Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Version of record first published: 04 Dec 2007.

To cite this article: Daqing Shi , Yucheng Wang , Zaisheng Lu & Guiyuan Dai (2000): Condensation of Aromatic Aldehydes with Acidic Methylene Compounds without Catalyst, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 30:4, 713-726

To link to this article: http://dx.doi.org/10.1080/00397910008087374

SYNTHETIC COMMUNICATIONS, 30(4), 713–726 (2000)

CONDENSATION OF AROMATIC ALDEHYDES WITH ACIDIC METHYLENE COMPOUNDS WITHOUT CATALYST

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ABSTRACT: The condensation of aromatic aldehyde with isopropylidene malonate or 5,5-dimethyl-1,3-cyclohexanedione is carried out in DMF as solvent without catalyst.

Knoevenagel condensation of carbonyl compounds with active methylene compounds is one of the most important synthetic methods of substituted alkenes. Reactions are generally catalyzed by bases or Lewis acids[1]. Recently, inorganic solid supports as catalysts, resulting in higher selectivity, milder conditions and easier work-up,

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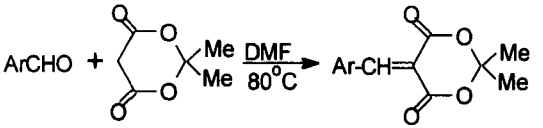
has been reported as useful catalysts for Knoevenagel reaction. Thus, aluminium oxide[2], xonotlite[3], $AlPO_4$-Al_2O_3[4], KF-Al_2O_3[5], ,K10-$ZnCl_2$[6] and cadmium iodide[7] have been reported. In this article, we would like to report that the condensation of aromatic aldehydes with isopropylidene malonate or 5,5-dimethyl-1,3-cyclohexanedione is carried out in DMF as solvent without catalyst.

When aromatic aldehydes **(1)** and isopropylidene malonate **(2)** are kept at 80℃ for 1 hour in DMF, the desired alkenes **(3)** are obtained in good yields.



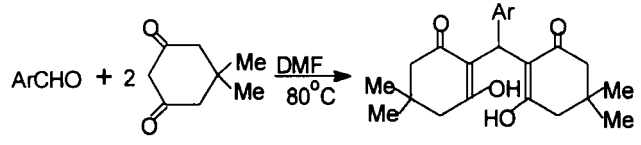
1 **2** **3**

Table 1. Condensation of aromatic aldehydes **1a-f** with isopropylidene malonate **2**

Entry	Ar	Yield(%)	mp(℃)
3a	4-$CH_3C_6H_4$	80	116-118
3b	4-OHC_6H_4	77	192-194
3c	3,4-$OCH_2OC_6H_3$	65	167-169
3d	4-OH-3-$OCH_3C_6H_3$	79	136-138
3e	4-$(CH_3)_2NC_6H_4$	81	162-164
3f	4-ClC_6H_4	74	158-160

In this reaction, the solvent DMF is very important. In the initial step, the solvent attaches to the active hydrogen atom of isopropylidene malonate to produce the carbanion, the latter then attaches to carbonyl of armatic aldehyde to afford the product.

Treatment of aromatic aldehydes **(1)** with 5,5-dimethyl-1,3-cyclohexanedione **(4)** under the same reaction conditions Knoevenagel condensation and Michael addition have taken place and 2,2'-arylmethylenebis(3-hydroxyl-5,5-dimethyl-2-cyclohexen-1-one) **(5)** are obtained in good yield.

