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Synthesis of α, α'-bis(substituted benzylidene)ketones catalysed by a $SOCl_2$/EtOH reagent

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The cross-aldol condensations of cyclopentanone, cyclohexanone and acetone with benzaldehyde or cinnamaldehyde were catalysed in the presence of $SOCl_2$, in anhydrous ethanol to synthesise α, α'-bis(substituted benzylidene) ketones with excellent yields(92–97%).

The aldol condensation reaction is one of the most versatile synthetic tools for construction of carbon–carbon bonds in organic chemistry.[1,2] New and powerful variants of this classical reaction have been developed in the last 30 years. Due to the importance of the methylene structural unit which is found in many naturally occurring compounds and antibiotics and the use of α, α'-bis(substituted benzylidene)ketones as precursors for the synthesis of bioactive pyrimidine derivatives, the condensation of cycloalkanones with aldehydes and ketones was of special interest.[3] Some catalytic crossed-aldol condensation reactions have been reported as main synthetical methods.[3-6] However, traditional acid- or base- catalysed reactions suffer from reverse reaction, and metal chlorides are reported to promote the self-condensation of ketones rather than the crossed-aldol condensation.[4] These factors frequently limit the utilisation of this efficient reaction.

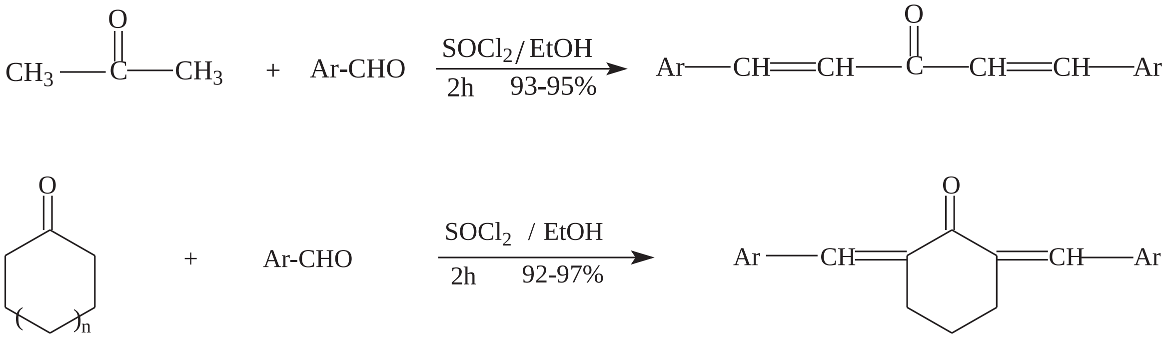
For this purpose, we studied the crossed-aldol condensation reactions of ketones which contain at least four α-hydrogens such as cyclopentanone, cyclohexanone and acetone with benzaldehyde or cinnamaldehyde to synthesise α,α'-bis(substituted benzylidene)ketones. In our study of the thionyl chloride chloride–anhydrous ethanol reagent catalysing aldol condensations, we found that in the presence of thionyl chloride, the crossed-aldol condensation of cycloalkanones or acetone with benzaldehyde in anhydrous ethanol can proceed well with excellent yields.

In the course of our studies on the reaction, the occurrence of self-condensation of ketones as a by-reaction was observed. In order to prevent the self-condensation of cycloalkanones or acetone, thionyl chloride and cycloalkatones or acetone were dropped into the mixture of benzaldehyde and anhydrous ethanol at the same time. Because high temperature leads to a decrease in the yields, the reaction was cooled below 0°C(ice-salt cold bath). When the reaction was carried out at room temperature without cooling, the yield of 2,6-dibenzylidene–cyclohexanone (g) was only 81%. The synthesis of single substituted benzylideneketones was also attempted by reducing the molar ratio of ketones to benzaldehyde (1:1.3), but only mixtures of bis-(substituted-benzylidene)ketones and self-aldol condensation products were obtained. Furthermore, we found that the alcohol was indispensable in the catalyst system as well as serving as reaction solvent. Other solvents such as methanol, toluene and pyridine were also used, but only alcohols catalysed the aldol reaction. There is not a significant variation of yields between anhydrous methanol and ethanol. The results of the condensation reactions are shown in Table 1.

Table 1 The cross-aldol condensation of ketones and benzaldehyde

Entry	Product	M.p./°C	M.p./°C^{lit}	Yields/%
1	a	110–111	112–112.5[7]	95
2	b	129–130	128–131[8]	95
3	c	145–146	146[9]	93
4	d	189–190	188–189[5]	92
5	e	210–211	210–211[5]	93
6	f	223–224	222–224[5]	95
7	g	115–116	116–117[5]	97
8	h	202–203	203–204[5]	94
9	i	179–181	179–180[5]	96

All the compounds obtained had IR and 1H NMR data which were compatible with their structures.



a: Ar = C_6H_5 **b**: Ar = p-CH_3O-C_6H_4 **c**: Ar= C_6H_4CH=CH
d: *n*= 0, Ar= C_6H_5 **e**: *n*= 0, Ar= *p*-CH_3O-C_6H_4 **f**: *n*= 0, Ar= C_6H_4CH=CH
g: *n*= 1, Ar= C_6H_5 **h**: *n*= 1, Ar= *p*-CH_3O-C_6H_4 **i**: *n*= 1, Ar= C_6H_4CH=CH

Scheme 1 The synthesis of α, α'-bis(substituted benzylidene)ketones.

