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UREIDOALKYLATIONS AND OXYALKYLATION OF AROMATIC COMPOUNDS WITH GLYOXYLIC ACID DERIVATIVES

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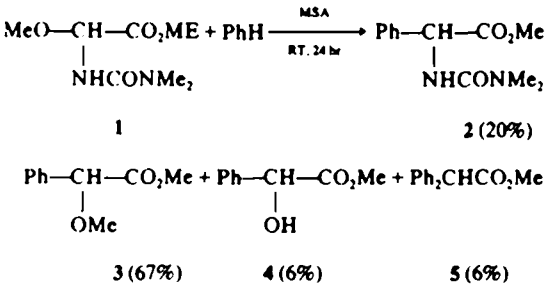
Abstract—The ureidoalkylation of benzene, toluene, xylene, anisole, phenol, acetanilide and chlorobenzene with *N,N*-dimethylurea-glyoxylic acid adducts **1** and **6** gives substituted *N,N*-dimethylcarbamoyl-DL-phenylglycine. The oxyalkylation of benzene with glyoxylic acid, methyl glyoxylate and methyl dimethoxyacetate is also described (see Table 1).

Recently we have described the reactions of ureas with glyoxylic acid which led to the formation of hydantoic acid (**1**) and allantoic acid (**6**) derivatives.[1] We have now tried to use these urea-glyoxylic acid adducts in the ureidoalkylation of aromatic compounds.

Reacting methyl δ,δ-dimethyl-α-methoxyhydantoate (**1**) with benzene in methanesulfonic acid at room temperature gave a mixture of products. To our surprise the main reaction product was not the expected derivative of phenylglycine **2** but the oxyalkylation product methyl α-methoxyphenylacetate (**3**). Oxyalkylation products were not observed in the amidoalkylation of aromatic compounds with amide-glyoxylic acid or carbamateglyoxylic acid adducts.[2]

These results were further confirmed when we repeated the ureidoalkylation of benzene with methyl δ,δ-dimethyl-α-hydroxyhydantoate. In the second case we obtained only 19% of the ureidoalkylation product **2** together with methyl α-methoxyphenylacetate (**3**), methyl mandelate (**4**) and methyl diphenylacetate (**5**):

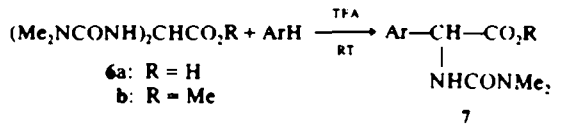


1 **2** (20%)

3 (67%) **4** (6%) **5** (6%)

In order to increase the yields of the ureidoalkylation products and reduce the amount of oxyalkylation, we tried to ureidoalkylate aromatic compounds with methyl $\delta,\delta,\delta',\delta'$-tetramethylallantoate (**6**).[1] It was indeed found that the bisadduct of methyl glyoxylate and *N,N*-dimethylurea (**6**) will ureidoalkylate toluene, xylene, anisole and phenol in trifluoracetic acid at room temperature to give the substituted phenylglycine **7** in 50–90% yield. The free allantoic acid **6a** reacted similarly with the aromatic compounds.

The reaction with benzene and chlorobenzene were carried out in methane-sulfonic acid and concentrated sulfuric acid respectively to give the expected phenylglycine derivatives in 53 and 39% yield. Acetanilide reacted in trifluoroacetic acid to give only 23% yield of



6a: R = H
b: R = Me

7

7a: Ar = Ph; R = H[a]	**g**: Ar = AcNHPh; R = Me
b: Ar = Ph; R = Me[a]	**h**: Ar = MeOPh; R = H[b]
c: Ar = MeC_6H_4; R = Me	**i**: Ar = MeOPh; R = Me[b]
d: Ar = MeC_6H_4; R = H	**j**: Ar = HOPh; R = H
e: Ar = p-$Me_2C_6H_3$; R = Me	**k**: Ar = ClPh; R = H[c]
f: Ar = AcNHPh; R = H	**l**: Ar = ClPh; R = Me[c]

[a]The product was obtained only if the reaction was carried out in MSA and not in TFA. [b]The expected product was obtained even in DCA (dichloracetic acid) at room temp. for 24 h. [c]The reaction was carried out in concentrated sulfuric acid.

product. The monosubstituted aromatics afforded a mixture of *ortho-para* isomers and the *para* isomers which predominated were obtained pure on crystallization or chromatography.

