Acetoacetylation with Diketene Catalyzed by 4-Dimethylaminopyridine

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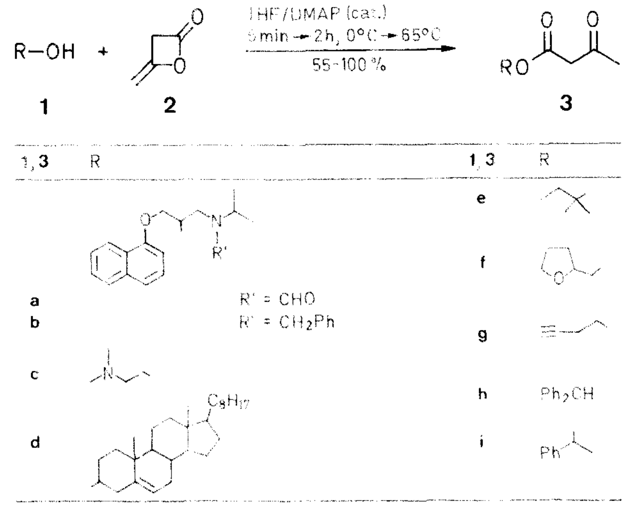
A useful procedure for the acetoacetylation of alcohols **1** with diketene **2** to acetoacetic esters **3** is reported.

Acetoacetic esters are versatile intermediates obtained most frequently by the treatment of alcohols with diketene in the presence of a variety of catalysts.[1] An alternative to diketene is 2,2,6-trimethyl-4*H*-3-dioxin-4-one, which reacts with alcohols in the absence of additional catalyst and gives only volatile byproducts but requires a high reaction temperature.[2]

Despite the wide use of 4-dimethylaminopyridine (DMAP) as an acylation catalyst,[3] there has apparently been only one report of its use in acetoacetylation, namely for primary allylic alcohols.[4] We wish to report that DMAP catalyzed acetoacetylation of alcohols is a useful, high yield process of wide utility.



In the Table are listed the various alcohols examined and the yields obtained in the presence of DMAP as compared with those obtained when other reported catalysts such as pyridine,

