solution of 1.17 g (1.18 mL, 10.0 mmol) of 2-methylbenzonitrile in 5 mL of THF was added dropwise from the addition funnel during 10 min. The reaction was stirred for 15 min at -78° and a solution of 1.73 g (1.20 mL, 10.1 mmol) of benzyl bromide in 5 mL of THF was added dropwise from the addition funnel. The reaction was stirred for 30 min at -78°, warmed to -20°, and quenched by addition of 15 mL of 5% NH_4Cl. The mixture was transferred to a separatory funnel using ether, the layers were separated, and the aqueous layer was extracted with ether (2x). The combined organic extracts were washed with 5% NaCl (1x), dried ($MgSO_4$), and concentrated under vacuum. The resulting oil was flash chromatographed on a 25-cm x 2-cm silica gel column eluted with 5-10% ether in hexanes to give 1.76 g (9.02 mmol, 90%) of **2b** as a light yellow oil.

IR 3085, 3067, 3035, 2228, 1602, 1495, 762, 705 cm^{-1}; ^1H NMR δ 7.61 (d, 1 H, J = 7.7 Hz), 7.48 (t, 1 H, J = 7.7 Hz), 7.32-7.17 (complex, 7 H), 3.14 (t, 2 H, J = 7.2 Hz), 2.97 (t, 2 H, J = 7.2 Hz); ^{13}C NMR δ 145.4, 140.5, 132.8, 132.7, 127.7, 128.5, 128.4, 126.6, 126.2, 118.0, 112.3, 37.1, 36.7; HRMS *m/z*: Calcd for $C_{14}H_{13}N$: 195.1048. Found: 195.1044.

Anal. Calcd for $C_{14}H_{13}N$: C, 86.15; H, 6.67. Found: C, 86.08; H, 6.69

2-(3-Butenyl)benzonitrile (2c): from reaction with allyl bromide; 1.35 g (8.60 mmol, 86%) as a light yellow oil; IR 3082, 2228, 1644, 1602, 1488, 997, 919, 756 cm^{-1}; ^1H NMR δ 7.61 (d, 1 H, J = 7.7 Hz), 7.51 (t, 1 H, J = 7.7 Hz), 7.31 (m, 2 H), 5.85 (ddt, 1 H, J = 17.0, 10.3, 6.7 Hz), 5.04 (d, 1 H, J = 17.0 Hz), 5.01 (d, 1 H, J = 10.3 Hz), 2.95 (t, 2 H, J = 7.7 Hz), 2.43 (m, 2 H); ^{13}C NMR δ 145.6, 136.7, 132.8, 132.6, 129.6, 126.5, 118.1, 115.9, 112.4, 34.7, 33.9; HRMS *m/z*: Calcd for $C_{11}H_{11}N$: 157.0892. Found: 157.0889.

Anal. Calcd for $C_{11}H_{11}N$: C, 84.08; H, 7.01. Found: C, 84.11; H, 7.03

2-Heptylbenzonitrile (2d): from reaction with 1-iodohexane; 1.45 g (7.21 mmol, 72%) as a light yellow oil; IR 3074, 3032, 2228, 1602, 1488, 1381 cm^{-1}; ^1H NMR δ 7.60 (d, 1 H, J = 7.7 Hz), 7.50 (t, 1 H, J = 7.7 Hz), 7.28 (m, 2 H), 2.83 (t, 2 H, J = 7.7 Hz), 1.67 (quintet, 2 H, J = 7.7 Hz), 1.36-1.17 (complex, 8 H), 0.88 (t, 3 H, J = 6.9 Hz); ^{13}C NMR δ 146.8, 132.7, 132.6, 129.4, 126.2, 118.2, 112.2, 34.6, 31.7, 30.9, 29.2, 29.0, 22.6, 14.1; HRMS *m/z*: Calcd for $C_{14}H_{19}N$: 201.1797. Found: 201.1793.

Anal. Calcd for $C_{14}H_{19}N$: C, 83.58; H, 9.45. Found: C, 83.42; H, 9.46

4-(3-Butenyl)benzonitrile (4b): from reaction with allyl bromide; 1.33 g (8.47 mmol, 85%) as a light yellow oil; IR 3082, 2228, 1645, 1609, 1509, 997, 919, 826 cm^{-1}; ^1H NMR δ 7.57 (d, 2 H, J = 8.5 Hz), 7.29 (d, 2 H, J = 8.5 Hz), 5.80 (ddt, 1 H, J = 17.0, 10.3, 6.6 Hz), 5.06-4.97 (complex, 2 H), 2.77 (t, 2 H, J = 7.3 Hz), 2.37 (m, 2 H); ^{13}C NMR δ 147.3, 136.9, 132.1, 129.2, 119.0, 115.7, 109.7, 35.3, 34.7; HRMS *m/z*: Calcd for $C_{11}H_{11}N$: 157.0892. Found: 157.0890.

