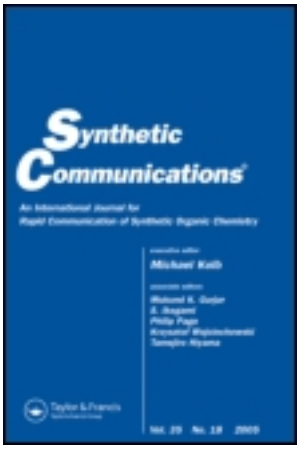

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Sigmatropic Rearrangement of Ammonium Ylides—Key Step in the Synthesis of Methyl 2-Formylphenyl Acetate

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SIGMATROPIC REARRANGEMENT OF AMMONIUM YLIDES—KEY STEP IN THE SYNTHESIS OF METHYL 2-FORMYLPHENYL ACETATE

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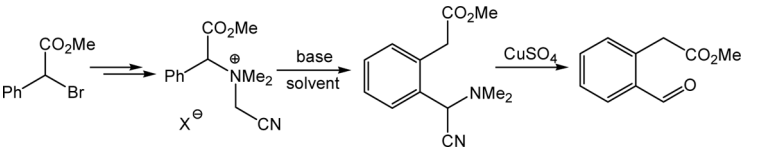
GRAPHICAL ABSTRACT



Abstract N-*Cyanomethyl*-N,N-*dimethyl*-N-*(α-methoxycarbonyl)benzylammonium salts* ***5*** *were synthesized and treated with different base/solvent systems, giving the products of sigmatropic rearrangements [2,3]* ***7*** *and [1,2]* ***8****. In reactions carried out in liquid ammonia, [2,3] rearrangement definitively prevailed. Pure* ***7*** *(or mixture of* ***7*** *and* ***8****) were deprotected to afford methyl 2-formylphenyl acetate (****9****) in good yield.*

Keywords Ammonium salts; ammonium ylides; methyl 2-formylphenyl acetate; sigmatropic rearrangement

INTRODUCTION

Aromatic compounds substituted at two neighboring carbon atoms with a strong electron-withdrawing group and active methylene one have been recognized as useful substrates in organic synthesis. Thus, the benzaldehyde, acetophenone, and benzophenone *ortho*-substituted with arylsulfonylmethyl group reacted with electrophilic alkenes in the presence of a base with formation of 1,2-di- or 1,2,3-tri-substituted naphthalenes.[1,2] 2-Cyanomethylbenzaldehyde,[3] under basic conditions, gave 1,3-di- and 1,2,3-trisubstituted naphthalenes or substituted 1-cyanobenzobicyclo-[2.2.2]octenes depending on the structure of the electrophilic alkene.[4] The aldehyde reacted also with ammonia and primary and secondary amines in the presence of a catalytic amount of trifluoroacetic acid, affording 3-aminoisoquinolines.[5]

The present study reports a practical methodology for the synthesis of methyl 2-formylphenylacetate (**9**).

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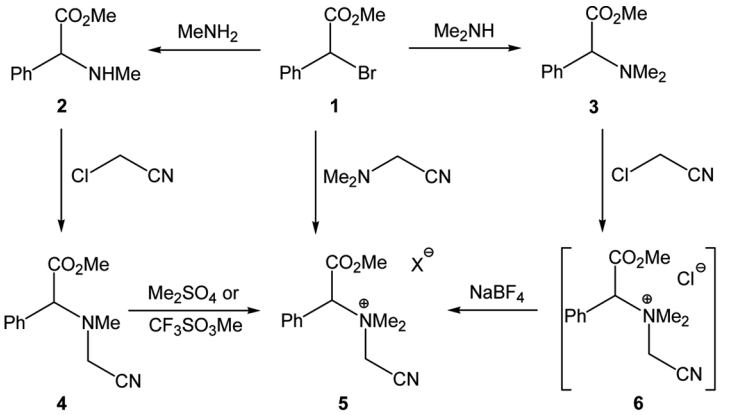
It has been well known that aldehyde **9** can be prepared by esterification of 2-formylphenylacetic acid[6,7] or hydrolysis of dimethylacetal of the parent aldehyde **9**.[8,9] According to the literature, 2-formylphenylacetic acid can be obtained either by ozonolysis of indene[1,7] or its derivatives[10,11] or by oxidative decarboxylation of 3-oxoisochromane-1-carboxylic acid.[11] In some cases, the desired acid was accompanied by other side products[6,7] or synthesized in poor yield.[11] Dimethyl acetal of **9** was obtained by irradiation of 1,3-bis(diazo)-2-indanone in methanol in yield of 35%[8] or 69%.[9]

Preliminary experiments revealed that aldehyde **9** is a useful substrate for the preparation of condensed carbocyclic compounds (e.g., the reaction of compound **9** with electrophilic alkenes under basic conditions gave substituted dihydronaphthalenes).

