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First Highly Efficient Synthesis of bis(Arylmethylidene)pyranones Mediated by Lithium Perchlorate

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Abstract: A remarkably efficient double-crossed aldol condensation of tetrahydropyran-4-one with a variety of aromatic aldehydes is described at room temperature in the presence of (trimethylsilyl)diethylamine and lithium perchlorate under solvent-free conditions. Excellent yields of 3,5-bis(arylmethylidene)pyranones are achieved in a facile one-pot general procedure.

Keywords: bis(Arylmethylidene)pyranones, crossed aldol condensation, lithium perchlorate, pyrans, solvent-free

Crossed aldol condensation has been employed for the synthesis of bis(arylmethylidene)cycloalkanones by the reaction of homocyclic ketones with aromatic aldehydes.^[1] Many developments have been achieved in recent years to enhance the synthetic scope of bis(arylmethylidene)cycloalkanones by optimizing the reaction temperature, time, and yields of products.^[2] More improvements have been gained by application of KF-supported reagents under microwave mediation and ultrasound irradiation.^[3] Lewis acid catalysis using Yb(OTf)₃,^[4] iodotrimethylsilane,^[5] TiCl₃(SO₃CF₃),^[6] RuCl₃,^[2b] Pd/C-Me₃SiCl,^[7] and SmI₃^[8]; InCl₃^[9] and FeCl₃^[10] in ionic

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liquids are also employed. However, many of these reactions suffer from drawbacks such as reverse and side reactions or require harsh reaction conditions. In addition, for similar reactions of tetrahydropyran-4-one 1, which is a key precursor for a vast number of synthetic preparations,^[11] there are only a few preliminary scattered data available^[12] and no spectroscopic structural characterization exists in the literature for 3.5-bisarylmethylidenes of pyranones. We are interested in the development of the chemistry of heterocyclics.^[13] Substituted derivatives of tetrahydropyran-4-one **1** are useful synthetic precursors and could be transformed to other heterocyclic structures.^[14] Therefore, a mild general protocol for synthesis of the title structures from ketone 1 is in demand. In recent years, mild Lewis acidic salts such as lithium perchlorate have been widely used for various organic transformations.^[15] We decided to extend our previous experiences on the synthetic application of iminium salts of aldehydes.^[16] In the present article, a onepot synthetic pathway for double condensation of pyran 1 with aromatic aldehydes in the presence of (trimethylsilyl)diethylamine (TMSNEt₂) and lithium perchlorate under solvent-free conditions is reported (Scheme 1).

Initially, treatment of benzaldehyde with TMSNEt₂ and anhydrous lithium perchlorate at room temperature facilitated in situ formation of the corresponding iminium salt **2a** because of the Lewis acidity of lithium ion and high polarity of the reaction medium.^[17] Subsequent addition of pyran **1** to the reaction mixture resulted in the formation of double-crossed aldol condensation product **3a** at room temperature. The reaction was found to be complete in about 3 h and the yield was 91% (Table 1, entry 1).

To test the chemoselectivity of the reaction, parallel reactions were carried out using pyran/benzaldehyde ratios of 1:1 and 1:2. In both cases the same product **3a** was formed in comparable quantities. Other control experiments were run to clarify the role of the reactants. A test reaction conducted in the absence of TMSNEt₂ gave no product. Omission of lithium perchlorate from the reaction medium also led to complete recovery of the starting materials. The generality of the method was demonstrated by the synthesis of similar products (**3b**-**h**) using other aromatic aldehydes



Scheme 1.

Entry	Aldehyde	Product	Yield ^a (%)	Melting point (°C)	
				Found	Reported
1	СНО		91	179–181	185–187 ^[12a]
2	Н3СО СНО	of the second se	86	170-172	175–177 ^[12a]
3	Н3С-СНО		86	180-182	110 ^[12b]
4	СІСНО		87	168-170	_
					(continued)

Table 1. Reaction of pyran 1 with aromatic aldehydes in the presence of LiClO₄ and TMSNEt₂

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Entry	Aldehyde	Product	Yield ^a (%)	Melting point (°C)	
				Found	Reported
5	СНО		88	192–194	_
6	СНО		91	170-172	_
7	СНО	S S 3gS	85	195–197	_
8	СНО	Ph O 3h Ph	90	206–208	_

^aIsolated yields.