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In summary, we report a novel and efficient method of synthesising α,α'-bis(substituted benzylidene)ketones using SOCl$_2$/EtOH as catalyst. The advantages of this method are a cheap catalyst, simple manipulation and excellent yields (92–97%). We believe that this method provides a very attractive route for the preparation of α,α'-bis(substituted benzylidene)ketones. The reaction is likely to proceed via the reaction of enol sulfurous esters of ketones. The by-product HCl also accelerates the reaction. The detailed mechanistic investigation and further applications of this reaction are under study in our laboratory.

Experimental

Melting points were determined on a Kofler micro melting point apparatus without correction. IR spectra were recorded on an FTS-40IR spectrophotometer using KBr pellets. ^{1}H NMR spectra were measured in CDCl$_3$ or DMSO on a Bruker AC-400NMR spectrometer using TMS as internal standard.

General procedure for cross-aldol condensation of ketones with aldehydes: To a stirred mixture of the benzaldehyde (13.3ml,0.13mol) and anhydrous ethanol (14.6ml, 0.25mol), thionyl chloride (3.6ml, 0.05mol) and cyclohexanone (10.3ml, 0.1mol) were dropped synchronously. The flask was cooled below 0°C(ice-salt cold bath). The solution turned deep red immediately. When stirred for 3–10min, the mixture coagulated. Then the flask was placed in an ice-salt cold bath for 2 hours. After completion of the reaction, saturated aqueous Na$_2$CO$_3$ was added and the mixture was filtered. The solid was washed twice successively with water (30ml), anhydrous ethanol (20ml) and ethyl ether (10ml).

Spectra data of the products

1,5-diphenyl-1,4-pentadien-3-one (a): M.p.: 110–111°C; ^{1}H NMR (CDCl$_3$): δ 7.12(d, 2H, *J*=15.98Hz), 7.42–7.66(m, 10H), 7.78 (d, 2H, *J*=15.98Hz); IR(KBr) ν_{max} (cm^{-1}) 3053, 1652, 1592, 1448, 1354, 1195, 983, 762, 696;

1,5-di(p-methoxyphenyl)-1,4-pentadien-3-one (b): M.p.:129–130°C; ^{1}H NMR(CDCl$_3$): δ 3.83 (s, 6H), 6.94–6.99(m, 6H), 7.59 (d, 4H, *J*=8.80Hz), 7.72 (t, 2H, *J*=15.98Hz); IR(KBr) ν_{max} (cm^{-1}) 2962, 1654, 1574, 1511, 1442, 1257, 1178, 759;

1,9-diphenyl-1,3,6,8-nonatetraen-5-one (c): M.p.: 145–146°C; ^{1}H NMR(DMSO): δ 6.60(d, 2H, *J*=15.32Hz), 6.94–7.00 (m, 4H), 7.34–7.70(m, 12H); IR(KBr) ν_{max} (cm^{-1}) 3020, 1695, 1614, 1447, 1357, 1068, 1004, 755, 693;

2,5-dibenylidenecyclopentanone (d): M.p.:189–190°C; ^{1}H NMR (CDCl$_3$): δ 3.33 (s, 4H), 7.29–7.48(m, 6H), 7.62–7.78(m, 6H); IR(KBr) ν_{max} (cm^{-1}) 3056, 2912, 1691, 1627, 1603, 1446, 1180, 766, 680;

2,5-di(p-methoxyphenylidene)cyclopentanone (e): M.p.: 210–211°C; ^{1}H NMR(CDCl$_3$): δ 3.10(s, 4H), 3.89 (s, 6H), 6.96–6.99(m, 4H), 7.57–7.60 (m,6H); IR(KBr) ν_{max} (cm^{-1}) 3030, 2843, 1697, 1634, 1617, 1598, 1255, 1172, 1030, 837;

2,5-dicinnamylidenecyclopentanone (f): M.p.: 223–224°C; ^{1}H NMR (CDCl$_3$): δ 2.97 (s, 4H), 6.99–7.04(m, 4H),7.25–7.44(m, 8H), 7.77 (d, 4H, *J*=7.20Hz); IR(KBr) ν_{max} (cm^{-1}) 3031, 2925, 1674, 1615, 1446, 1282, 968, 756, 688;

2,6-dibenzylidenecyclohexanone (g): M.p.:115–116°C; ^{1}H NMR (CDCl$_3$): δ 1.67(m, 2H), 2.80 (t, 4H, *J*=5.80Hz), 7.20(s, 2H), 7.30–7.70(m, 10H); IR(KBr) ν_{max} (cm^{-1}) 3024, 2934, 1660, 1607, 1574, 1276, 1170, 772, 695;

2,6-di(p-methoxyphenylidene)cyclohexanone (h): M.p.: 202–203°C; ^{1}H NMR(CDCl$_3$): δ 1.77(m, 2H), 2.99(t, 4H, *J*=5.80Hz), 3.80(s, 6H), 6.89–7.70(m, 10H); IR(KBr) ν_{max} (cm^{-1}) 3031, 2923, 1653, 1610, 1582, 1448, 1286, 1174, 760, 692;

2,6-dicinnamylidenecyclohexanone (i): M.p.: 179–181°C; ^{1}H NMR (CDCl$_3$): δ 1.91 (m, 2H), 2.80 (t, 4H, *J*=5.80Hz), 6.95–7.05 (m, 4H), 7.10–7.60 (m, 12H); IR(KBr) ν_{max} (cm^{-1}) 3028, 2940, 1658, 1595, 1509, 1163, 1142, 1114, 836, 737, 692.

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