The First Synthesis of Bis(arylmethylidene)dioxan-5-ones: Potential Scaffolds to Access Vicinal Tricarbonyl Derivatives

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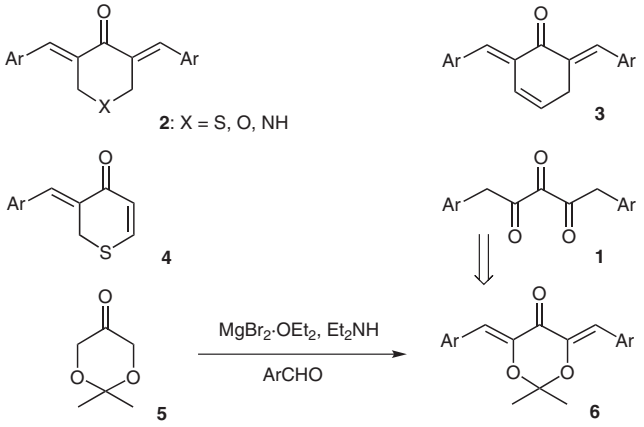
Abstract: Double crossed-aldol condensation of a variety of aromatic aldehydes with 1,3-dioxan-5-one in the presence of magnesium bromide diethyl etherate and diethylamine at room temperature is described. Excellent yields of 4,6-bis(arylmethylidene)dioxan-5-ones are achieved in a facile, one-pot, general procedure. The structure and the *Z,Z*-configuration of the exocyclic double bonds of the products were determined by spectroscopic methods and X-ray crystallography, respectively.

Key words: dioxanone, aldol condensation, $MgBr_2{\cdot}Et_2O$, heterocycles

The first synthesis of vicinal tricarbonyl compounds[1] (e.g. **1**; Scheme 1) was reported in 1890 by de Neufville and von Pechmann.[2] These compounds or their derivatives have found synthetic applications as coupling reagents for biopolymer conjugates,[3] antibiotic drugs,[4] contact allergen,[5] and photoconductive agents.[6] In addition, the α,β-diketoester and amide derivatives of these compounds[7] have found synthetic applications in the preparation of various natural products or their precursors such as fused-ring β-lactams,[8] indole alkaloids,[9] marine metabolites,[10] enzyme inhibitors,[11] and bioactive depsipeptides.[12]

In the framework of our extensive investigations on the synthesis of bisarylmethylidenes of cyclic ketones,[13] we recently reported a facile synthesis of several derivatives of thiopyranone (**2**: X = S),[14] pyranone (**2**: X = O),[15] piperidinone (**2**: X = NH),[16] and cyclic enone (**3**)[17] compounds using mild Lewis-acidic conditions. Very recently, we also introduced a general procedure through which to access novel 3-substituted thiopyran-4-ones (**4**).[18] We have now applied this method to the preparation of bisarylmethylidene derivatives of the 1,3-dioxan-5-one system (e.g. **5**)[19] in order to synthesize compounds of type **6** as potential scaffolds to access 1,2,3-trione compounds via removal of their acetonide protecting functionality.

In recent years, magnesium bromide diethyl etherate ($MgBr_2{\cdot}Et_2O$) has been used as a mild Lewis-acid in order to facilitate various synthetic organic transformations.[20] In this context, we have demonstrated the usefulness of $MgBr_2{\cdot}Et_2O$ in Diels–Alder cycloadditions,[21] Cannizzaro reactions,[22] aldol condensation,[23] α-aminonitrile syntheses,[24] alcohol protection,[25] Knoevenagel condensation,[26] and nucleophilic ring-opening of epoxides with thiols[27] and amines.[28] In this study, we report an efficient room temperature procedure for solvent-free aldol condensation of ketone **5** with various aldehydes in the presence of $MgBr_2{\cdot}Et_2O$ and diethylamine (Et_2NH), leading to the formation of various novel 4,6-bis(arylmethylidene)dioxan-5-ones (**6**).