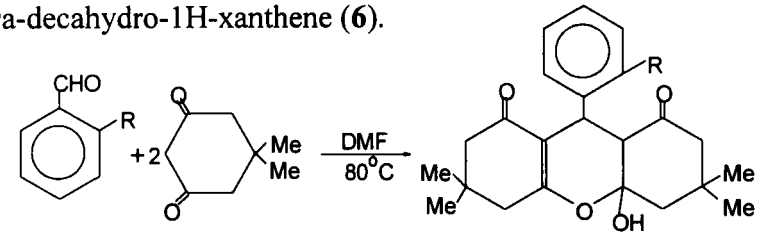


1 **4** **5**

Table2. Reaction of aromatic aldehyde **1**a-h with 5,5-dimethyl-1,3-cyclohexanedione **4**

Entry	Ar	Yield(%)	mp(℃)
5a	4-$CH_3C_6H_4$	86	126-128
5b	4-OHC_6H_4	88	190-192
5c	3,4-$OCH_2OC_6H_3$	81	168-170
5d	4-OH-3-$OCH_3C_6H_3$	82	192-194
5e	4-$(CH_3)_2NC_6H_4$	90	186-188
5f	4-ClC_6H_4	84	140-142
5g	C_6H_5	80	188-190
5h	4-$NO_2C_6H_4$	90	188-190

However, treatment of 2-substituted benzaldehyde with 5,5-dimethyl-1,3-cyclohexanedione under the same reaction conditions afforded 3,3,6,6-tetramethyl-4a-hydroxyl-9-aryl-1,8-dioxo-2,3,4,4a,5,6,7,9,9a-decahydro-1H-xanthene (**6**).

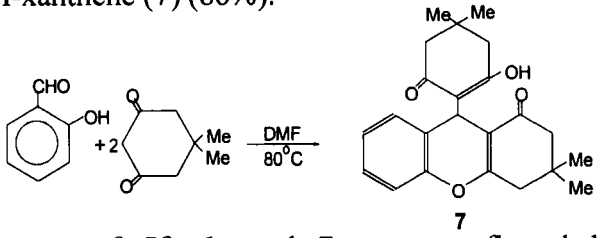


6

Table3. Reaction of 2-substituted benzaldehyde with 5,5-dimethyl-1,3-cyclohexanedione

Entry	R	Yield(%)	mp(℃)
6a	OCH_3	80	184-186
6b	OC_2H_5	65	196-198
6c	Cl	86	202-203
6d	NO_2	80	186-188

On the other hand, the reaction of 2-hydroxy benzaldehyde(salicylal) with 5,5-dimethyl-1,3-cyclohexanedione under the same reaction conditions afforded 3,3-dimethyl-9-(5,5-dimethyl-3-hydroxyl-2-cyclohexene-1-one-2-yl)-1-oxo-2,3,4,,9-tetrahydro-1H-xanthene (**7**) (86%).



7

The structures of **5f**, **6a** and **7** were confirmed by X-ray analysis[8,9,10].

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a FT IR-8101 spectrometer. ^{1}H NMR spectra were measured on a JEOL FX-90Q spectrometer using TMS as internal standard. Elemental analysis were determined

