Reinvestigation of the Synthetic Reaction of Dimethylamino-1,3-indandione

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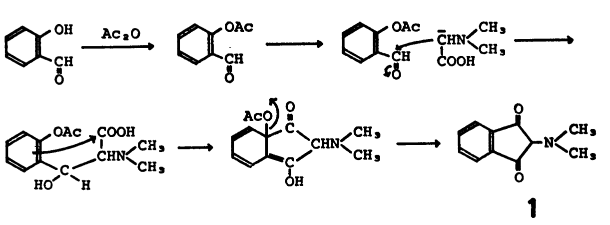
Synopsis. One step preparation of dimethylamino-1,3-indandione (**1**) from salicylaldehyde with glycine betaine was reinvestigated. Reaction conditions to give the best yield of **1**, characterization of a minor product (2-acetoxybenzylidene diacetate), and reaction pathway were described.

The reaction of salicylaldehyde with (carboxymethyl)trimethylammonium hydroxide inner salt (glycine betaine) in acetic anhydride provides a convenient procedure for the preparation of dimethylamino-1,3-indandione (**1**).[1,2]

The pathway of the reaction is proposed as depicted in Scheme 1. The reaction is based on an acetylation of the hydroxyl group of salicylaldehyde, a nucleophilic attack of α-carboxy(dimethylamino)methanide ion which is formed from the glycine betaine, and an acetylation of the benzene ring accompanied by elimination of the acetoxyl group.

The reaction mixture containing salicylaldehyde and the glycine betaine in acetic anhydride was refluxed at 150 °C for 7 h. After removal of the volatile matters, the resulting residue was recrystallized from benzene to give pale yellow crystals of **1**. The optimum reaction conditions for this reaction were investigated on several ratios of acetic anhydride and the glycine betaine *versus* the salicylaldehyde, and on the reaction time as shown in Tables 1 and 2. To obtain optimum yield of **1**, the reaction must be conducted at 150 °C for 7 h using 2—2.5 mol of the glycine betaine and 2 mol of acetic anhydride *versus* one mol of salicylaldehyde.



Scheme 1.

Table 1. Yields of the 1,3-indandione **1** and by-product **2**[a)]

Run	Molar ratio of glycine betaine : salicylaldehyde : Ac$_2$O	Yield[b)]/% 1	2
1	1 : 1 : 1	42.6	none
2	1 : 1 : 2	53.5	10.2
3	1 : 1 : 5	52.5	21.0
4	1.5 : 1 : 2	69.3	5.4
5	2 : 1 : 2	78.7	2.4
6	2.5 : 1 : 2	80.1	1.6
7	3 : 1 : 2	77.8	trace
8	1 : 2 : 2	61.1	trace

a) The reaction was carried out at 150 °C for 7 h. b) Yields are based on salicylaldehyde used. Determined by GLC.

Table 2. Effect on reaction time for yields

Run	Reaction time/min	Yield/% 1	2
9	15	55.1	4.9
10	30	61.5	3.6
11	60	68.4	4.5
12	180	72.6	3.6

Reaction conditions: Molar ratio of the glycine betaine : salicylaldehyde : acetic anhydride = 2 : 1 : 2, temp: 150 °C. Yields are based on salicylaldehyde used. Determined by GLC.

It is found that this reaction is accompanied by formation of 2-acetoxybenzylidene diacetate (**2**) as a minor product. By-product **2** will be formed by acetalyzing and acetylation of salicylaldehyde with acetic anhydride. The formation of **2** increases in yield when acetic anhydride is used in large quantities. The structure of **2** was confirmed by the analytical and spectral data, and by the fact that compound **2** is hydrolyzed to salicylaldehyde.

The similar reaction using hydroxybenzoic acids, methyl salicylate in place of salicylaldehyde did not give the product **1**, and in the case of methyl salicylate it gave only methyl 2-acetoxybenzoate.