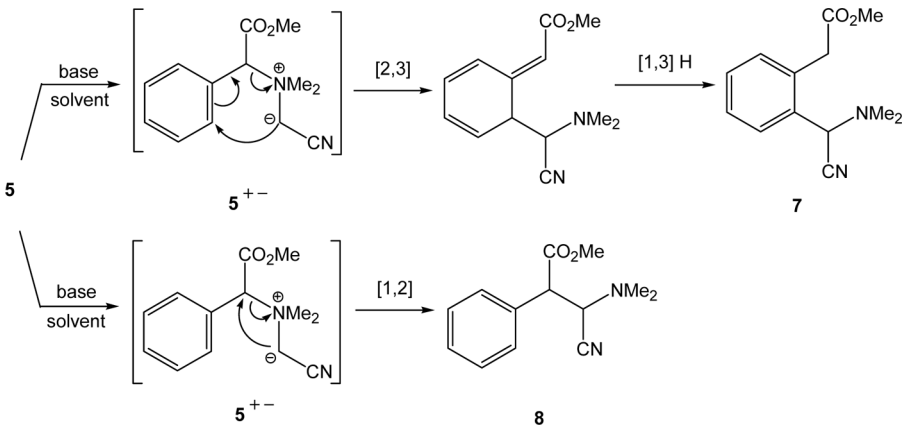
The synthesis of aldehyde **9** is based on a strategy similar to the synthesis of cyanomethyl substituted derivative.[3] An initial study was carried out using the following compounds: methyl α-methylamino- (**2**),[12,13] methyl α-dimethylamino- (**3**),[13,14] and methyl α-bromo-phenylacetate (**1**).[15] The reaction of **1** with dimethylaminoacetonitrile proceeded to afford crystalline bromide **5a**. Aminoester **2** was *N*-cyanomethylated with chloroacetonitrile to give **4** and subsequently quaternized with methylating agent to form **5b,c**, whereas in the reaction of dimethylamino derivative **3** with chloroacetonitrile, yellow and viscous quaternary chloride **6** was produced. Crystalline salt **5d** was obtained from chloride **6** by the anion exchange with sodium tetrafluoroborate (Scheme 1).

As shown in Scheme 2, in the reactions of salts **5**, carried out using various base/solvent systems, cyanomethyl ammonium ylide $\mathbf{5}^{+-}$ was generated, which gave products **7** and **8**[16] by [2,3] and [1,2] sigmatropic rearrangements, respectively.



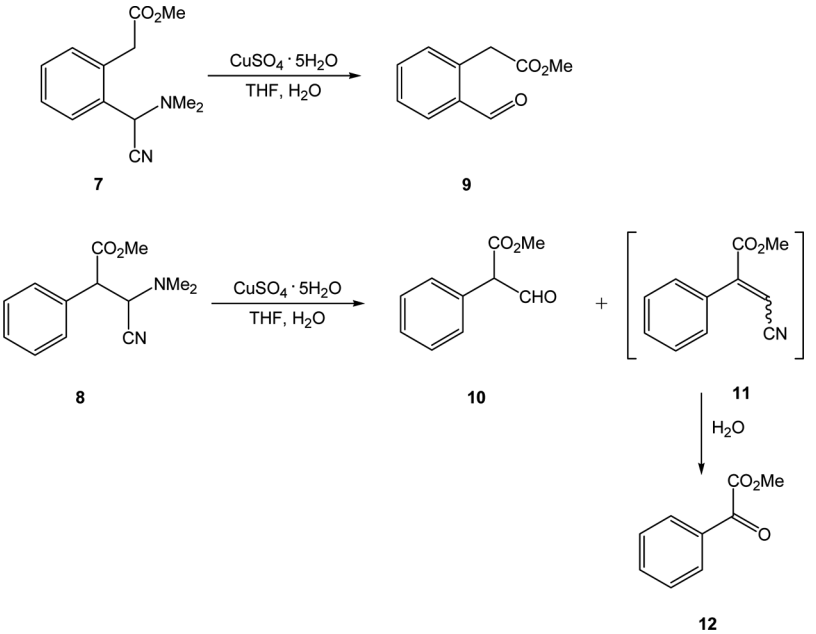
Salt **5**	**a**	**b**	**c**	**d**
X	Br	$MeSO_4$	CF_3SO_3	BF_4
Yield (%)	75–88	95	91–96	52–66