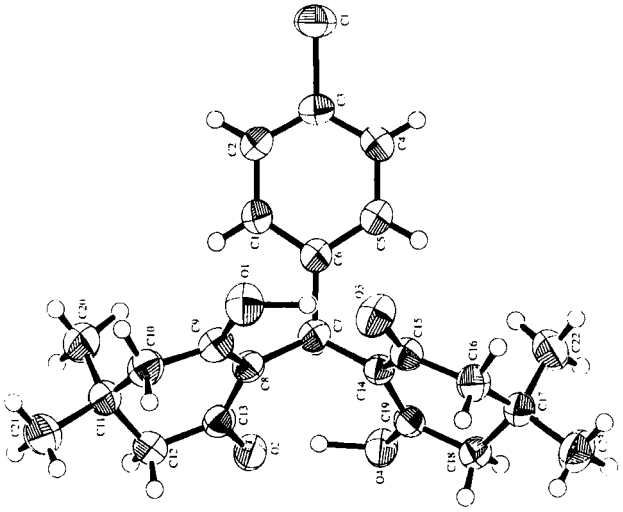


Fig.1 X-ray crystal structure of **5f**

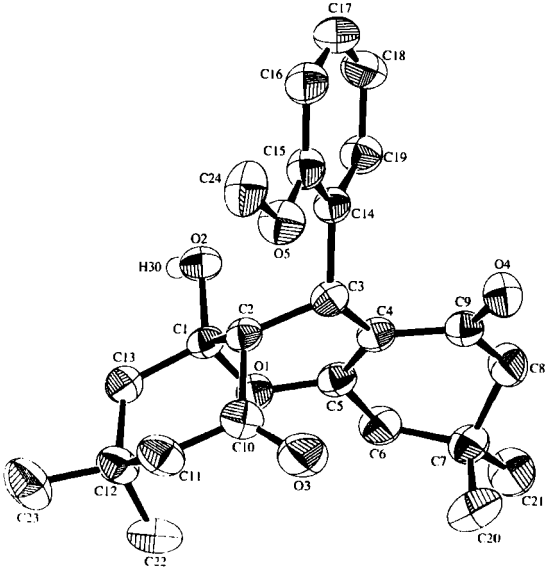


Fig.2 X-ray crystal structure of **6a**

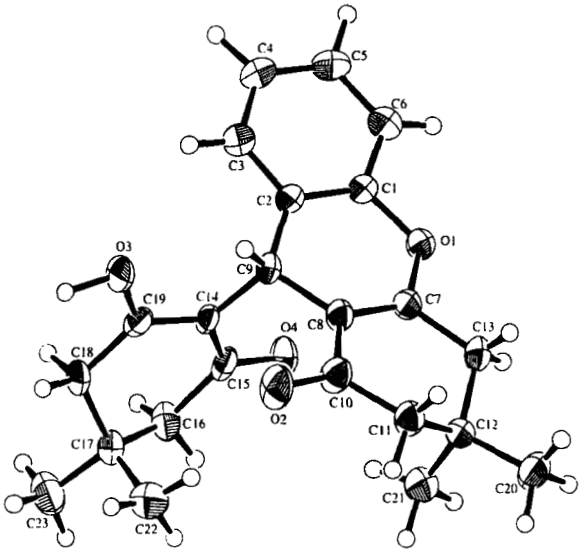


Fig.3 X-ray crystal structure of **7**

using Perkin-Elmer 240C elemental analyser. X-ray diffraction were measured on a Rigaku 7R CAD4 diffractometer.

General procedure:

A dry 100-mL flask was charged with aromatic aldehyde (10 mmol), isopropylidene malonate (**2**) or 5,5-dimethyl-1,3-cyclohexanedione (**4**) (10 mmol) and DMF (20mL). The mixture was kept at 80℃ for 1h, then cooled to room temperature. The reaction mixture was poured into 200 mL water . The white solid was filtered

off, then washed with water and CCl_4. The crude solid was purified by recrystallization from 95% EtOH to give **3** or **5** or **6** or **7**.

3a: m.p. 116~118℃; IR(KBr, ν, cm^{-1}): 3000, 1770, 1730, 1600, 1380, 1275, 1190, 1175, 820; ^1H NMR($CDCl_3$, δ, ppm): 1.79(6H, s, 2×CH_3), 2.43(3H, s, CH_3), 7.28(2H, d, J=8.3Hz, ArH), 8.01(2H, d, J=8.3Hz, ArH), 8.38(1H, s, CH); Elemental analysis: found(%): C,68.51; H, 5.48; Calcd. for $C_{14}H_{14}O_4$(246.26): C, 68.28; H, 5.73.

3b: m.p. 192~194℃; IR(KBr, ν, cm^{-1}): 3270, 1750, 1690, 1590, 1450, 1270, 1200, 1180, 840; ^1H NMR($CDCl_3$, δ, ppm): 1.76(6H, s, 2×CH_3), 6.91(2H, d, J=8.8Hz, ArH), 8.14(2H, d, J=8.8Hz, ArH), 8.29(1H, s, CH); Elemental analysis: found(%): C,63.27; H, 4.76; Calcd. for $C_{13}H_{12}O_5$(248.23): C, 62.90; H, 4.87.

3c: m.p. 167~169℃; IR(KBr, ν, cm^{-1}): 3125, 1740, 1710, 1560, 1450, 1265, 1180, 790; ^1H NMR ($CDCl_3$, δ, ppm): 1.78(6H, s, 2×CH_3), 6.11(2H, s, OCH_2O), 6.91(1H, d, J=8.3Hz, ArH), 7.5~7.6(1H, m, ArH), 8.0~8.1(1H, m, ArH), 8.27(1H, s, CH); Elemental analysis: found(%): C,60.69; H, 4.21; Calcd. for $C_{14}H_{12}O_6$(276.24): C, 60.87; H, 4.38.