Experimental

All melting points were uncorrected. The IR, ^{1}H NMR, UV, and Mass spectra were recorded on a Shimadzu IR-400, a JEOL JNM-PMX-60 using TMS as internal standard, a Shimadzu MPS-5000, and a Shimadzu LKB-9000 spectrometer, respectively. The analytical GLC were performed on a Shimadzu GC-4B apparatus equipped with a data processor, Chromatopac C-R1B, and with a 1.5 m glass column packed 10% Silicone OV-17 at 210 °C. Acetic anhydride was purified by refluxing with CaC_2 and by distillation before use.

Preparation of Dimethylamino-1,3-indandione (1). A mixture of the glycine betaine (29.3 g, 0.25 mol) and salicylaldehyde (12.2 g, 0.1 mol) in acetic anhydride (20.4 g, 0.2 mol) was refluxed at 150 °C for 7 h. After sufficient water was added to decompose the excess acetic anhydride, the mixture was extracted with benzene, washed with water, dried over sodium sulfate, and evaporated to leave a crude product 15.2 g of the 1,3-indandione **1** in 80.1% yield (based on salicylaldehyde, obtained on GLC datum). An analytical sample was recrystallized from benzene, a pale yellow crystal: mp 85—86 °C; UV$_{max}$ (EtOH) 245 (ε 8100) and 340 nm (ε 14400); ^{1}H NMR (CDCl$_3$): δ=2.98 (6H, s), 6.69 (1H, s), 7.27 (4H, s); IR (KBr): 1705 (C=O) cm^{-1}; MS (*m*/*e*) 189 (M$^+$); Found: C, 69.56; H, 5.77; N, 7.40%. Calcd for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40%.

The reactions shown in Tables 1 and 2 were carried out under the full range of the reaction conditions noted above.

2-Acetoxybenzylidene Diacetate (**2**). *Isolation of* **2**: A mixture of the glycine betaine (5.9 g, 0.05 mol), salicylaldehyde (6.1 g, 0.05 mol) in acetic anhydride (25.5 g, 0.25 mol) was refluxed at 150 °C for 7 h. After the usual work-up, the residue was chromatographed on silica-gel column. From a benzene elute, 2.4 g, (18.0%) of **2** was obtained. Colorless crystals; mp 102.7—103.4 °C; ^{1}H NMR (CDCl$_3$): δ=2.12 (6H, s), 2.34 (3H, s), 7.06—7.73 (4H, m), 7.91 (1H, s); IR (KBr): 1755—1745 (C=O) cm^{-1}; Found: C, 58.57; H, 5.33%. Calcd for $C_{13}H_{14}O_6$: C, 58.64; H, 5.30%. Mol wt (Rast, benzene) 267. Calcd 266.24. E.V. 48.24. Calcd 48.51. The saponification value was determined by hydrolysis with a 0.5 M ethanolic KOH solution for 1 h.

Preparation of **2**: A mixture of salicylaldehyde (12.2 g, 0.1 mol) in acetic anhydride (25.5 g, 0.25 mol) was refluxed at 150 °C for 2 h. After cooling, a crystalline product was filtered and recrystallized from benzene to give **2** (19.3 g, 72.5%). The product was identified by means of gas chromatography in comparison with the isolated product described above.

Reaction of 2-Acetoxybenzylidene Diacetate (**2**) *with the Glycine betaine and Acetic Anhydride.* A mixture of 2.7 g (0.01 mol) of **2** and 2.3 g (0.02 mol) of the glycine betaine in 3 g (0.03 mol) of acetic anhydride was refluxed at 150 °C for 4.5 h. After the usual work-up, 0.19 g (47.6% based on **2** used) of the 1,3-indandione (**1**) was obtained on GLC. Its IR and ^{1}H NMR spectra data agreed with those of **1** obtained as noted above.

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References

1) M. ITO, U. S. Patent 4302602 (Nov. 24, 1981).

2) On using anhydrous sodium acetate instead of anhydrous glycine betaine a Perkin's reaction occurs.