Scheme 1. Preparation of salts **5a**–**d**.



Scheme 2. Sigmatropic rearrangements of **5** to **7** and **8**.

The required aldehyde **9** was obtained from isolated ester **7** by the deprotection of formyl group with $CuSO_4$. Aminonitrile **8** reacted with $CuSO_4$ to afford a mixture of unstable methyl α-formylphenylacetate (**10**)[17] and methyl phenylglyoxalate (**12**).[18] The formation of compound **10** was confirmed by ^{1}H NMR spectral data, and compound **12** was isolated in poor yield (13–28%) and fully identified by spectral means and elemental analysis. We assumed that the consecutive elimination of dimethylamine from **8** occurred to give methyl 2-phenyl-3-cyanoacrylate (**11**), followed by its cleavage to ketoester **12** (Scheme 3).



Scheme 3. Cleavage of **7** to ester **9** and ester **8** to **10** and **12**.

Therefore, we aimed to find the optimal reaction conditions that provided us with compounds **7** and **8** in high ratio of **7/8** and in good yield with high purity. The selected results of the study are reported in Table 1. As shown in Table 1, salt **5d** in the reactions carried out with 5% aqueous sodium hydroxide, solid sodium hydrogen carbonate, or potassium carbonate in dimethylformamide (DMF) afforded the mixture of **7** and **8** in poor yields (26–48%). The ratio **7**/**8** ranged from 0.05 to 0.3. A significant increase of yield (ca. 80%) was achieved by using of potassium carbonate in dimethylsulfoxide (DMSO) or 25% aqueous ammonia in dichloromethane. Furthermore, the purity of the mixtures obtained under these base/solvent conditions was at least 95%, but undesired product **8** still prevailed (ratio **7**/**8** ca 0.5–0.9). Unsatisfied content of **7** in the reaction mixtures prompted us to examine other basic systems.

Further optimization with various base/solvent systems revealed that salts **5a–d** can be efficiently converted into compound **7** in triethylamine/dichloromethane in good yield (87–98%), high purity (≥96%), and better excess of **7** (**7**/**8** ca 2.6–4.9). The use of triethylamine in cyclohexane, ethyl ether, or carbon tetrachloride in the reaction of salts **5a,d** gave pure **8** (**7**/**8** ca 0.04), while in DMF or tetrahydrofuran (THF) ratio of **7**/**8** increased to 2.3–2.5. In all cases, the yield of rearranged products exceeded 84%. Greater content of **7** in the reaction mixture was obtained in the experiment carried out in 1,4-diazabicyclo[2.2.2.]octane (DABCO)/dichloromethane system (**7/8** ca 3.6–5.9).

Being unsatisfied with the poor ratio of **7**/**8**, we continued the screening of base/solvent systems. Salts **5a–d** reacted with triethylamine in liquid ammonia at −33 °C to give the mixtures of products **7** and **8** in good yield with high content of required **7** (ratio of **7/8** ca. 16.1–25.1). The ratio of products **7** and **8** was not