Scheme 1

Table 1 shows the summarized results for the reactions of various aromatic aldehydes with ketone **5**. We first studied reactions of benzaldehyde with **5** under a range of conditions. Optimal results were obtained when the reaction was conducted at room temperature in the presence of Et_2NH, catalytic amounts of $MgBr_2{\cdot}Et_2O$ and no solvent. Consequently, formation of a single product (**6a**) was observed in 88% yield within two hours. In order to test the chemoselectivity of the reaction, parallel experiments were carried out using ratios of **5** to benzaldehyde of 1:1 and 1:2. In both cases the same product, **6a**, was formed quantitatively. Additional experiments clarified the role of the reactants; in the absence of $MgBr_2{\cdot}Et_2O$ or Et_2NH, no significant amount of product was observed after 24 hours and the majority of the starting materials were recovered under these conditions. The generality of the method was demonstrated by the synthesis of similar products (**6b–h**) using a range of aromatic aldehydes bearing electron-withdrawing or electron-releasing groups under the same conditions. All the reactions proceeded cleanly, the products were easily separated from the mix-

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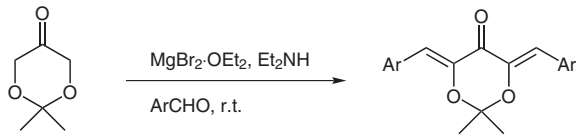
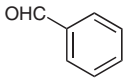
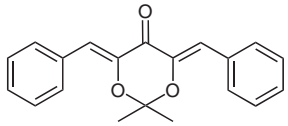
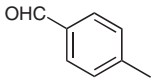
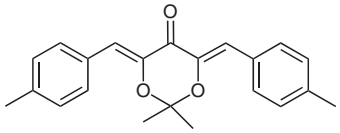
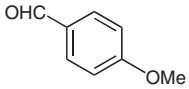
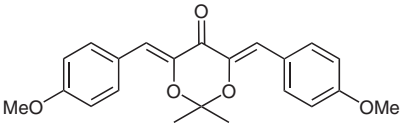
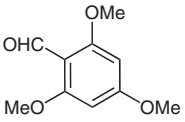
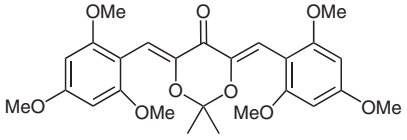
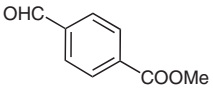
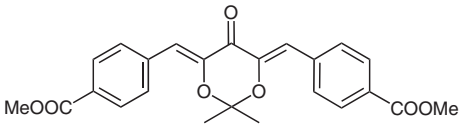
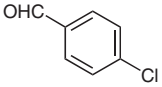
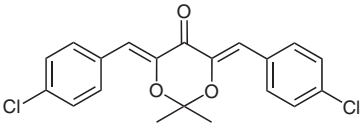
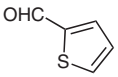
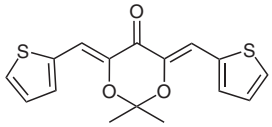
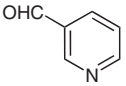
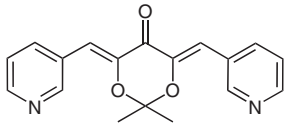
Table 1 Aldol Condensation of 1,3-Dioxan-5-one (**5**) with Aromatic Aldehydes



5 **6a–h**

Entry	Aldehyde	Product		Time (h)	Yield (%)[a]
1			**6a**	2	88
2			**6b**	2	93
3			**6c**	2	83
4			**6d**	4	79
5			**6e**	5	77
6			**6f**	2	92
7			**6g**	2	90
8			**6h**	4	86

[a] Isolated yield.

tures, and the formation of no other side-products was observed.

In order to verify the proposed structures and distinguish between possible exocyclic *Z*,*Z*- and *E*,*E*-isomers, a single crystal of **6a** was prepared and its crystal structure was determined by X-ray diffraction methods. The results, depicted in Figure 1, clearly indicate the formation of **6a** with its *Z*,*Z*-double-bond configuration. The molecule shows C_s symmetry in the crystal and the backbone deviates significantly from planarity.

Based on these results, the mechanistic pathway illustrated in Figure 2 can be suggested. In the presence of Et_2NH, $MgBr_2{\cdot}Et_2O$ assists enolization of **5** into form **b**. This discrete intermediate is then added to the starting aldehyde to form the aldol product **d**. Elimination of water and subsequent repetition of the process yields bis-aldol products of type **6**.