3d: m.p. 136~138℃; IR(KBr, ν, cm^{-1}): 3300, 1740, 1700, 1550, 1510, 1360, 1290, 1160, 810; ^1H NMR($CDCl_3$, δ, ppm): 1.78(6H, s,

2×CH_3), 3.94(3H, s, OCH_3), 6.96(1H, d, J=8.3Hz, ArH), 7.3~7.4(1H, m, ArH), 8.31(2H, s, ArH and CH); Elemental analysis: found(%): C,60.73; H, 4.96; Calcd. for $C_{14}H_{14}O_6$(278.26): C, 60.43; H, 5.07.

3e: m.p. 162~164℃; IR(KBr, ν, cm^{-1}): 3075, 1730, 1700, 1620, 1510, 1370, 1290, 1160, 1130, 820; ^1H NMR($CDCl_3$, δ, ppm): 1.75(6H, s, 2×CH_3), 2.49(6H, s, $(CH_3)_2N$), 6.70(2H, d, J=9.5Hz, ArH), 8.2~8.3(3H, m, ArH and CH); Elemental analysis: found(%): C,65.80; H, 5.97; N, 4.83; Calcd. for $C_{15}H_{17}NO_4$(275.30): C, 65.44; H, 6.22; N, 5.09.

3f: m.p. 158~160℃(Lit.[11] m.p. 162℃); IR(KBr, ν, cm^{-1}): 3000, 1770, 1740, 1380, 1320, 1200, 1020, 820; ^1H NMR ($CDCl_3$, δ, ppm): 1.80(6H, s, 2×CH_3), 7.45(2H, d, J=8.6Hz, ArH), 8.03(2H, d, J=8.6Hz, ArH), 8.36(1H, s, CH).

5a: m.p. 126~128℃(Lit.[12] m.p. 128~130℃); IR(KBr, ν, cm^{-1}): 3000~2500, 2950, 2875, 1600, 1510, 1370, 1250, 1160, 920, 820; ^1H NMR($CDCl_3$, δ, ppm): 1.15(12H, s, 4×CH_3), 2.28(3H, s, CH_3), 2.37(8H, s, 4×CH_2), 5.49(1H, s, CH), 7.0~7.3(4H, m, ArH), 9.12(1H, br., s, OH), 11.86(1H, br., s, OH).

5b: m.p. 190~192℃(Lit.[12] m.p. 180~183℃); IR(KBr, ν, cm^{-1}): 3420, 3000~2500, 2950, 2875, 1600, 1510, 1370, 1250, 1210, 1170,

1040, 840; ^{1}H NMR($CDCl_3$, δ, ppm): 1.15(12H, s, 4×CH_3), 2.38(8H, s, 4×CH_2), 5.47(1H, s, CH), 6.64(2H, d, J=8.8Hz, ArH), 6.91(2H, d, J=8.8Hz, ArH), 9.40(1H, br., s, OH), 11.90(1H, br., s, OH).

5c: m.p. 168~170℃; IR(KBr, ν, cm^{-1}): 3000~2500, 2950, 2875, 1600, 1480, 1370, 1300, 1250, 1230, 1040, 940, 920, 860, 810; ^{1}H NMR($CDCl_3$, δ, ppm): 1.15(12H, s, 4×CH_3), 2.37(8H, s, 4×CH_2), 5.44(1H, s, CH), 5.89(2H, s, OCH_2O), 6.5~6.8(3H, m, ArH), 9.70(1H, br., s, OH), 11.92(1H, br., s, OH); Elemental analysis: found(%): C, 70.11; H, 6.59; Calcd. for $C_{24}H_{28}O_6$(412.48): C, 69.88; H, 6.84.