Anal. Calcd for $C_{11}H_{11}N$: C, 84.08; H, 7.01. Found: C, 84.13; H, 7.04

4-Heptylbenzonitrile (4c): from reaction with 1-iodohexane; 1.76 g (8.76 mmol, 88%) as a light yellow oil; IR 3078, 3032, 2228, 1608, 1502, 1381, 840 cm^{-1}; ^1H NMR δ 7.56 (d, 2 H, J = 8.4 Hz), 7.27 (d, 2 H, J = 8.4 Hz), 2.65 (t, 2 H, J = 7.5 Hz), 1.60 (quintet, 2 H, J = 7.5 Hz), 1.34-1.25 (complex, 8 H), 0.88 (t, 3 H, J = 7.0 Hz); ^{13}C NMR δ 148.6, 132.1, 129.1, 119.2, 109.4, 36.1, 31.7, 30.9, 29.1, 29.0, 22.6, 14.0; HRMS *m/z*: Calcd for $C_{14}H_{19}N$: 201.1797. Found: 201.1793.

Anal. Calcd for $C_{14}H_{19}N$: C, 83.58; H, 9.45. Found: C, 83.48; H, 9.42

Representative Procedure for Acylation of 2-Methylbenzonitrile with *N*-Methoxy-*N*-methylamides: 1-(2-Cyanophenyl)-2-propanone (2e).- The procedure described for the alkylation of 2-methylbenzonitrile was used substituting *N*-methoxy-*N*-methylacetamide[9] for the alkyl halide. The reaction was quenched by addition of 15 mL of 1 M HCl, transferred to a separatory funnel using ether, the layers were separated, and the aqueous layer was extracted with ether (2x). The combined organic extracts were washed with 5% NaCl (1x), dried ($MgSO_4$), and concentrated under vacuum. The resulting oil was flash chromatographed on a 25-cm x 2-cm silica gel column eluted with 25-30% ether in hexanes to give 1.29 g (8.11 mmol, 81%) of **2e** as a light yellow oil.

IR 3067, 3030, 3010, 2228, 1723, 1602, 1495, 769 cm^{-1}; ^1H NMR δ 7.66 (d, 1 H, J = 7.7 Hz), 7.57 (t, 1 H, J = 7.7 Hz), 7.38 (t, 1 H, J = 7.7 Hz), 7.31 (d, 1 H, J = 7.7 Hz), 3.99 (s, 2 H), 2.30 (s, 3 H); ^{13}C NMR δ 203.5, 138.1, 132.9, 132.7, 130.8, 127.6, 117.7, 113.3, 48.5, 30.0; HRMS *m/z*: Calcd for $C_{10}H_9NO$: 159.0684. Found: 159.0682.

Anal. Calcd for $C_{10}H_9NO$: C, 75.47; H, 5.66. Found: C, 75.71; H, 5.70

2-(2-Cyanophenyl)-1-phenyl-1-ethanone (2f): from reaction with *N*-methoxy-*N*-methylbenzamide;[9] 1.91 g (8.64 mmol, 86%) as a light yellow solid, mp. 109-110° from hexane-ether (lit.[3b] mp. 110.5-111.5° from petroleum ether-benzene); IR 3067, 3032, 3011, 2228, 1667, 1602, 1495, 769, 755, 691 cm^{-1}; ^1H NMR δ 8.05 (d, 2 H, J = 7.2 Hz), 7.70 (d, 1 H, J = 8.0 Hz), 7.64-7.37 (complex, 6 H), 4.56 (s, 2 H); ^{13}C NMR δ 195.4, 138.5, 136.2, 133.7, 132.8, 131.0, 128.8, 128.4, 127.6, 117.9, 113.6, 43.6; HRMS *m/z*: Calcd for $C_{15}H_{11}NO$: 221.0841. Found: 221.0838.

Anal. Calcd for $C_{15}H_{11}NO$: C, 81.44; H, 4.98. Found: C, 81.25; H, 5.02

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