The fact that in some of the ureidoalkylation reactions even the allantoate **6** afforded mandelic acid and diphenylacetic acid as by products encouraged us to attempt oxyalkylation of benzene with glyoxylic acid itself, methyl glyoxylate and methyl dimethoxyacetate.[3] These non-nitrogenous compounds can be formed by the hydrolysis of the allantoates or hydantoates. The reactions were carried out in methanesulfonic acid at room temperatures using a five fold excess of benzene over the glyoxylic acid derivative. The results are summarized in Table 1.

In all cases we obtained a mixture of mandelic and diphenylacetic acid derivatives. The ratio of the two types of product varied from 3:1 in the case of methyl dimethoxyacetate (experiment I) to 1:2 in the case of glyoxylic acid itself (experiment V). Methyl mandelate and methyl α-methoxyphenylacetate, which are probably the first formed products, were found to react further with benzene under the same experimental conditions to give methyl diphenylacetate (experiments II and IV). In the case of methyl glyoxylate hemiacetal (experiment II) the ratio of methyl mandelate to methyl α-methoxyphenylacetate was about 1:3 probably because the hydroxy group is a better leaving group than the methoxy group under the acidic conditions used.

Methyl *N,N*-dimethylcarbamylphenylglycinate (**2**) was found to be stable under the reaction conditions used. It did not react further with benzene or methanol in

Table 1.

	Starting Materials		Products		Overall yield
I.	$(MeO)_2CHCO_2Me$	PhH / MSA →	$PhCH(OMe)-CO_2Me$ +	Ph_2CHCO_2Me	
			77%	23%	80%
II.	$MeO-CH(OH)-CO_2Me$	" →	63%	23%	98%
III.	$Ph-CH(OMe)-CO_2Me$	" →	27%	73%	70%
IV.	$Ph-CH(OH)-CO_2Me$	" →		84%	89%
V.	$(HO)_2CH-CO_2H$	" →	$Ph-CH(OH)-CO_2H$ +	Ph_2CHCO_2H	91%
			35%	65%	

methanesulfonic acid and cannot be an intermediate in the formation of the non-nitrogenous products.

EXPERIMENTAL

General. M.ps are uncorrected. The IR spectra were recorded on Perkin-Elmer 237 spectrophotometer. NMR spectra were obtained on a Varian T-60 spectrometer. Chemical shifts are reported in ppm downfield from TMS.