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under the same conditions. All reactions proceeded rapidly at room temperature and complete conversions were observed in less than 3 h. The results are summarized in Table 1. Under present conditions, a sole product is formed in each reaction and no other product normally observed under classical aldol reactions is detected. The present one-pot protocol involves mild reaction conditions, great efficiency, short reaction times, high product yields, and use of inexpensive commercially available materials.

In conclusion, we have presented the first general and efficient synthetic protocol for the preparation of 3,5-bis(arylmethylidene)pyranones at room temperature. The generality of this versatile reaction makes it an attractive addition to the present literature of pyrans chemistry. We are currently exploring the feasibility of converting these products to other heterocyclic systems. Extension of the results to the synthesis of bisarylmethylidenes of other heterocyclic ketones is also underway. Caution: Although we did not have any accidents using lithium perchlorate (LiClO₄), it is advisable to dry lithium perchlorate in a hood behind a laboratory shield.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded using KBr disks on a Bruker Vector-22 infrared spectrometer. ¹H NMR and ¹³C NMR spectra were obtained on a Bruker AC 80-MHz instrument as CDCl₃ solutions using TMS as internal standard reference. Reagents were purchased from commercial sources. Aldehydes were redistilled or recrystallized before use.

Typical Procedure for the Preparation of bis(Arylmethylidene)pyranones

Pyranone 1 (1 mmol) was added to the mixture of the aldehyde (2 mmol), $LiClO_4$ (1 mmol), and $TMSNEt_2$ (2 mmol), and the mixture was stirred at room temperature. Reactions were monitored by TLC. After about 3 h, the reactions were complete and the products precipitated out. The precipitates were washed by 0.5 M of hydrochloric acid solution and brine. The precipitates were recrystalized by means of ethyl acetate. Isolated yields of products were 85–91%.

(3Z,5Z)-3,5-Dibenzylidene-tetrahydropyran-4-one (3a). Yellow crystals were obtained in 91% yield, mp 179–181°C (reported mp 185–187°C)^[12a]; IR (KBr, cm⁻¹) 1668, 1610, 1581; ¹H NMR (CDCl₃) δ 4.87 (d, 4H, J = 2 Hz), 7.20–7.45 (m, 10H), 7.78 (t, 2H, J = 2 Hz); ¹³C NMR (CDCl₃): δ 68.6, 128.6, 129.3, 130.4, 133.2, 134.8, 136.4, 185.5; MS (70 eV) m/z (%) 276 (M⁺), 144, 131, 115. Calcd. for C₁₉H₁₆O₂: C, 82.6; H, 5.8. Found: C, 82.2; H, 5.8.

(3Z,5Z)-3,5-bis(4-Methoxybenzylidene)-tetrahydropyran-4-one (3b). Yellow crystals were obtained in 86% yield, mp 170–172°C (reported mp 175–177°C)^[12a]; IR (KBr, cm⁻¹) 1593, 1560, 1508; ¹H NMR (CDCl₃) δ 3.78 (s, 6H), 4.87 (d, 4H, J = 2 Hz), 6.86 (d, 4H, J = 9 Hz), 7.23 (d, 4H, J = 9 Hz), 7.72 (t, 2H, J = 2 Hz); ¹³C NMR (CDCl₃) δ 55.4, 68.6, 114.2, 127.6, 131.5, 132.4, 135.6, 160.6, 185.4; MS (70 eV) m/z (%) 336 (M⁺), 305, 146, 131. Calcd. for C₂₁H₂₀O₄: C, 75.0; H, 6.0. Found: C, 74.5; H, 6.0.

(3Z,5Z)-3,5-bis(4-Methylbenzylidene)-tetrahydropyran-4-one (3c). Yellow crystals were obtained in 86% yield, mp 180–182°C (reported mp 110° C)^[12b]; IR (KBr, cm⁻¹) 1665, 1605, 1508, 1266; ¹H NMR (CDCl₃) δ 2.32 (s, 6H), 4.87 (d, 4H, *J* = 2 Hz), 7.16 (s, 8 H), 7.75 (t, 2H, *J* = 2 Hz); ¹³C NMR (CDCl₃) δ 21.4, 68.6, 129.4, 130.7, 132.0, 132.4, 136.2, 139.7, 185.5; MS (70 eV) m/z (%) 304 (M⁺), 289, 130, 115. Calcd. for C₂₁H₂₀O₂: C, 82.9; H, 6.6. Found: C, 82.5; H, 6.6.