Table 1. Sigmatropic rearrangements of salts **5a–d**

Entry	Salt	Base/solvent/temperature	Products (%)[a]		Ratio of **7**/**8**	Yield[b] (%)
			[2,3] **7** (%)	[1,2] **8** (%)		
1	**5d**	5% aq NaOH	5.5	93.5	0.06	48
2	**5d**	$NaHCO_3$/DMF/−30 °C	21.6	75.4	0.3	26
3	**5d**	K_2CO_3/DMF/−35 °C	4.7	91.0	0.05	33
4	**5d**	K_2CO_3/DMSO/rt	35.6	71.3	0.5	80
5	**5d**	25% NH_3/CH_2Cl_2/−25 °C	45.0	51.7	0.9	80
6	**5a-d**	Et_3N/CH_2Cl_2/rt[c]	69.3–81.1	16.6–26.5	2.6–4.9	87–98
7	**5a,d**	Et_3N/c-C_6H_{11} or Et_2O or CCl_4/rt	3.0–3.5	92.5–93.6	0.03–0.04	91–96
8	**5d**	Et_3N/DMF or THF/rt	67.8–69.9	27.6–29.9	2.3–2.5	84–87
9	**5a-d**	DABCO/CH_2Cl_2/rt	75.7–83.8	14.2–21.2	3.6–5.9	91–98
10[c]	**5a-d**	Et_3N/NH_3 liq/−33 °C	89.3–91.8	3.4–6.0	16.1–25.1	82–90[d,e]
11[f]	**5a,d**	NH_3 liq/−33 °C	90.7–91.1	4.4–5.0	18.1–20.7	90–92[d,e]
12[g]	**5a,d**	NH_3 liq/−75 °C	86.7–91.1	2.2–3.0	30.4–37.2	71–86[d,e]

[a]Estimated by GC in crude reactions mixtures.
[b]Yield of a crude mixture of **7** and **8**.
[c]Results obtained in 12–15 experiments.
[d]Unidentified impurity formed in ca. 1–6% was removed under vacuum (ca. 20 °C/0.05 Torr).
[e]In some experiments 2–4% of aldehyde **9** was formed.
[f]Results obtained in three experiments.
[g]Results obtained in six experiments.

dependent on the excess of triethylamine (1–5 equivalents). These results suggest that liquid ammonia is a sufficiently strong base to deprotonate **5** and to induce the rearrangement of the corresponding ylide $\mathbf{5}^{+-}$. Lowering the reaction temperature to −33 °C and −75 °C resulted in very high **7/8** ratios: ca. 20 and ca. 35, respectively. In the latter case, the yield of crude mixture was lower and the observation has been reported previously.[19]

As shown in Table 1, the desired product **7** was always accompanied by **8**. However, we found the conditions of sigmatropic rearrangements of ylide $\mathbf{5}^{+-}$ generated from **5** to form **8** as a minor component. The reactions carried out in liquid ammonia gave 1–6% of unidentified impurity and in some cases 2–4% of aldehyde **9**.

Products **7** (yield 60–78%) and **8** (yield 81–83% as a mixture of diastereoisomers) were isolated from the reaction mixtures obtained in the experiments carried out in liquid ammonia (entries 10–12, Table 1), in triethylamine/cyclohexane, in ethyl ether, or in carbon tetrachloride (entry 7, Table 1), respectively. Deprotection of the formyl group in the isolated compound **7** proceeded to give the expected aldehyde **9** in 93% yield. On the other hand, because of some difficulties separating compounds **7** and **8** by crystallization, the deprotection reaction was also carried out without any separation. All the by-products, especially ketoester **12**, were easily separated by column chromatography, and aldehyde **9** was obtained in yield 44–52% (from salt **5**, rearranged in NEt_3/CH_2Cl_2/rt system) or 60–67% (from salt **5**, rearranged in liquid ammonia at −33 °C).

In conclusion, we have developed a simple method for the preparation of the title aldehyde **9**. Further studies on the application of the reaction to the construction of condensed ring compounds are under investigation.

EXPERIMENTAL

Melting points were measured on a capillary apparatus and were not corrected. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were measured on a Varian Mercury 400BB spectrometer in $CDCl_3$ or dimethylsulfoxide (DMSO-d_6); chemical shifts (δ) are given in parts per million (ppm) related to tetramethylsilane (TMS), coupling constants *J* are given in hertz (Hz). Elemental analyses were performed on a Perkin-Elmer 2400 Series II CHNS/O microanalyzer. Gas chromatographic analysis (GC) was performed on an Agilent 6850 Series GC system fitted with HP-50+ (30 m) column. Column chromatography was performed on Merck silica gel (240–400 mesh). Commercial methyl α-bromo-phenylacetate (**1**), obtained according to literature procedure,[14] was used.