Reaction of methyl α-methoxy-δ,δ-dimethyl hydantoate (1) with benzene in methanesulfonic acid (MSA). To a cooled and stirred suspension of methyl α-methoxy-δ,δ-dimethylhydantoate (0.95 g, 0.005 mole) in methanesulfonic acid (5 ml) there was added benzene (2.5 ml). After stirring at room temp. for 24 hr the solution was poured into crushed ice (100 g) and extracted with EtOAc (2 × 50 ml). The organic layer was washed with aqueous $NaHCO_3$ (10 ml, 1M), with water, dried over $MgSO_4$ and evaporated to dryness to give 0.95 g (80.4%) of a yellow oil. According to TLC ($CHCl_3$, Alumina) and the NMR spectrum the crude oil was a mixture of 4 components: 1. *Methyl dimethylcarbamoyl-DL-phenylglycinate* (2, 20.3%) m.p. 105–106°; IR ($CHCl_3$): 3490, 1735, 1650 and 1495 cm^{-1}; NMR ($CDCl_3$) δ: 7.41 (s, 5H); 5.56 (d, 1H, J = 7 c/s); 5.4 (d broad, 1H); 3.74 (s, 3H); 2.53 (s, 6H); MS (HR): *m/e* 236.1170 $C_{12}H_{16}N_2O_3$ calcd 236.1160. (Found: C, 61.13; H, 6.79; N, 11.90. $C_{12}H_{16}N_2O_3$ requires: C, 61.00; H, 6.83; N, 11.86%). 2. *Methyl α-methoxyphenylacetate* (3, 67.2%), IR ($CHCl_3$): 2990, 2950, 2930, 2890, 1745 (CO) 1450, 1270, 1175, 1110 and 1015 cm^{-1}; NMR ($CDCl_3$) δ: 7.44 (d, 5H, J = 5 c/s); 4.81 (s, 2H); 3.73 (s, 3H, CO_2Me); 3.43 (s, 3H, OMe); MS (HR): *m/e* 180.0796 $C_{10}H_{12}O_3$ calcd 180.0786. 3. *Methyl diphenylacetate* (5, 5.8%), m.p.: 59–61°; IR ($CHCl_3$): 3050, 2960, 1735 (CO), 1600, 1495, 1455, 1440, 1355, 1310, 1280, 1280, 1155 and 1015 cm^{-1}; NMR ($CDCl_3$) δ: 7.35 (s, 10H); 5.06 (s, 1H); 3.72 (s, 3H); MS (HR): *m/e* 226.0883 $C_{16}H_{14}O_2$ calcd 226.0893. 4. *Methyl α-hydroxyphenylacetate* (4, 5.8%), IR ($CHCl_3$): 3050, 2960, 1735 (CO), 1440, 1230, 1070 and 980 cm^{-1}; NMR ($CDCl_3$) δ: 7.40 (s, 5H); 5.19 (s, 1H); 3.72 (s, 3H); MS (HR): *m/e* 166.0639 $C_9H_{10}O_3$ calcd 166.0630.

Reaction of methyl α-hydroxy-δ,δ-dimethylhydantoate with benzene in MSA. A mixture of methyl α-hydroxy-δ,δ-dimethylhydantoate (0.88 g, 0.005 mole) and benzene (2.5 ml) in MSA (5 ml) was treated as described above. The crude oil (0.61 g, 61.4%) was a mixture of methyl dimethylcarbamoylphenylglycinate (2, 18.7%); methyl α-methoxy phenylacetate (3, 29.2%), methyl mandelate (4, 26%) and methyl diphenylacetate (5, 26%).

Ureidoalkylation of aromatic compounds with allantoates in methanesulfonic acid. General procedure A. To a cooled and stirred suspension of δ,δ,δ',δ'-tetramethylallantoic acid or its methyl ester (6, 2.46 g, 0.01 mole) in MSA (10 ml) there was added the aromatic component (0.02–0.05 mole). The suspension was stirred at room temperature for 24 h, poured into crushed ice (100 g) and extracted with EtOAc.

Dimethylcarbamoyl-DL-phenylglycine was prepared from δ,δ,δ',δ'-tetramethylallantoic acid (6a) and benzene by the general procedure A. The crude product (54%) was chromatographed over a silica column and eluted with $CHCl_3$. The pure acid melted at 131–133°; IR ($CHCl_3$): 3430, 1730, 1640 and 1505 cm^{-1}; NMR ($CDCl_3$) δ: 9.49 (s, 1H); 7.40 (s, 5H); 5.55 (s + m, 2H); 2.85 (s, 6H); MS (HR): *m/e* 222.0970 calcd for $C_{11}H_{14}N_2O_3$ 222.0104; (Found: C, 59.57; H, 6.34; N, 12.55. $C_{11}H_{14}N_2O_3$ requires: C, 59.45; H, 6.35; N, 12.60%).

