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# Divergent Mechanisms for the Dealkoxycarbonylation of a 2-(3-Azetidinyl)malonate by Chloride and Cyanide

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**Abstract:** The reaction of dimethyl 2-(1-benzylazetidin-3-yl)propane-1,3-dioate with NaCN in wet DMSO at high temperature afforded methyl 2-(1-benzylazetidin-3-yl)acetate, whereas similar treatment with NaCl gave methyl 3-benzylazabicyclo-[3.1.0]hexan-2-onecarboxylate. These results provide additional evidence that chloride- and cyanide-mediated cleavages of esters may proceed by different mechanisms.

Ester cleavage via nucleophilic dealkylation is an attractive method for converting esters into acids under neutral, nonaqueous conditions, when the lability of other acid-or base-sensitive functional groups present in the substrate is a concern.[1] Typically, the reaction is performed with a methyl or ethyl ester in a polar solvent at high temperature, sometimes in the presence of water. The addition of alkali metal salts accelerates the rate of reaction via nucleophilic displacement of carboxylate anion by an $S_N2$-type process (Equation 1). For malonates or β-ketoesters, this displacement is followed by rapid decarboxylation.

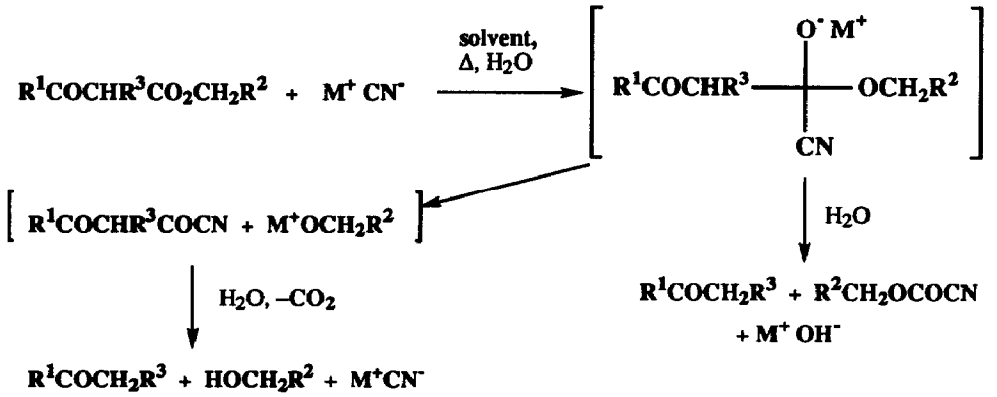
$$R^1CO_2CH_2R^2 + M^+X^- \xrightarrow{\text{solvent, } \Delta, \pm H_2O} R^1CO_2^-M^+ + R^2CH_2X \qquad (1)$$

The above mechanism has been challenged for some reactions of malonates or β-ketoesters with alkali metal cyanides.[1-3] In these cases, nucleophilic attack on the carbonyl carbon, followed by fragmentation of the tetrahedral intermediate, has been proposed (Scheme 1) since alcohol or cyanoformate side products have been isolated.

During the course of our research on CNS-active drugs, we recently have investigated the cleavage of azetidinyl malonate **1** with chloride and cyanide nucleophiles (Scheme 2) and have discovered an interesting skeletal rearrangement of **1** after treatment with chloride, which provides additional evidence that chloride- and cyanide-mediated cleavages of esters may proceed by different mechanisms. Diester **1** is prepared by the reaction of the methanesulfonate ester of 1-benzyl-3-azetidinol[4] with dimethylmalonate anion. Treatment of **1** with 3.24 molar equivalents of sodium cyanide in wet DMSO at 110 °C gives exclusively methyl 2-(1-benzylazetidin-3-yl)acetate **4** in 72% yield, whereas the reaction with 2.13 molar equivalents sodium chloride at 150 °C affords methyl 3-benzyl-2-azabicyclo[3.1.0]hexan-2-onecarboxylate **6**[5] in 42% yield. Considerable decomposition occurs at 150 °C in the cyanide-mediated reaction, which is minimized by running the experiment at 110 °C. We propose the reactions proceed through bridged intermediate **2**, which can fragment differently in the presence of chloride or cyanide anions. The formation of this proposed intermediate is analogous to the

known cyclization of γ-halo amines.[6] Chloride attacks intermediate **2** to provide **5**, which can then undergo an intramolecular cyclization to **6**. Neither ester **6** nor the cyano counterpart of the protonated form of **5** were detected in the reaction with cyanide. The latter product might be found in an $S_N2$-type process since cyanide is more nucleophilic than chloride at a saturated carbon center in polar solvents.[7-8] It is possible that cyanide may react directly with **1**, bypassing **2**, to generate intermediate **3**, which can be converted to **4** by the mechanisms outlined in Scheme 1. The available data can not distinguish between these two possibilities, but they do argue strongly against an $S_N2$-type ester cleavage for the cyanide-mediated reaction.