Methyl α-(*N*-Methylamino)phenylacetate (2)

To a magnetically stirred solution of **1** (11.45 g, 50 mmol) in MeOH (50 mL), 40% aqueous methylamine (19.41 g, 21.6 mL, 250 mmol) was added dropwise at 20–35 °C for ca. 30 min. The mixture was stirred at ambient temperature until GC analysis indicated total consumption of **1** (ca. 1 h), and then it was diluted with H_2O (70 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were washed with H_2O (3 × 40 mL) and dried ($MgSO_4$). The solvent was evaporated, and the residue was distilled to give **2** (5.74 g, yield 62%).

Compound 2: bp 68–69 °C/0.2 Torr (lit.[12] bp 132–134 °C/2 Torr). ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 2.06$ (1H, s, N*H*), 2.39 (3H, s, NH-CH_3), 3.69 (3H, s, OCH_3), 4.27 (1H, s, C*H*-CO_2CH_3), 7.27–7.37 (5H, m, *Ph*).

Methyl α-(*N,N*-Dimethylamino)phenylacetate (3)

To a magnetically stirred solution of **1** (11.45 g, 50 mmol) in MeOH (50 mL), 40% aqueous dimethylamine (28.18 g, 31.66 mL, 0.25 mol) was added dropwise at 20–35 °C for ca 30 min. The mixture was stirred at ambient temperature until GC analysis indicated total consumption of **1** (ca. 1 h), and then it was diluted with H_2O (70 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were washed with H_2O (3 × 40 mL) and dried ($MgSO_4$). The solvent was evaporated to give crude **3** (9.08 g, yield 94%), purity ca. 97% (by GC), which was used in the next step without further purification.

Compound 3: ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 2.24$ [6H, s, N(CH_3)$_2$], 3.69 (3H, s, OCH_3), 3.86 (1H, s, C*H*-CO_2CH_3), 7.28–7.36 (3H, m, *Ph*), 7.39–7.44 (2H, m, *Ph*).

Methyl α-(*N*-Cyanomethyl-*N*-methylamino)phenylacetate (4)

Chloroacetonitrile (11.33 g, 9.49 mL, 150 mmol) was added dropwise to a vigorously stirred mixture of **2** (8.96 g, 50 mmol), MeCN (40 mL), powdered K_2CO_3 (13.82 g, 100 mmol), and tetrabutylammonium bromide (0.32 g, 1 mmol) for 10 min. The reaction was stirred at 65–70 °C until GC analysis indicated total consumption of **2** (ca. 10 h). The mixture was diluted with CH_2Cl_2 (60 mL) and filtered; the solid was washed with CH_2Cl_2 (2 × 10 mL). The combined filtrates were washed with H_2O (3 × 30 mL) and dried ($MgSO_4$). The solvent was evaporated, and the residue was distilled under reduced pressure to give **4** (8.74 g, 80.1%) as yellow oil.

Compound 4: bp 115–118 °C/0.2 Torr. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 2.46$ (3H, s, N-CH_3), 3.40 and 3.57 (2H, ABq, *J* 17.6, CH_2CN), 3.69 (3H, s, OCH_3), 4.19 (1H, s, C*H*-CO_2CH_3), 7.34–7.40 (3H, m, *Ph*), 7.43–7.48 (2H, m, *Ph*). ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 40.73$, 42.76, 52.41, 71.12, 114.33, 128.60, 129.09, 129.23, 134.63, 171.11. Anal. calcd. for $C_{12}H_{14}N_2O_2$ (218.26 g/mol) (%): C, 66.04; H, 6.47; N, 12.84. Found: C, 65.85; H, 6.64; N, 12.80.

N-Cyanomethyl-*N,N*-dimethyl-*N*-(α-methoxycarbonyl)benzylammonium Bromide (5a)

Dimethylaminoacetonitrile (5.05 g, 5.85 mL, 60 mmol) was added in one portion to a solution of **1** (11.45 g, 50 mmol) in CH_2Cl_2 (15 mL) at ambient temperature. The mixture was left for 10–14 days, the solvent was evaporated, and the solid residue was ground, washed with Et_2O (6 × 10 mL), and dried in air to give **5a** (11.75–13.78 g, yield 75–88%).

