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Note

Solvent free Stobbe condensation: A green approach

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Solvent free Stobbe-condensation of methyl β benzoyl propionate **1c** and methyl β-naphthoyl propionate **1d** with benzaldehyde, anisaldehyde and furfural using dry solid potassium tertiary butoxide at room temperature and at 80°C gives β arylidene β benzoyl propionic acid **2a-c** and β arylidene β naphthoyl propionic acid **2d-f** respectively. Base-catalysed solvent free Stobbe condensation of dimethyl succinate **1e** and aliphatic and aromatic ketones at room temperature gives 1,1-alkylidene monomethyl succinate **3a,b** and 1,1-arylidene monomethyl succinate **3c** respectively.

Keywords: Stobbe reaction, solvent-free method, classical method

The present work describes a simple and convenient method (economical, hazard-free and eco-friendly) for Stobbe condensation[1].

β-Benzoyl propionic acid **1a** (Ref. 2) was found to be a very exciting molecule with remarkable properties having two reactive methylenes as it underwent Perkin condensation at the α-methylene and also Stobbe condensation at the β methylene[3].

Under the green aspect, where the solvent is omitted and reaction proceeds smoothly in the presence of solid base (potassium *tert.* butoxide, in this case), Stobbe reaction[4-8], an important C-C bond forming reaction[9-11] was carried out using different aromatic aldehydes. Stobbe condensation under solvent-free conditions using solid potassium *tert.* butoxide was done with methyl β-benzoyl propionate and benzaldehyde, anisaldehyde, furfural when the products **2a, 2b** and **2c** were obtained respectively. The same reaction was tried using methyl β-naphthoyl propionate when the condensation with benzaldehyde, anisaldehyde and furfural gave **2d**, **2e** and **2f** respectively. The same products **2a-f** were also obtained in better yields when the solvent free Stobbe condensation were carried out at 80°C. The previous workers did the classical Stobbe condensation of **1c** with benzaldehyde where the product **2a** was obtained[3]. We tried the classical Stobbe condensation of **1c** with anisaldehyde and furfural when the products **2b** and **2c** were obtained respectively.

Stobbe condensation under solvent-free conditions using solid potassium tertiary butoxide was done by us with dimethyl succinate **1e** and different aliphatic (acetone, ethyl methyl ketone) and aromatic (acetophenone) ketones, the acid-ester products being the same as with classical method carried out by the previous workers[12]. Previously[12], the non-separable mixture of the stereoisomers[13] in the acid-ester product of the acetophenone condensation (in butanol-butoxide base), namely, 1,1-methyl benzylidene monomethyl succinate **3c** was saponified to the corresponding diacid **3f** (*E* and *Z* isomeric mixture); where the *E* and *Z* isomers were obtained in the ratio 90:10 [the *Z*-isomer being identified by the cyclization of the same with conc. H_2SO_4 into a corresponding indenone **4**]. However, we got non-separable isomeric acid-ester products, by solvent-free method, which could be saponified into *E-Z* mixture of the corresponding diacid **3f**. After recrystallization, the isomers were separated into different types of crystals collected by hand-picking in the ratio 60:40 (confirmed by weight measurement method). When the Stobbe condensation was carried out with dimethyl succinate and ethyl methyl ketone under solvent-free conditions, crystallized acid-ester product showed doubling of peaks in the NMR spectra[14] indicating the presence of both *E* and *Z* non-separable isomers (**Figure 1**).

Experimental Section

^1H NMR spectra were recorded in $CDCl_3$ on a Perkin-Elmer R-32 spectrometer using TMS as internal standard, IR spectra in KBr pellets and Nujol-mull and UV-Vis spectra in spectroscopic ethanol on a DMS-80 (Varian) spectrophotometer.

β-Arylidene β-aroyl propionic acid, 2a-f

To an *in-situ* generated potassium tertiary butoxide solution formed by dissolving 1 g potassium in 25 mL