In conclusion, we have presented a reliable and efficient general synthetic protocol for the solvent-free preparation of novel 4,6-bis(arylmethylidene)dioxan-5-ones at room

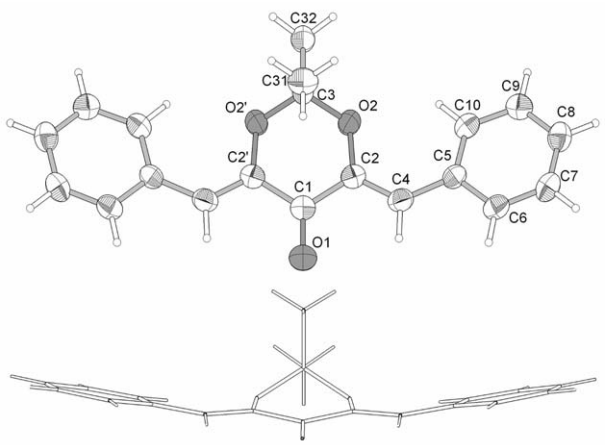
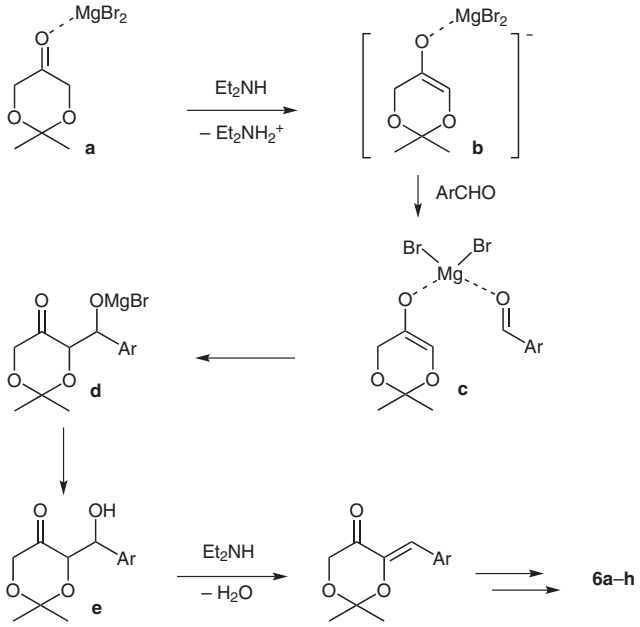


Figure 1 Crystal structure of **6a** showing displacement ellipsoids at 50% probability level (top) and a wire model projected along the phenyl planes (bottom)



Scheme 2 Proposed mechanism for the formation of **6a–h**

temperature. The generality of this versatile reaction makes it an attractive addition to the present literature. Attempts to convert the products into their vicinal tricarbonyl counterparts or their derivatives are currently under investigation in our laboratories.

Melting points are uncorrected. IR spectra were recorded using KBr disks on a Bruker Vector-22 infrared spectrometer. NMR spectra were obtained on a FT-NMR Bruker Ultra Shield™ (500 MHz) as $CDCl_3$ solutions using TMS as internal standard reference. Elemental analyses were performed using a Thermo Finnigan Flash EA 1112 instrument. GC-MS spectra were obtained on a Fisons 8000 Trio instrument at ionization potential of 70 eV. TLC experiments were carried out on pre-coated silica gel plates (hexane–EtOAc, 5:1). Compound **5**[29] and $MgBr_2{\cdot}Et_2O$[30] were prepared according to known methods. Solvents and reagents were purchased from commercial sources. Aldehydes were redistilled or recrystallized before use.

Synthesis of 6a–h; General Procedure

A mixture of compound **5** (3 mmol), aldehyde (6 mmol), Et_2NH (8 mmol) and $MgBr_2{\cdot}Et_2O$ (78 mg, 10 mol%) was stirred at 25 °C under an inert atmosphere for the time indicated in Table 1. After TLC showed complete disappearance of the starting materials, the mixture was diluted with Et_2O (10 mL) and washed with brine (2 × 10 mL). The organic layer was dried over Na_2SO_4 and the volatile portion was evaporated under reduced pressure. Solid products **6a–h** were obtained after column chromatography (hexane–EtOAc, 5:1) in 77–93% yields. The structure and the geometry of the products were determined by spectroscopic methods and confirmed by X-ray crystallography.