Compound 5a: mp 136–138 °C. ^{1}H NMR (400 MHz, DMSO-d_6) $\delta = 3.40$ (s, 3H, N^+-CH_3), 3.41 (s, 3H, N^+-CH_3), 3.76 (s, 3H, OCH_3), 5.08 and 5.16 (ABq, 2H, J 16.4, CH_2CN), 6.15 (s, 1H, C*H*-CO_2CH_3), 7.56–7.68 (5H, m, *Ph*). ^{13}C NMR (100 MHz, DMSO-d_6) $\delta = 50.33$, 50.74, 51.01, 53.93, 74.29, 111.55, 125.76, 129.77, 131.81,

132.03, 165.97. Anal. calcd. for $C_{13}H_{17}Br\,N_2O_2$ (313.20 g/mol) (%): C, 49.86; H, 5.47; N, 8.94. Found: C, 49.91; H, 5.42; N, 8.96.

N-Cyanomethyl-*N,N*-dimethyl-*N*-(α-methoxycarbonyl)benzyl-ammonium Methylsulfate (5b)

Dimethyl sulfate (1.89 g, 1.42 mL, 15 mmol) was added in one portion to a cooled solution of **4** (2.18 g, 10 mmol) in CH_2Cl_2 (10 mL), and the mixture was left overnight in a refrigerator. Next the solvent was evaporated, and the viscous yellowish oil that solidified was ground, washed with Et_2O (5 × 8 mL), and dried on air to give **5b** (3.27 g, yield 95%).

Compound 5b: mp 155–157 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 3.35 (s, 3H, N^+-C*H*$_3$), 3.37 (s, 3H, C*H*$_3$SO$_4$), 3.38 (s, 3H, N^+-C*H*$_3$), 3.77 (s, 3H, OC*H*$_3$), 4.94 and 5.07 (ABq, 2H, *J* 16.4, C*H*$_2$CN), 5.93 (s, 1H, C*H*-CO_2CH_3), 7.55–7.68 (5H, m, *Ph*). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 50.56, 50.75, 51.09, 52.89, 53.98, 74.69, 111.58, 125.68, 129.86, 131.86, 132.09, 165.97. Anal. calcd. for $C_{14}H_{20}N_2O_6S$ (344.39 g/mol) (%): C, 48.83; H, 5.85; N, 8.13. Found: C, 48.68; H, 5.74; N, 8.12.

N-Cyanomethyl-*N,N*-dimethyl-*N*-(α-methoxycarbonyl)benzyl-ammonium Trifluoromethanesulfonate (5c)

Methyl trifluoromethanesulfonate (2.46 g, 1.70 mL, 15 mmol) was added in one portion to a cooled solution of **4** (2.18 g, 10 mmol) in CH_2Cl_2 (10 mL), and the mixture was left overnight in a refrigerator. The crystals were filtered, washed with Et_2O (5 × 8 mL), and dried on air to give **5c** (3.48–3.67 g, yield 91–96%). When the product did not crystallize in a refrigerator, the solvent was evaporated, and the product **5c** was isolated as in the case of **5b**.

Compound 5c: mp 131–132 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 3.34 (s, 3H, N^+-C*H*$_3$), 3.37 (s, 3H, N^+-C*H*$_3$), 3.77 (s, 3H, OC*H*$_3$), 4.91 and 5.06 (ABq, 2H, *J* 16.4, C*H*$_2$CN), 5.92 (s, 1H, C*H*-CO_2CH_3), 7.55–7.69 (5H, m, *Ph*). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 50.59, 50.75, 51.10, 53.98, 74.69, 111.60, 125.64, 129.86, 131.84, 132.09, 165.95. Anal. calcd. for $C_{14}H_{17}F_3N_2O_5S$ (382.36 g/mol) (%): C, 43.98; H, 4.48; N, 7.33. Found: C, 44.00; H, 4.36; N, 7.37.