Table. Acetoacetic Esters **3** Prepared

Alcohol	Reaction Conditions Temp. (°C)/ Time	Product	Yield (%)	mp (°C) or bp (°C)/ mbar	Molecular Formula[a] or Lit. Data	^{1}H-NMR ($CDCl_3$/TMS) δ, *J* (Hz)	MS (CI) *m/z* ($M^+ + 1$)
1a	46/2 h	**3a**	55[b]	oil	$C_{21}H_{25}NO_5$ (371.4)	1.32, 1.35 [2d, 3H each, *J* = 7, $CH(C\underline{H}_3)_2$]; 2.24 (s, 3H, CH_3CO); 3.50 (s, 2H, CH_2CO); 3.64, 3.73 (2dd, 1H each, *J* = 14.5, 5.5 and *J* = 14.5, 7, NCH_2); 3.81 (sept, 1H, *J* = 7, CHN); 4.27, 4.34 (2dd, 1H each, *J* = 10.5, 4 and *J* = 10.5, 6, OCH_2); 5.64 (dddd, 1H, *J* = 7, 6, 5.5, 4, OCH); 6.80 (dd, 1H_{arom}, *J* = 7.5, 1, H-2); 7.36 (dd, 1H_{arom}, *J* = 8, 7.5, H-3); 7.40–7.50 (m, 3H_{arom}, H-4, H-6, H-7); 7.80 (m, 1H_{arom}, H-5); 8.18 (m, 1H_{arom}, H-8); 8.27 (s, 1H, HCO)	372
1b	35/2 h	**3b**	96	oil	$C_{27}H_{31}NO_4$ (433.6)	1.18, 1.21 [2d, 3H each, *J* = 7, $CH(C\underline{H}_3)_2$]; 2.19 (s, 3H, CH_3CO); 2.77, 2.88 (2dd, 1H each, *J* = 13.5, 8 and *J* = 13.5, 6, NCH_2); 2.99 (sept, 1H, *J* = 7, CHN); 3.40 (s, 2H, CH_2CO); 3.63, 3.70 (ABq, 2H, *J* = 14, $C\underline{H}_2Ph$); 4.13, 4.25 (2dd, 1H each, *J* = 10.5, 3.5 and *J* = 10.5, 6, OCH_2); 5.36 (m, 1H, OCH); 6.68 (dd, 1H_{arom}, *J* = 7.5, 1, H-2); 7.20–7.50 (m, 9H_{arom}); 7.76 (m, 1H_{arom}, H-5); 8.14 (m, 1H_{arom}, H-8)	434
1c	65/0.5 h	**3c**	~100[c]	120/1.3	120/1.3[8]	2.27 (s, 3H, CH_3CO); 2.29 (s, 6H, NMe_2); 2.58 (t, 2H, *J* = 5.5, NCH_2); 3.49 (s, 2H, CH_2CO); 4.24 (t, 2H, *J* = 5.5, OCH_2)	–
1d	48/5 min	**3d**	99[d]	96	96–97[9]	0.68 (s, 3H, H-18); 0.86, 0.87 (2d, 3H each, *J* = 6.5, H-26, H-27); 0.91 (d, 3H, *J* = 6.5, H-21); 1.02 (s, 3H, H-19); 2.27 (s, 3H, CH_3CO); 2.34 (m, 2H, H-4); 3.43 (s, 2H, CH_2CO); 4.67 (m, 1H, H-3); 5.38 (dm, 1H, *J* = 4.5, H-6)[e]	–
1e	20/5 min	**3e**	73	80–81	–[f]	0.90 (t, 3H, *J* = 7.5, $CH_2C\underline{H}_3$); 1.46 [s, 6H, $C(CH_3)_2$]; 1.79 (q, 2H, *J* = 7.5, $C\underline{H}_2CH_3$); 2.27 (s, 3H, CH_3CO); 3.37 (s, 2H, CH_2CO)	173
1f	20/5 min	**3f**	80	oil	–[f]	1.62, 1.85–2.05 (2m, 1H and 3H, resp., CH_2CH_2); 2.27 (s, 3H, CH_3CO); 3.50 (s, 2H, CH_2CO); 3.7–3.9, 4.15–4.25 (2m, 2H and 3H, resp., CH_2O, CHO)	187
1g	20/5 min	**3g**	73	102–103	–[f]	2.02 (t, 3H, *J* = 2.5, CH); 2.29 (s, 3H, CH_3CO); 2.56 (dt, 2H, *J* = 7, 2.5, CCH_2); 3.49 (s, 2H, CH_2CO); 4.26 (t, 2H, *J* = 7, OCH_2)	155
1h	20/10 min	**3h**	87	46–47	–[f]	2.22 (s, 3H, CH_3CO); 3.54 (s, 2H, CH_2); 6.92 (s, 1H, CH); 7.3–7.4 (m, 10H, Ph_2)	–
1i	20/10 min	**3i**	82	oil	–[f]	1.57 (d, 3H, *J* = 8, CH_3); 2.23 (s, 3H, CH_3CO); 3.46 (s, 2H, CH_2); 5.93 (q, 1H, *J* = 8, CH); 7.20–7.40 (m, 5H, Ph)	–

[a] Satisfactory microanalyses obtained: C ±0.3, H ±0.3, N ±0.32.

[b] In the presence of pyridine or NaOAc at 80–85 °C for 17 h, the yield was only 6%.

[c] In the presence of pyridine at 80–85 °C for 1 h, the yield was 75%.

[d] In the presence of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one and TsOH in toluene at 80–85 °C for 5 h, the yield was 82%.[9]

[e] Only relevant proton signals are given.

[f] Original data not available for **1e**–**1i**, however reported in references 10–14, respectively.

sodium acetate or *p*-toluenesulfonic acid were used. The reaction proceeds rapidly, frequently at room temperature and gives better yields than previous reaction conditions, which required prolonged times and high temperatures. Particular note should be made to alcohol **1a** where the yield of product was 6% in the presence of pyridine or sodium acetate as compared with the 55% yield obtained with DMAP. Moreover, S_N1-active alcohols such as benzhydrol (**1h**) and *sec*-phenethyl alcohol (**1i**) react satisfactorily. Only with 4-nitrophenol, which due to its acidity probably forms a salt with DMAP,[4] the reaction failed to give the desired acetoacetate even in the presence of equimolar amounts of DMAP and/or a large excess of diketene and at high temperature.

Acetoacetic Esters 3; General Procedure:

To an ice cold solution of a primary, secondary, or tertiary alcohol (1–100 mmol) and a catalytic amount of DMAP (0.05–0.08 mmol DMAP/mmol alcohol) in anhydrous THF (20–25 mL), is added slowly freshly distilled diketene (2 mmol/mmol alcohol). The mixture is stirred for 5 min to 2 h at 0–65 °C (see Table). The reaction is monitored by TLC (ether/*n*-hexane, 1 : 1), and the product is isolated by distillation or flash chromatography on silica gel (ether/*n*-hexane, 1 : 1). (Table).

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