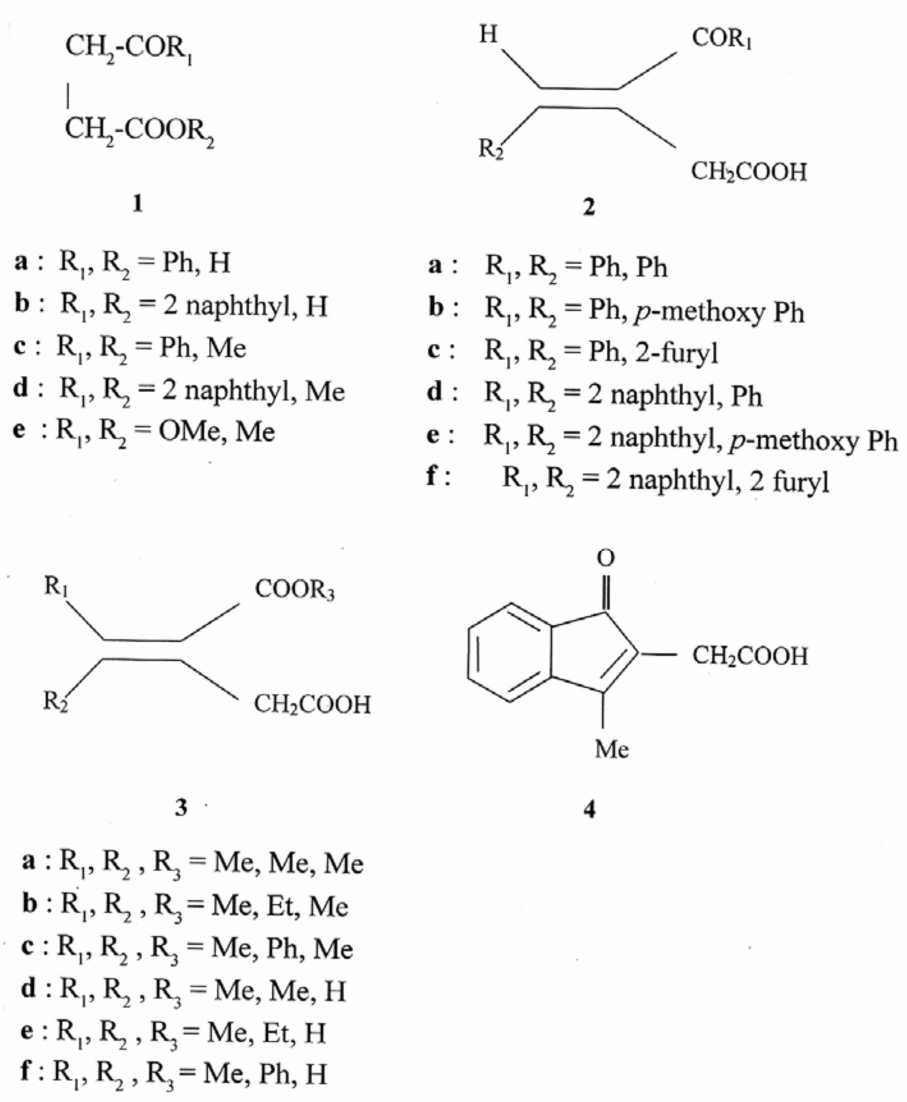

Figure 1

*t*BuOH, was added a neat mixture of **1c** (1.92 g, 10 mmoles) and benzaldehyde (1.06 g, 10 mmoles) and stirred for 1 hr. The reaction mixture was neutralized with ice-cold 3N HCl and the tertiary butanol removed under reduced pressure. After extraction with diethyl ether and washing with 10% sodium bicarbonate solution under ice-cold conditions, acidification resulted in the isolation of crude β-benzylidene β-benzoyl propionic acid **2a** in 55.2% yield which was recrystallized from benzene-*n* hexane. The same reaction was tried by solvent free method in which a neat mixture of **1c** (1.92 g, 10 mmoles) and benzaldehyde (1.06 g, 10 mmoles) was taken in a dry mortar and to it was added dried solid potassium tertiary butoxide (1.13 g, 10 mmoles) well ground with a pestle at RT for 10 min. The reaction was exposed to air. After usual work-up[10] and recrystallisation from benzene-*n* hexane, **2a** was obtained in 62.31% yield. The yield was increased to 66.11% when the same reaction was carried out by heating the reaction mixture at 80°C for 10 min.

Similarly, anisaldehyde (1.36 g, 10 mmoles) and furfural (0.96 g, 10 mmoles) gave **2b** and **2c** respectively. The characterization of the products were done by melting point, mixed melting point, equivalent weight determination by titration method and by spectral (UV-Vis, IR[15], NMR) analysis (**Table I**). Solvent-free Stobbe condensation was carried out using methyl β-naphthoyl propionate **1d** (2.42 g, 10 mmoles) with benzaldehyde (1.06 g, 10 mmoles) and dried potassium *tert.* butoxide (1.13 g, 10 mmoles) to give β-benzylidene β-naphthoyl