(4*Z*,6*Z*)-4,6-Dibenzylidene-2,2-dimethyl-1,3-dioxan-5-one (6a)

Yield: 88%; yellow crystals; mp 103–105 °C.

IR (KBr): 1591, 1275, 1138 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.88 (s, 6 H), 7.00 (s, 2 H), 7.38 (d, *J* = 7.3 Hz, 2 H), 7.45 (dd, *J* = 7.3, 7.7 Hz, 4 H), 7.85 (d, *J* = 7.7 Hz, 4 H).

^{13}C NMR ($CDCl_3$): δ = 26.8, 101.7, 116.5, 129.0, 129.4, 131.2, 134.0, 145.8, 178.3.

MS (70 eV): *m*/*z* = 306 [M^+], 278, 192, 132, 118.

Anal. Calcd for $C_{20}H_{18}O_3$: C, 78.41; H, 5.92. Found: C, 78.63; H, 5.87.

(4*Z*,6*Z*)-2,2-Dimethyl-4,6-bis(4-methylbenzylidene)-1,3-dioxan-5-one (6b)

Yield: 93%; yellow crystals; mp 128–130 °C.

IR (KBr): 1585, 1275, 1175 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.87 (s, 6 H), 2.44 (s, 6 H), 6.99 (s, 2 H), 7.25 (d, *J* = 8.1 Hz, 4 H), 7.74 (d, *J* = 8.1 Hz, 4 H).

^{13}C NMR ($CDCl_3$): δ = 22.0, 26.7, 101.6, 116.6, 129.8, 131.2, 131.4, 139.7, 145.4, 178.3.

MS (70 eV): *m*/*z* = 334 [M^+], 306, 146, 132.

Anal. Calcd for $C_{22}H_{22}O_3$: C, 79.02; H, 6.63. Found: C, 78.90; H, 6.64.

(4*Z*,6*Z*)-4,6-Bis(4-methoxybenzylidene)-2,2-dimethyl-1,3-dioxan-5-one (6c)

Yield: 83%; yellow crystals; mp 132–134 °C.

IR (KBr): 1597, 1249, 1145 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.85 (s, 6 H), 3.89 (s, 6 H), 6.96 (s, 2 H), 6.98 (d, *J* = 8.8 Hz, 4 H), 7.79 (d, *J* = 8.8 Hz, 4 H).

^{13}C NMR ($CDCl_3$): δ = 26.7, 55.7, 101.4, 114.5, 116.4, 127.0, 132.9, 144.7, 160.5, 178.2.

MS (70 eV): *m*/*z* = 366 [M^+], 339, 162, 148, 120.

Anal. Calcd for $C_{22}H_{22}O_5$: C, 72.12; H, 6.05. Found: C, 71.76; H, 6.01.

(4*Z*,6*Z*)-2,2-Dimethyl-4,6-bis(2,4,6-trimethoxybenzylidene)-1,3-dioxan-5-one (6d)

Yield: 79%; yellow crystals; mp 240–242 °C.

IR (KBr): 1581, 1278, 1146 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.70 (s, 6 H), 3.85 (s, 12 H), 3.87 (s, 6 H), 6.17 (s, 4 H), 6.99 (s, 2 H).

^{13}C NMR ($CDCl_3$): δ = 26.5, 55.8, 56.0, 91.0, 100.6, 105.0, 109.1, 145.8, 159.9, 162.2, 178.1.

MS (70 eV): *m*/*z* = 486 [M^+], 458, 318, 275, 208.

Anal. Calcd for $C_{26}H_{30}O_9$: C, 64.19; H, 6.22. Found: C, 64.03; H, 6.16.

Dimethyl 4,4′-(1*Z*,1′*Z*)-(2,2-Dimethyl-5-oxo-1,3-dioxane-4,6-diylidene)bis(methan-1-yl-1-ylidene)dibenzoate (6e)
Yield: 77%; brown crystals; mp 224–226 °C.

IR (KBr): 1720, 1274, 1141 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.89 (s, 6 H), 3.97 (s, 6 H), 6.98 (s, 2 H), 7.78–8.13 (m, 8 H).