N-Cyanomethyl-*N,N*-dimethyl-*N*-(α-methoxycarbonyl)benzyl-ammonium Tetrafluoroborate (5d)

The mixture of **3** (9.66 g, 50 mmol) and chloroacetonitrile (5.66 g, 4.75 mL, 75 mmol) was left for 10–14 days. The oil was dissolved in distilled water (ca. 10–20 mL), the organic products were extracted with Et_2O (3 × 10 mL), and the water phase was treated with $NaBF_4$ (50 mmol, 5.49 g) and left for 48–72 h. The solid was filtered, washed with H_2O (6 × 5 mL) and Et_2O (5 × 10 mL), and dried in air to give **5d** (8.32–10.56 g, yield 52–66%).

Compound 5d: mp 132–134 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 3.34 (s, 3H, N^+-C*H*$_3$), 3.37 (s, 3H, N^+-C*H*$_3$), 3.77 (s, 3H, OC*H*$_3$), 4.91 and 5.07 (ABq, 2H, *J* 16.4, C*H*$_2$CN), 5.93 (s, 1H, C*H*-CO_2CH_3), 7.55–7.68 (5H, m, *Ph*). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 50.59, 50.75, 51.10, 53.98, 74.68, 111.60, 125.65, 129.86, 131.84,

132.09, 165.95. Anal. calcd. for $C_{13}H_{17}BF_4N_2O_2$ (320.09 g/mol) (%): C, 48.78; H, 5.35; N, 8.75. Found: C, 48.90; H, 5.25; N, 8.81.

2-(Methoxycarbonymethyl)-α-(dimethylamino)phenylacetonitrile (7) by Rearrangement of 5

Method 1. To a stirred liquid ammonia (ca. 50 mL), salt **5** (10 mmol) was added in one portion at −33 °C. Stirring was continued for 3–5 h, ammonia was evaporated overnight, and the residue was diluted with CH_2Cl_2 (70 mL) and H_2O (50 mL). The phases were separated, the water phase was extracted with CH_2Cl_2 (2 × 15 mL), and the combined organic extracts were washed with H_2O (3 × 30 mL) and dried ($MgSO_4$). The solvent was evaporated, and the residue (2.09–2.28 g of yellow oil) was analyzed by GC. The crude product was used for preparation of **9**.

Alternatively, 2-(methoxycarbonymethyl)-α-(dimethylamino)phenylacetonitrile (**7**) was isolated from the crude reaction mixture by crystallization from hexane in yield ca. 60–68% (1.39–1.58 g, purity ≥98.5% by GC). The filtrate was evaporated, and the residue was crystallized from MeOH to give pure mixture of **7** and **8**. Further recrystallization of this mixture from hexane afforded **7** (total yield 70–78%, 1.62–1.81 g).

Method 2. Triethylamine (5.06 g, 6.97 mL, 50 mmol) was added to a stirred mixture of **5** (10 mmol) in CH_2Cl_2 (25 mL). Stirring was continued at ambient temperature for 2 h, the mixture was diluted with water (50 mL), the phases were separated, the water phase was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic extracts were washed with H_2O (3 × 20 mL) and dried ($MgSO_4$). The solvent was evaporated, and the residue (2.03–2.27 g of yellowish oil) was analyzed by GC (Table 1, entry 6). The crude product (mixture of **7** and **8**) was used for preparation of **9**.

Compound 7: Mp 56–58 °C (hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.23 [s, 6H, N(C*H*$_3$)$_2$], 3.55 and 3.94 (ABq, *J* 15.6, 2H, C*H*$_2$CO$_2$CH$_3$), 3.66 (s, 3H, OC*H*$_3$), 5.07 (s, 1H, C*H*CN), 7.25–7.39 (m, 4H, *Ph*), 7.59–7.62 (m, 1H, *Ph*). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 38.34, 41.17, 51.98, 61.42, 114.64, 127.49, 128.56, 129.33, 131.93, 132.06, 133.60, 171.43. Anal. calcd. for $C_{13}H_{16}N_2O_2$ (232.28 g/mol) (%): C, 67.22; H, 6.94; N, 12.06. Found: C, 67.01; H, 6.89; N, 11.95.