(**3Z,5Z)-3,5-bis(4-Chlorobenzylidene)-tetrahydropyran-4-one (3d).** Yellow crystals were obtained in 87% yield, mp 168–170°C; IR (KBr, cm⁻¹) 1671, 1612, 1559, 1263, 1090; ¹H NMR (CDCl₃): δ 4.80 (d, 4H, J = 2 Hz), 7.25 (d, 4H, J = 7 Hz), 7.40 (d, 4H, J = 7 Hz), 7.70 (t, 2H, J = 2 Hz); ¹³C NMR (CDCl₃) δ 68.2, 128.0, 128.8, 131.4, 133.1, 133.3, 135.0, 188.4; MS (70 eV) m/z (%) 344 (M⁺), 253, 141, 115. Calcd. for C₁₉H₁₄Cl₂O₂: C, 66.1; H, 4.1. Found: C, 64.9; H, 4.3.

(3Z,5Z)-Tetrahydro-3,5-bis[(pyridine-3-yl)methylene]pyran-4-one (3e). Yellow crystals were obtained in 88% yield, mp 192–194°C; IR (KBr, cm⁻¹) 1672, 1616, 1272; ¹H NMR (CDCl₃) δ 4.86 (d, 4H, J = 2 Hz), 7.18–7.70 (m, 8H), 8.50 (br s, 2H), ¹³C NMR (CDCl₃) δ 68.2, 123.4, 130.4, 132.8, 134.6, 136.9, 149.9, 150.9, 187.0; MS (70 eV) m/z (%) 278 (M⁺), 117, 90.

(3Z,5Z)-3,5-bis[(Furan-2-yl)methylene]-tetrahydropyran-4-one (3f). Yellow crystals were obtained in 91% yield, mp 170–172°C; IR (KBr, cm⁻¹) 1665, 1268, 756; ¹H NMR (CDCl₃) δ 4.97 (d, 4H, J = 2 Hz), 6.57–6.45 (m, 4H), 7.35–7.52 (m, 4H); ¹³C NMR (CDCl₃) δ 68.4, 112.6, 117.4, 121.1, 130.1, 145.5, 151.8, 187.0; MS (70 eV) m/z (%) 256 (M⁺), 134, 115, 106, 78.

(**3Z,5Z)-Tetrahydro-3,5-bis**[(thiophen-2-yl)methylene]pyran-4-one (**3**g). Yellow crystals were obtained in 85% yield, mp 195–197°C; IR (KBr, cm⁻¹) 1662, 1592, 1186; ¹H NMR (CDCl₃): 4.90 (d, 4H, J = 2 Hz), 7.00–7.50 (m, 6H), 7.87 (br s, 2H); ¹³C NMR (CDCl₃) δ 68.3, 127.9, 128.2, 130.9, 133.3, 138.3, 184.2; MS (70 eV) m/z (%) 288 (M⁺), 260, 122. Calcd. for C₁₅H₁₂O₂S₂: C, 62.5; H, 4.2. Found: C, 52.0; H, 4.3.

(3Z,5Z)-Tetrahydro-3,5-bis[(E)-3-phenylallylidene]tetrahydropyran-4-one (3 h). Orange crystals were obtained in 90% yield, mp 206–208°C; IR (KBr, cm⁻¹) 1734, 1660, 1587, 1216; ¹H NMR (CDCl₃) δ 4.77 (d, 4H, *J* = 2 Hz),

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6.80–7.80 (m, 16H); ¹³C NMR (CDCl₃) δ 67.3, 122.0, 127.4, 127.9, 128.2, 132.2, 134.8, 137.4, 142.6, 187.2; MS (70 eV) m/z (%) 328 (M⁺), 209, 141, 128, 115. Calcd. for C₂₃H₂₀O₂: C, 84.1; H, 6.1. Found: C, 83.6; H, 6.1.

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