Methyl dimethylcarbamoylphenylglycinate was prepared from methyl δ,δ,δ',δ'-tetramethylallantoate and benzene by the general procedure A. The crude ester (41%) was triturated with hexane and crystallized from ethyl acetate-hexane; m.p. 105–106°. The IR and NMR spectra are described above. The aqueous $NaHCO_3$ solution was acidified and extracted with ethyl acetate to give 21% of the acid 7a bringing the overall yield to 62%. The methyl ester 7b was hydrolyzed in methanolic KOH at room temperature to give an acid (m.p. 131–132°) identical with 7a. (IR, NMR and mixed m.p.).

Ureidoalkylation of aromatic compounds with allantoates in trifluoroacetic acid (TFA). General procedure B. To a cooled (ice-water) and well stirred suspension of methyl δ,δ,δ',δ'-tetramethylallantoate 6b or the free acid 6a (0.01 mole) in TFA (10 ml), there was added the aromatic component (0.02–0.05 mole). The suspension was stirred at room temp. for 24–48 h, poured into crushed ice (100 g) and extracted with EtOAc. The organic phase was washed with water (3 × 50 ml), aqueous $NaHCO_3$ and dried over $MgSO_4$.

Methyl dimethylcarbamoyl-p-methylphenylglycinate (7c). This compound was prepared from methyl allantoate 6b (2.46 g, 0.01 mole) and toluene (5 ml) by the general procedure B. The crude product obtained after 48 h (1.1 g, 88%) was according to the NMR a mixture of *para-ortho* isomers (3:1). Trituration and crystallization from ethyl acetate-hexane afforded the pure *para* isomer: m.p. 117.5–118°; IR ($CHCl_3$): 3430, 3050 (sh); 2985, 2950, 2925, 1735, 1650, 1500, 1440, 1380, 1310, 1175 cm^{-1}; NMR ($CDCl_3$) δ: 7.51–7.11 (m, 4H); 5.54 (d, J = 6.5, 1H); 5.4 (sh, 1H); 3.75 (s, 3H); 2.95 (s, 6H), 2.37 (s, 3H); MS (HR): *m/e* 250.1317 calcd for $C_{13}H_{18}N_2O_3$ 250.1317; (Found: C, 62.49; H, 7.19; N, 11.15. $C_{13}H_{18}N_2O_3$ requires: C, 62.38; H, 7.25; N, 11.19%).

The free acid 7d was prepared by reacting the allantoic acid 6a with toluene by the general procedure B. The acidification of the $NaHCO_3$ solution and extraction into EtOAc afforded 2.30 g (92.5%) crude consisting of a mixture of isomeric *para* and *ortho* ureidoalkylated acid in a ratio of 3:1. Trituration with ether enabled the separation of isomers, from which the main *para*-isomer could be recrystallized for analysis, from ethyl acetate; m.p. 171°C, IR (KBr): 3385, 3050 (sh), 2950, 2915, 2850 (sh), 2480 (wide), 1720, 1595 (wide), 1515, 1415, 1390, 1315, 1240, 1215, 1190, 1180, 985, 925, 770, 730 cm^{-1}; NMR (DMSO-d_6) δ: 7.37, 7.21 (ABq, J = 8, 4H), 6.51 (d, J = 8, 1H), 5.26 (d, J = 8, 1H), 3.85 (s, 6H), 2.32 (s, 3H); MS (HR): *m/e* 236.1162 calcd for $C_{12}H_{16}N_2O_3$ 236.1161. (Found: C, 60.86; H, 6.69; N, 11.79. $C_{12}H_{16}N_2O_3$ requires: C, 61.00; H, 6.83; N, 11.86%).