Table I — NMR chemical shift (δ) data

Compd	Type of proton					
	Aromatic	C=C—H	OCH_3	CH_2	CH_3	CH_3—CH_2
2a	7.84(5H)s, 7.62(5H)s	7.5(1H)s	—	2.57(2H)s	—	—
2b	7.52(5H)s, 7.73(5H)s	8.03(1H)s	3.89(3H)s	1.57(2H)s	—	—
2c	7.26(5H)s, 7.47(3H)m	7.48(1H)s	—	0.88(2H)s	—	—
2d	7.44(7H)s, 8.00(5H)s	8.01(1H)s	—	0.54(2H)s	—	—
2e	7.53(7H)s, 7.71(5H)s	7.35(1H)s	2.59(3H)s	1.2(2H)s	—	—
2f	7.14(7H)s, 6.53(3H)m	7.15(1H)s	—	2.2(2H)s	—	—
3a	—	—	3.74(3H)s	3.44(2H)s	1.86(3H)s 2.19(3H)s	—
3b	—	—	3.7(3H)s	3.45(2H)s	1.86(3H)s 2.14(3H)s	2.19(2H)q 2.52(2H)q 1.06(3H)t 1.09(3H)t
3c	7.15(5H)s	—	3.65(3H)s	3.25(2H)s	2.02(3H)s	—
3d	—	—	—	3.27(2H)s	1.83(3H)s 2.1(3H)s	—
3e	—	—	—	3.36(2H)s	1.88(3H)s	0.9-1.24(3H)t 2.04-2.38(2H)q
3f	7.37(5H)s	—	—	3.2(2H)s	2.39(3H)s	—
4	6.4-7(4H)m	—	—	9.26(2H)s	2.49(3H)s	—

Table II — Physical characterization data

Compd	Mol. Formulae	m.p. ºC Found	Lit. m.p. ºC	Yield (%)			Equivalent Weight	
				Traditional	Green (RT)	Green (80°C)	*Found	(Calcd)
2a	$C_{17}H_{14}O_3$	132	129	55.20	62.30	66.11	262.90	(266.26)
2b	$C_{18}H_{16}O_4$	115	-	48.20	52.11	77.90	290.56	(296.28)
2c	$C_{15}H_{12}O_4$	186	-	52.14	54.76	78.34	252.89	(256.22)
2d	$C_{21}H_{16}O_3$	104	-	61.05	63.96	69.21	315.94	(316.33)
2e	$C_{22}H_{18}O_4$	178	-	76.01	78.96	85.70	339.50	(346.34)
2f	$C_{19}H_{14}O_4$	130	-	59.29	65.29	71.50	301.85	(306.28)
3a	$C_8H_{12}O_4$	Oil	58	60.00	72.00	-	171.00	(172.14)
3b	$C_9H_{14}O_4$	103-05	105	62.00	78.00	-	186.20	(186.17)
3c	$C_{13}H_{14}O_4$	106-07	107-09	88.00	95.00	-	236.00	(234.21)
3d	$C_7H_{10}O_4$	164	165	78.00	85.00	-	80.08	(79.06)
3e	$C_8H_{12}O_4$	147-49	149	76.00	83.00	-	85.40	(86.07)
3f	$C_{12}H_{12}O_4$	162(*E*) 150(*Z*)	164	92.00	95.00	-	110.11	(110.09)
4	$C_{12}H_{10}O_3$	169.8	-	-	72.00	-	202.02	(202.18)

*Possibility of bond migration at 80°C for **3a-f** propionic acid **2d** in 63.96% yield. Similarly, anisaldehyde (1.36 g, 10 mmoles) and furfural (0.96 g, 10 mmoles) gave **2e** and **2f** respectively in 78.96% and 65.29% yield. The yields were further improved at 80°C (**Table II**, compounds **2a-f**).

1,1-Alkylidene monomethyl succinate, 3a,b

1,1-Arylidene monomethyl succinate, 3c

To a solution of 1 g potassium in 25 mL tertiary butyl alcohol under inert anhydrous conditions, was added a homogenous mixture of **1e** (1.4 g, 10 mmoles) and acetone (0.58 g, 10 mmoles) and stirred for 1 hr. Usual work up[16] and recrystallization from benzene pet. ether gave 1,1-isopropylidene monomethyl succinate **3a** in 60% yield. The yield was improved to 72% by solvent-free method in which a clear mixture of **1e** (1.4 g, 10 mmoles), acetone (0.58 g, 10 mmoles) and dried potassium tertiary butoxide (1.13 g, 10 mmoles) was taken in a mortar, well ground with a pestle, stirred for 10 min, exposed to air and worked up[10]. Solvent free Stobbe condensation was done using ethyl methyl ketone (0.72 g, 10 mmoles) and acetophenone (1.2 g, 10 mmoles), each with **1e** (1.4 g, 10 mmoles) to give the acid-esters **3b** and **3c** respectively in 78% and 95% yield.

1,1-Alkylidene succinic acid, 4a,b

1,1-Arylidene succinic acid, 4c

1,1-Isopropylidene monomethyl succinate **3a** (1.72 g, 10 mmoles) was added to 30 mL 8% alcoholic KOH solution and refluxed for 8 hr. After filtration and cooling to 0°C, the acidification of reaction mixture with ice-cool conc. HCl gave 1,1-isopropylidene succinic acid **3d** and recrystallized from ethanol-water as pale yellow solid. Similarly, acid-esters **3b** (1.78 g, 10 mmoles) and **3c** (2.34 g, 10 mmoles) were saponified to the corresponding diacids **3e** (as non-seperable *E-Z* isomers) and **3f** (seperable into *E* and *Z* isomers) respectively.

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