5d: m.p. 192~194℃; IR(KBr, ν, cm^{-1}): 3450, 3000~2500, 2950, 2875, 1600, 1510, 1370, 1280, 1240, 1150, 1030, 850, 810, 780; ^{1}H NMR($CDCl_3$, δ, ppm): 1.16(12H, s, 4×CH_3), 2.37(8H, s, 4×CH_2), 3.73(3H, s, OCH_3), 5.48(1H, s, CH), 6.5~6.8(3H, m, ArH), 9.54(1H, br., s, OH), 11.97(1H, br., s, OH); Elemental analysis: found(%): C, 70.03; H, 6.98; Calcd. for $C_{24}H_{30}O_6$(414.50): C, 69.54; H, 7.29.

5e: m.p. 186~188℃(Lit.[12] m.p. 185~187℃); IR(KBr, ν, cm^{-1}): 3000~2500, 2950, 2875, 1600, 1520, 1370, 1310, 1260, 1170, 910, 810; ^{1}H NMR($CDCl_3$, δ, ppm): 1.15(12H, s, 4×CH_3), 2.36(8H, s, 4×CH_2), 2.89(6H, s, $(CH_3)_2N$), 5.46(1H, s, CH), 6.64(2H, d, J=8.4Hz,

ArH), 6.94(2H, d, J=8.4Hz, ArH), 9.43(1H, br., s, OH), 11.90(1H, br., s, OH).

5f: m.p. 140~142℃(Lit.[12] m.p. 134~135℃); IR(KBr, ν, cm^{-1}): 3050~2500, 2950, 2875, 1600, 1490, 1370, 1300, 1250, 840; ^1H NMR($CDCl_3$, δ, ppm): 1.15(12H, s, 4×CH_3), 2.37(8H, s, 4×CH_2), 5.45(1H, s, CH), 7.0~7.3(4H, m, ArH), 9.45(1H, br., s, OH), 11.85(1H, br., s, OH).

5g: m.p. 188~190℃(Lit.[12] m.p. 186~189℃); IR(KBr, ν, cm^{-1}): 3050~2500, 2950, 2875, 1600, 1450, 1370, 1300, 1250, 1160, 870, 840, 775, 690; ^1H NMR($CDCl_3$, δ, ppm): 1.16(12H, s, 4×CH_3), 2.38(8H, s, 4×CH_2), 5.53(1H, s, CH), 7.0~7.4(5H, m, ArH), 9.32(1H, br., s, OH), 11.90(1H, br., s, OH).

5h: m.p. 188~190℃(Lit.[12] m.p. 182~183℃); IR(KBr, ν, cm^{-1}): 3030~2500, 2950, 2875, 1600, 1510, 1370, 1340, 1300, 1250, 1150, 1040, 850; ^1H NMR($CDCl_3$, δ, ppm): 1.17(12H, s, 4×CH_3), 2.41(8H, s, 4×CH_2), 5.53(1H, s, CH), 7.23(2H, d, J=8.9Hz, ArH), 8.12(2H, d, J=8.9Hz, ArH), 9.77(1H, br., s, OH), 11.78(1H, br., s, OH).

6a: m.p. 184~186℃; IR(KBr, ν, cm^{-1}): 3400, 3030, 2950, 1720, 1640, 1600, 1495, 1470, 1380, 1290, 1250, 1140, 1070, 1025, 985,

745; ^{1}H NMR($CDCl_3$, δ, ppm): 1.08(12H, s, 4×CH_3), 2.32(9H, s, CH and 4×CH_2), 3.70(3H, s, OCH_3), 5.56(1H, s, CH), 6.7~7.3(4H, m, ArH); Elemental analysis: found(%): C, 72.61; H, 7.23; Calcd. for $C_{24}H_{30}O_5$(398.50): C, 72.34; H, 7.59.