Methyl dimethylcarbamoyl-2,5-dimethylphenylglycinate (**7e**). This compound was prepared from the allantoate **6b** (0.01 mole) and *p*-xylene (5 ml) by the general procedure B. After 24 h at room temp. the crude yellowish oil was triturated with pentane to give a crystalline material (1.59 g, 60.2%). It was crystallized from petroleum ether 40–60°: m.p. 95–96°C; IR ($CHCl_3$): 3430, 3045 (sh), 2990, 2955, 2925, 2870, 1735, 1600, 1500–1510, 1440, 1380, 1305, 1180 cm^{-1}; NMR ($CDCl_3$) δ: 7.06 (s, wide, 3H), 5.7 (d, J = 7, 1H); 5.21 (d, J = 7, 1H), 3.74 (s, 3H), 2.95 (s, 6H), 2.45 (s, 3H), 2.32 (s, 3H); MS (HR): *m/e* 264.1499 for $C_{14}H_{20}N_2O_3$ calcd 264.1473. (Found: C, 63.64; H, 7.49; N, 10.48. $C_{14}H_{20}N_2O_3$ requires: C, 63.63; H, 7.63; N, 10.60%). From the aqueous bicarbonate ext. after acidification 0.134 gr or 10% hydrolyzed product was detected according to NMR spectrum, thus increasing the total yield to 70%.

Methyl dimethylcarbamoyl-p-acetamidophenylglycinate (**7f**). This compound was prepared from the allantoate **6b** (0.01 mole) and acetanilide (0.01 mole) by the general procedure B. The crude was triturated with ether to give (0.200 g, 13.7%) pure product m.p. 242–244°C which was recrystallized for analysis from methanol, m.p. 242.5–244.5°C; IR (KBr): 3460 (sh), 3280, 3235, 3175, 3110, 3040, 2950, 2870 (sh), 1750, 1675, 1620 (wide), 1525, 1440, 1420, 1385, 1370, 1325, 1280, 1235, 1205, 1175, 1035, 935, 860, 775 cm^{-1}; NMR (DMSO-d_6) δ: 7.61, 7.37 (*ABq*, J = 9, 4H); 6.74 (d, J = 7, 1H); 5.26 (d, J = 7, 1H), 3.63 (s, 3H), 2.85 (s, 6H); 2.07 (s, 3H); MS (HR): *m/e* 293.1378 calcd for $C_{14}H_{19}N_3O_4$ 293.1375. (Found: C, 57.60; H, 6.21; N, 14.35. $C_{14}H_{19}N_3O_4$ requires: C, 57.32; H, 6.53; N, 14.33%). The bicarbonate extract was also acidified and extracted into ethyl acetate. According to the NMR spectrum it was a mixture of the hydrolyzed product together with some ester carried as well, thus increasing the yield of ureidoalkylated product to 36.2%. The free acid was obtained in 23% yield on reacting **6a** with acetanilide by the general procedure B. Trituration with ether afforded a solid m.p.: 200°C (dec); NMR (DMSO-d_6) δ: 4.9 (s, wide, 1H); 7.79–7.16 (q, not well defined, 4H); 6.51 (d, J = 7, 1H); 5.21 (d, J = 7, 2H); 2.84 (s, 6H); 2.03 (s, 3H).