3-Cyano-3-dimethylamino-2-phenylpropionic Acid Methyl Ester (8) by Rearrangement of 5a,d

Triethylamine (1.01 g, 1.39 mL, 10 mmol) was added to a stirred mixture of **5a** (0.63 g, 2 mmol) or **5d** (0.64 g, 2 mmol) in cyclohexane or diethyl ether or CCl_4 (5 mL). Stirring was continued at ambient temperature for 5 h, the mixture was diluted with water (15 mL), the phases were separated, the water phase was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were washed with H_2O (3 × 10 mL) and dried ($MgSO_4$). The solvent was evaporated, and the residue was crystallized from MeOH to give **8** (0.37–0.38 g, yield 80–83%) as mixture of diastereoisomers (ratio from 1/1.7 to 1/2.7).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.26 (s, 6H minor, N(C*H*$_3$)$_2$), 2.41 [s, 6H major, N(C*H*$_3$)$_2$], 3.71 (s, 3H both, OC*H*$_3$), 3.90 and 4.26 (ABq, *J* 12.0, 2H major,

C*H*-C*H*), 3.94 and 4.25 ABq, *J* 11.6, 2H minor, C*H*-C*H*), 7.26–7.43 (m, 5H both, *Ph*). ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 41.77$, 42.06, 52.57, 52.64, 52.79, 60.29, 62.62, 114.23, 115.40, 127.84, 128.36, 128.39, 128.91, 129.13, 133.01, 133.68, 170.71, 170.94. Anal. calcd. for $C_{13}H_{16}N_2O_2$ (232.28 g/mol) (%): C, 67.22; H, 6.94; N, 12.06. Found: C, 67.01; H, 7.02; N, 11.98.

Methyl 2-Formylphenylacetate (9)

Preparation of 9 from pure 7. A solution of **7** (21.6 g, 93 mmol) (purity ca. 97% by GC) in THF (280 mL) was added in one portion to a vigorously stirred solution of $CuSO_4 \times 5H_2O$ (46.44 g, 186 mmol) in H_2O (280 mL). The reaction was stirred, refluxed for 2 h, and cooled; the phases were separated. The water phase was extracted with CH_2Cl_2 (3×100 mL), and the combined organic extracts were washed with H_2O (3×100 mL) and dried ($MgSO_4$). The solvent was evaporated to give **9** (15.38 g, yield 93%, purity ca. 97% by GC) as a yellowish oil. After passing this oil dissolved in CH_2Cl_2 (ca. 10 mL) through a short layer of silica gel (hexane/ethyl acetate 92/8) the product **9** was obtained as a nearly a colorless oil, solidifying in freezer. The analytical sample was distilled on Kugelrohr apparatus.

Preparation of 9 from Crude Mixture of 7 and 8

Crude rearranged products (4.23 g, containing 89.6% of **7**, 5.3% of **8**, 1.0% of **9** obtained from 20 mmol of **5a** in NEt_3/NH_3 liq/$-33\,^\circ$C system) were deprotected as described previously. The residue was purified by column chromatography (hexane/ethyl acetate, gradient) giving 2.29 g of **9** (yield 64% from **5a**).

Crude rearranged products (4.47 g, containing 71.2% of **7**, 26.2% of **8** obtained from 20 mmol of **5a** in NEt_3/CH_2Cl_2/rt system) were deprotected as described previously. The residue was purified by column chromatography (hexane/ethyl acetate, gradient) giving 0.15 g of **12** (yield 4.6% from **5a**) and 1.71 g of **9** (yield 48% from **5a**).

Compounds 9 and 12

Compound 9: bp 112–115 °C/0.09 Torr (kugelrohr). ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 3.69$ (s, 3H, O*CH*$_3$), 4.05 (s, 2H, *CH*$_2$CO$_2$CH$_3$), 7.27–7.31 (m, 1H, *Ph*), 7.47–7.58 (m, 2H, *Ph*), 7.82–7.85 (m, 1H, *Ph*), 10.10 (s, 1H, *CH*O). ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 38.82$, 52.00, 127.90, 132.26, 133.69, 134.31, 134.36, 135.41, 171.36, 192.96.

Compound 12: ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 3.98$ (s, 3H, O*CH*$_3$), 7.49–7.54 (m, 2H, *Ph*), 7.64–7.69 (m, 1H, *Ph*), 8.00–8.03 (m, 2H, *Ph*). ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 52.75$, 128.88, 130.05, 132.39, 134.95, 164.00, 186.02. Anal. calcd. for $C_9H_8O_2$ (164.16 g/mol) (%): C, 65.85; H, 4.91. Found: C, 65.71; H, 5.14.

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