^{13}C NMR ($CDCl_3$): δ = 26.9, 52.7, 102.3, 115.3, 130.3, 130.6, 130.9, 142.7, 146.7, 167.1, 177.9.

MS (70 eV): *m*/*z* = 422 [M^+], 394, 176, 145.

Anal. Calcd for $C_{24}H_{22}O_7$: C, 68.24; H, 5.25. Found: C, 68.33; H, 5.25.

(4*Z*,6*Z*)-4,6-Bis(4-chlorobenzylidene)-2,2-dimethyl-1,3-dioxan-5-one (6f)
Yield: 92%; yellow crystals; mp 136–138 °C.

IR (KBr): 1602, 1280, 1146 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.85 (s, 6 H), 6.92 (s, 2 H), 7.39 (d, *J* = 8.6 Hz, 4 H), 7.74 (d, *J* = 8.6 Hz, 4 H).

^{13}C NMR ($CDCl_3$): δ = 26.8, 101.9, 115.3, 129.3, 132.3, 132.4, 135.2, 145.8, 177.9.

MS (70 eV): *m*/*z* = 374 [M^+], 225, 152, 136.

Anal. Calcd for $C_{20}H_{16}Cl_2O_3$: C, 64.02; H, 4.30. Found: C, 63.92; H, 4.29.

(4*Z*,6*Z*)-2,2-Dimethyl-4,6-bis(thiophen-2-ylmethylene)-1,3-dioxan-5-one (6g)
Yield 90%; yellow crystals; mp 146–148 °C.

IR (KBr): 1604, 1272, 1144 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.88 (s, 6 H), 7.14 (dd, *J* = 3.6, 5.1 Hz, 2 H), 7.34 (s, 2 H), 7.40 (d, *J* = 3.6 Hz, 2 H), 7.54 (d, *J* = 5.1 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 26.4, 102.7, 111.5, 127.7, 130.7, 131.9, 136.9, 143.7, 176.5.

MS (70 eV): *m*/*z* = 318 [M^+], 232, 193, 138, 124.

Anal. Calcd for $C_{16}H_{14}O_3S_2$: C, 60.35; H, 4.43. Found: C, 60.41; H, 4.29.

(4*Z*,6*Z*)-2,2-Dimethyl-4,6-bis(pyridin-3-ylmethylene)-1,3-dioxan-5-one (6h)
Yield: 86%; yellow crystals; mp 162–164 °C.

IR (KBr): 1598, 1277, 1146 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.85 (s, 6 H), 6.92 (s, 2 H), 7.34 (dd, *J* = 4.8, 8 Hz, 2 H), 8.10 (d, *J* = 8 Hz, 2 H), 8.56 (dd, *J* = 1, 4.8 Hz, 2 H), 8.97 (d, *J* = 1 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 26.8, 102.3, 113.1, 123.9, 129.9, 137.4, 146.7, 149.8, 152.1, 177.3.

MS (70 eV): *m*/*z* = 308 [M^+], 265, 221, 133, 119, 103.

Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23. Found: C, 69.80; H, 5.14.

X-ray Crystal Structure Analysis of 6a
Yellow crystals were grown from EtOAc. Data was collected on an IPDS area detector system (Stoe) at –80 °C using MoKα-radiation. Empirical formula $C_{20}H_{18}O_3$; Formula weight 306.36; Crystal system = orthorhombic; Space group $Cmc2_1$; *Z* = 4; Unit cell dimensions *a* = 18.4110(11) Å, *b* = 11.2053(7) Å, *c* = 7.6475(6) Å; *V* = 1577.69(18) $Å^3$; D (calculated) = 1.290 g cm^{-3}; *m* = 0.086 mm^{-1}. 7570 reflections to θ = 25.9°, 854 independent, 724>4σ (*F*), *wR*2 = 0.057 (all refl.), *R*1 = 0.025 [for *F*>4σ(*F*)], Δρ (min/max) 0.116/–0.103 e$Å^{-3}$. H-atoms localized but include riding on idealized positions. Absolute structure was not determined (Friedel pairs merged). Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-660972. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [E-mail: deposit@ccdc.cam.ac.uk; Fax: +44(1223)336033 or via www.ccdc.cam.ac.uk/conts/retrieving.html].

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