Methyl dimethylcarbamoyl-p-methoxyphenylglycinate (**7i**). This compound was prepared from the allantoate **6b** (0.01 mole) and anisole (5 ml) by the general procedure B. The crude oily product was according to the NMR a mixture of isomeric products and anisol. Trituration until ether-petroleum ether afforded a crude solid which was further triturated with ether and crystallized from ether-petroleum ether (1.30 g, 49%); m.p. 68–70°C; IR ($CHCl_3$): 3430, 3050 (sh), 2990, 2950, 2840, 1735, 1600 (wide), 1615, 1500 (sh), 1380, 1310, 1225 (wide), 1180, 1035 cm^{-1}; NMR ($CDCl_3$) δ: 7.31, 6.88 (*ABq*, J_{AB} = 8.5, 4H), 5.4 (s, 1H) NH under, 3.78 (s, 3H), 3.72 (s, 3H), 2.93 (s, 6H); MS (HR): *m/e* 266.1258 calcd for $C_{13}H_{18}N_2O_4$ 266.1266. (Found C, 58.60; H, 6.66; N, 10.38. $C_{13}H_{18}N_2O_4$ requires: C, 58.63; H, 6.81; N, 10.52%). The free acid **7h** was prepared by reacting the allantoic acid **6a** with anisole by the general procedure B. Acidification of the aqueous $NaHCO_3$ and extraction into EtOAc afforded a crude mixture of *ortho-para* isomers (2.5 g, 1:3). Trituration with ether and crystallization from EtOAc gave the pure *para* isomer (1.26 g, 50.1%); m.p. 170°, IR (KBr): 3380, 3060 (sh), 2435, 2840, 2680, 2490, 1725, 1600 (wide), 1515, 1470, 1385, 1315, 1270, 1235, 1210, 1180, 1040 cm^{-1}; NMR (DMSO-d_6) δ: 7.39, 6.96 (*ABq*, J = 9, 4H), 6.5 (d, J = 8, 1H), 5.2 (d, J = 8, 1H), 4.5 (sh, 1H); 3.75 (s, 3H); 2.83 (s, 6H); MS (HR): *m/e* 252.1125 for $C_{12}H_{16}N_2O_4$ calcd 252.1115. (Found: C, 56.92; H, 6.26; N, 10.99. $C_{12}H_{16}N_2O_4$ requires: C, 57.13; H, 6.39; N, 11.11%).

N-Dimethylcarbamoyl-p-hydroxyphenylglycine (**7j**)

This compound was prepared from **6a** (2.32 g, 0.01 mole) and phenol (1.04 g, 0.011 mole) by the general procedure B. The crude product obtained after the acidification of the aqueous $NaHCO_3$ and extraction into EtOAc was triturated with ether (0.458 g, 19.3%), m.p. 165–167°. It was purified for analysis by triturations in ether m.p.: 176° (decp); IR (KBr): 3500 (sh), 3380, 3150, 3010, 2900, 2830 (sh), 2550, 1720, 1705, 1635, 1600, 1530, 1510, 1455, 1380, 1270, 1235, 1180, 935, 850 cm^{-1}; NMR (DMSO-d_6) δ: 7.37, 6.9 (*ABq*, J = 9, 4H); 6.54 (d, J = 7, 1H); 5.25 (d, J = 7, 1H); 2.92 (s, 6H); MS (HR): *m/e* 238.0960 for $C_{11}H_{14}N_2O_4$ calcd 238.0953. (Found: C, 55.49; H, 5.97; N, 11.67. $C_{11}H_{14}N_2O_4$ requires: C, 55.45; H, 5.92; N, 11.76%).

From the EtOAc phase left after the $NaHCO_3$ wash the neutral fraction could be isolated or namely the closed ring product resulting from the *ortho*-isomer of the ureidoalkylation. Indeed after trituration under ether of the obtained oil a crystalline powder (0.379 g, or 17.2%) product m.p. 199–203°C was identified by its physical data. It was further recrystallized for analysis from EtOAc m.p. 207.5–209°C; IR (KBr): 3250, 3050 (sh), 2915, 1805, 1635, 1540, 1525, 1480, 1465, 1385, 1325, 1255, 1230, 1195, 1060, 890, 760 cm^{-1}; NMR (DMSO-d_6) δ: 7.7 (d, J = 7 1H); 7.44–7.06 (m, 4H), 5.2 (d, J = 7, 1H); 2.82 (s, 6H); MS (HR): *m/e* 220.0845 for $C_{11}H_{12}N_2O_3$ calcd 220.0848. (Found: C, 59.95; H, 5.54; N, 12.73. $C_{11}H_{12}N_2O_3$ requires: C, 59.99; H, 5.49; N, 12.72%).