6b: m.p. 196~198℃; IR(KBr, ν, cm^{-1}): 3400, 3030, 2950, 1720, 1640, 1610, 1495, 1385, 1290, 1250, 1230, 1070, 1020, 985, 740; ^{1}H NMR($CDCl_3$, δ, ppm): 1.08(12H, s, 4×CH_3), 1.34(3H, t, J=6.9Hz, CH_3), 2.33(9H, s, CH and 4×CH_2), 3.93(2H, q, J=6.9Hz, OCH_2), 5.63(1H, s, CH), 6.6~7.3(4H, m, ArH); Elemental analysis: found(%): C, 72.94; H, 7.55; Calcd. for $C_{25}H_{32}O_5$(412.52): C, 72.79; H, 7.82.

6c: m.p. 202~203℃; IR(KBr, ν, cm^{-1}): 3400, 3030, 2950, 1720, 1610, 1480, 1380, 1290, 1235, 1140, 1100, 1070, 980, 745; ^{1}H NMR($CDCl_3$, δ, ppm): 1.09(12H, s, 4×CH_3), 2.36(9H, s, CH and 4×CH_2), 5.62(1H, s, CH), 7.1~7.4(4H, m, ArH); Elemental analysis: found(%): C, 68.81; H, 6.46; Calcd. for $C_{23}H_{27}ClO_4$(403.00): C, 68.55; H, 6.75.

6d: m.p. 186~188℃; IR(KBr, ν, cm^{-1}): 3250, 3030, 2960, 1720, 1620, 1525, 1390, 1360, 1290, 1240, 1070, 990, 840, 750; ^{1}H NMR($CDCl_3$, δ, ppm): 1.07(12H, s, 4×CH_3), 2.36(9H, s, CH and

4×CH_2), 6.02(1H, s, CH), 7.2~7.5(4H, m, ArH); Elemental analysis: found(%): C, 67.03; H, 6.67; Calcd. for $C_{23}H_{27}NO_6$(413.46): C, 66.81; H, 6.58.

7: m.p. 203~205℃(Lit.[12] m.p. 198~200℃); IR(KBr, ν, cm^{-1}): 3180, 2970, 1640, 1590, 1490, 1380, 1320, 1260, 1230, 755; ^1H NMR($CDCl_3$, δ, ppm): 0.99(6H, s, 2×CH_3), 1.03(3H, s, CH_3), 1.12(3H, s, CH_3), 1.97(2H, s, CH_2), 2.33(4H, s, 2×CH_2), 2.53(2H, s, CH_2), 4.67(1H, s, CH), 7.0~7.3(4H, m, ArH), 10.42(1H, s, OH).

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8. X-ray analysis of **5**f: Empirical formula $C_{23}H_{27}O_4Cl$, F.W. 402.92, T=293K, monoclinic, space group $P2_1/a$, a=13.270(2)Å, b=11.806(2)Å, c=15.017(3)Å, β=115.05(1)°, V=2131.3(7)Å^3, Z=4, D_c=1.256g·cm^{-3}, F(000)=856, λ(MoKα)=0.71069Å, μ=2.04cm^{-1}, 6<2θ<45°, R=0.034, R_w=0.043, largest diff. peak 0.12eÅ^{-3}.

9. X-ray analysis of **6**a: Empirical formula $C_{24}H_{30}O_5$, F.W. 398.50, T=293K, monoclinic, space group C2/c, a=33.942(6)Å, b=7.273(1)Å, c=22.667(4)Å, β=128.989(9)°, V=4349(1)Å^3, Z=8, D_c=1.217g·cm^{-3}, F(000)=1712, λ(MoKα)=0.71069Å, μ=0.84cm^{-1}, 6<2θ<50°, R=0.043, R_w=0.052, largest diff. peak 0.19eÅ^{-3}.

10. X-ray analysis of **7**: Empirical formula $C_{23}H_{26}O_4$, F.W. 366.46, T=293K, monoclinic, space group $P2_1/c$, a=7.056(7)Å, b=20.263(3)Å, c=13.665(2)Å, β=93.32(1)°, V=1950.7(4)Å^3, Z=4, D_c=1.248g·cm^{-3}, F(000)=784, λ(MoKα)=0.71069Å, μ=0.84cm^{-1}, 6<2θ<50°, R=0.068, R_w=0.075, largest diff. peak 0.28eÅ^{-3}.

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(Received in the USA 01 July 1999)