**Scheme 1**




**Experimental Section**[9]:

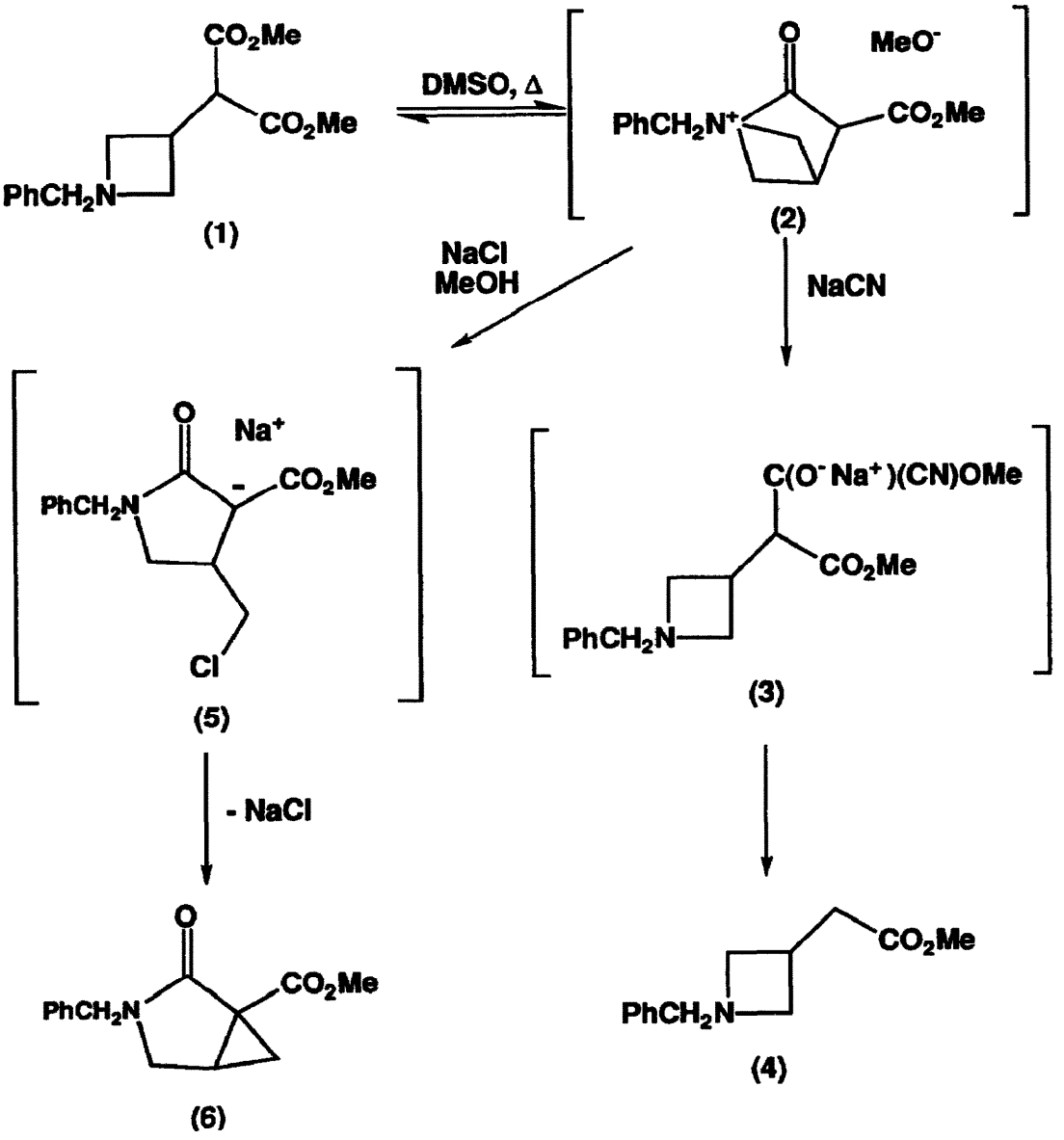
Dimethyl 2-(1-benzyl-3-azetidinyl)-propane-1,3-dioate **1**:

Dimethyl malonate (14.0 mL, 122 mmol) was added to a magnetically stirred suspension of sodium hydride (60% dispersion in mineral oil, 5.33 g, 111 mmol, washed with hexanes) in anhydrous THF (200 mL) under a nitrogen atmosphere. After 15 min, 1-benzyl-3-methanesulfonyloxyazetidine[10-13] (13.4 g, 55 mmol) was added in anhydrous THF (100 mL). The clear solution was then refluxed for 18 h. After being cooled to room temperature, it was poured into water (500 mL) and extracted three times with $CHCl_3$. The combined extracts were dried over $MgSO_4$, filtered and evaporated under vacuum to give a light yellow oil. The oil was purified by column chromatography with 3% MeOH in $CHCl_3$ ($R_f$ 0.31) to give a pale yellow oil (12.3 g, 80% yield): $^1$H-NMR ($CDCl_3$): 7.25 (m, 5H), 3.75 (s, 6H), 3.7 (m, 1H), 3.6 (s, 2H), 3.45 (t, 2H, J=5), 3.1-3.0 (m, 1H), 3.0-2.9 (m, 2H) ; CI-HRMS ($NH_3$): Calcd for $C_{15}H_{19}NO_4$: 278.1392 (M+H); Found: 278.1381.

Methyl 2-(1-benzylazetidin-3-yl) acetate **4**:

A solution of **1** (8.58 g, 30.9 mmol), sodium cyanide (4.90 g, 100 mmol), and water (1.17 mL, 65 mmol) in DMSO (500 mL) was heated at 110 °C for 6 h. After being cooled to room temperature, it was poured into a mixture of water (2 L) and a saturated $NaHCO_3$ solution (50 mL) and extracted three times with $CHCl_3$. The combined extracts were washed once with water, dried over $MgSO_4$, filtered, and solvent was removed under vacuum to give a pale yellow oil (3.33 g, 49% yield): $^1$H-NMR ($CDCl_3$): 7.2-7.4 (m, 5H), 3.65 (s, 3H), 3.6 (s, 2H), 3.45 (t, 2H, J=7), 2.95-2.85 (m, 2H), 2.85-2.75 (m, 1H), 2.6 (d, 2H, J=7); CI-HRMS ($NH_3$): Calcd for $C_{13}H_{17}NO_2$: 220.1338 (M + H); Found: 220.1340.

Scheme 2




Methyl 3-benzylazabicyclo[3.1.0]hexa-2-onecarboxylate 6:

A mixture of malonate 1 (5.21g, 18.8 mmol), NaCl (2.34 g, 40.0 mmol), water (0.72 mL) and DMSO (100 mL) was stirred at 150 °C for 2 h under a nitrogen atmosphere. After being cooled to ambient temperature, the reaction mixture was diluted tenfold with water and extracted three times with $CHCl_3$. The combined organic layers were washed three times with water, dried over $MgSO_4$ and filtered. Solvent was removed *in*

*vacuo* to give an oil. Column chromatography (EtOAc:hexanes::1:1) afforded the title product as an oil (1.43 g, 31% yield): $^1$H-NMR ($CDCl_3$, 400 MHz): 7.35-7.25 (m, 3H), 7.2 (d, 2H, J=7), 4.45 (d, 1H, J=14), 4.3 (d,1H, J=10), 3.8 (s, 3H), 3.45 (dd, 1H, J=10,7), 3.1 (d, 1H, J= 10), 2.35-2.25 (m, 1H), 1.9 (dd, 1H, J=10,5), 1.1 (t, 1H, J=5); $^{13}$C-NMR-DEPT ($CDCl_3$, 75.43 MHz): 169.1, 169.0, 136.2, 128.6 (CH), 128.1 (CH), 127.6 (CH), 52.4 ($CH_3$), 46.45 ($CH_2$), 46.4 ($CH_2$), 31.5, 22.8 (CH), 20.7 ($CH_2$); CI-HRMS ($NH_3$): Calcd for $C_{14}H_{15}NO_3$: 246.1130 (M + H); Found: 246.1130.

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