Dimethylcarbamoyl-p-chlorophenylglycine (**7k**)

To 5 ml H_2SO_4 (96%) at 0° was added $\delta,\delta,\delta',\delta'$-tetramethylallantoic acid (1.16 g, 0.005 m) and 2.5 ml chlorobenzene. The resulting colored suspension was allowed to stir at r.t. for 24 hr. It was then poured into 100 ml crushed ice and extracted with ethyl acetate (100 ml, 2 × 50 ml). The organic extractions were back-extracted with aq. $NaHCO_3$ (30 ml, 1N), acidified (HCl conc.) and again reextracted into ethyl acetate. The organic portion was washed (H_2O), dried ($MgSO_4$) and evaporated to dryness to give 0.5 g (39%) ureidoalkylation product NMR (DMSO-d_6) δ: 7.47 (s); 7.41 (s); 6.99–6.63 (m); 5.79 (d, J = 7); 5.34 (d, J = 7); 5.34 (d, J = 7); 2.88 (s) as a mixture of *ortho* and *para* isomer in 1:2 ratio. Trituration of the crude under ether afforded (0.200 g, 15.6%) pure *para* isomer which could be recrystallized from ethyl acetate to give an analytical sample; m.p. 171–172°C; IR (KBr): 3495, 3050 (sh), 2920, 2500 (wide), 1725, 1600, 1520, 1385, 1210, 1095, 755, 770 cm^{-1}; NMR (DMSO-d_6) δ: 7.39 (wide s, 4H); 6.02 (sh, H); 5.89 (d, J = 7, 1H); 5.41 (d, J = 7, 1H); 2.95 (s, 6H); MS (HR): *m/e* 258.0588 for $C_{11}H_{13}N_2O_3Cl_2$ calcd 258.0558 and 256.0629 for $C_{11}H_{13}N_2O_3Cl_{35}$ calcd 256.0615. (Found: C, 51.26; H, 4.96; N, 10.76; Cl, 13.53. $C_{11}H_{13}O_3N_2Cl$ requires: C, 51.71; H, 4.74; N, 10.96; Cl, 13.87%). From the ether phase the *ortho*-isomer could be isolated and purified as well, m.p. 146–147° decomp., NMR (DMSO-d_6) δ: 7.74–7.28 (m, 4H); 6.81 (d, J = 8, 1H); 5.77 (d, J = 8, 1H); 2.85 (s, 6H); MS (HR) (*m/e*-Cl) 221.0924 calcd for $C_{11}H_{11}N_2O_3$ 221.0926.

Reaction of methyl dimethoxyacetate with benzene in MSA. To a (1.34 g, 0.01 mol) sample of methyl dimethoxyacetate cooled in an ice-water bath was added 10 ml MSA and 5 ml benzene. The colored solution was stirred at ambient temp. overnight whereupon it was poured into 100 g ice-water and extracted with ethyl acetate (100 ml, 2 × 50 ml). The organic layers were washed with aq. sodium bicarbonate, with water, dried over $MgSO_4$ and concentrated *in vacuo* to yield 1.53 g (80.6%) crude which according to its NMR spectrum contained two components: methyl α-methoxy phenylacetate 77.4%, and methyl diphenylacetate 22.6%. The crude was purified on a fluorisil column chromatography (60 g) to afford 16% pure methyl diphenylacetate on elution with benzene: pet. ether 40–60° (1:1), and 53% methyl α-methoxy phenylacetate with benzene.

Reaction of methylglyoxylate monoacetal with benzene in MSA. To an ice-cooled and well stirred weighed amount of methyl glyoxylate monoacetal (1.2 g, 0.01 m) was added 10 ml MSA and 5 ml benzene to give a colored solution. The reaction was allowed to proceed 24 hr at room temp. whereupon it was poured into 100 g ice and extracted with ethyl acetate (100 ml, 2 × 50 ml). The extracts were combined, washed with aq. sodium bicarbonate, water, dried over $MgSO_4$ and concentrated *in vacuo* to give 1.97 g (99.1%) crude colored oil which according to its NMR spectrum consisted of methyl α-methoxy phenylacetate 60%, and methyl diphenylacetate 40%.

Reaction of glyoxylic acid monohydrate with benzene in MSA. To an ice-chilled MSA (10 ml) was added consecutively glyoxylic acid monohydrate (0.92 g, 0.01 m) and benzene (5 ml). The yellowish suspension thus obtained was allowed to stir at ambient temp. 24 h. It was then poured into 100 ml ice and the yellowish solid was extracted with ether (100 ml, 50 ml). The ether extracts were back extracted with aq. sodium bicarbonate

and acidified with HCl conc. to give a white oily solid. The solid was again extracted into ether which after water extraction and drying ($MgSO_4$), was evaporated to dryness to yield 1.73 g (90.6%) yellowish oil identified by NMR as a mixture of diphenylacetic acid (65.0%), and mandelic acid (35.0%).

Reaction of methyl mandelate with benzene in MSA. To a weighed sample of methyl mandelate (1.66 g, 0.01 m) kept at 0° was added 10 ml MSA and 5 ml benzene. The colored suspension thus obtained was stirred 24 h at ambient temp, it was then poured into 100 ml ice and extracted with ethyl acetate (100 ml, 2 × 50 ml). The colored organic layer was washed with aq. sodium bicarbonate, with water, dried over $MgSO_4$ and evaporated to dryness to afford 1.9 g (84%) crude methyl diphenylacetate, as an oil, identified by its physical data IR ($CHCl_3$): 2950, 1735, 1600, 1500, 1455, 1435, 1355, 1155, 1020 cm $^{-1}$; NMR ($CDCl_3$) δ: 7.34 (s, 10H); 5.06 (s, 1H); 3.73 (s, 3H), which upon standing solidified. From the water phases 0.090 g (4.2%) diphenyl acetic acid NMR ($CDCl_3$) δ: 9.63 (s, 1H), 7.34 (s, 10H), 5.06 (s, 1H) was obtained as well.

Reaction of methyl α-methoxyphenylacetate with benzene in MSA. A (0.628 g, 0.0033 m) sample of methyl α-methoxyphenylacetate was chilled before being dissolved in 3.5 ml MSA and combined with 1.7 ml benzene. The reaction suspension was allowed to stir at room temp. for 24 hr. It was then poured into ~75 ml ice to form a colored oil which was extracted into ethyl acetate (100 ml, 2 × 50 ml). The extracts were washed with aq. $NaHCO_3$(1N), with water, dried over $MgSO_4$ and concentrated under reduced pressure to yield 0.52 g (69.4%) crude composed of methyl diphenylacetate and unreacted starting material in ratio 74.0% to 26.0% according to the NMR of the sample, or 53.6% oxyalkylation product. The acidic phase was combined with the bicarbonate extract and after acidification HCl (conc.) and extraction into ethyl acetate; again traces of both above hydrolyzed compounds were identified by NMR.

On the stability of methyl N,N-dimethylcarbamoylphenylglycinate (7b). 7b (1.28 g, 0.005 mol) was added together with 2.5 ml benzene to 5 ml MSA at 0°C. The resulting suspension was allowed to stir at room temp. for 24 h and poured into ice, extracted into EtOAc, and with aq. sodium bicarbonate. From the neutral fraction 0.841 g (65.8%) crude solid was obtained identified as starting material m.p. 102.5–104°, NMR ($CDCl_3$) δ: 7.39 (s, wide, 5H); 5.4 (d, J = 7, 1H) under NH, 3.73 (s, 3H), 2.93 (s, 6H). From the bicarbonate extract an acidic fraction was obtained, 0.34 g (30.6%) as an oil, showing the NMR of the hydrolyzed starting material, which under EtOAc-pet. ether gave 0.210 g (19%) starting material m.p. 127°C, NMR ($CDCl_3$) δ: 10.1 (1H), 7.38 (s, 5H); 5.35 (m, CH, NH, 2H), 2.8 (s, 6H), pure acid. The important conclusion of this experiment is that the product is stable to further alkylation but sensitive to hydrolysis which can be as high as 31%.

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