Mn(III) Acetate Mediated Diasteroselective [3+2] Oxidative Addition Of 1,3-Dicarbonyl Compounds With Chalcones

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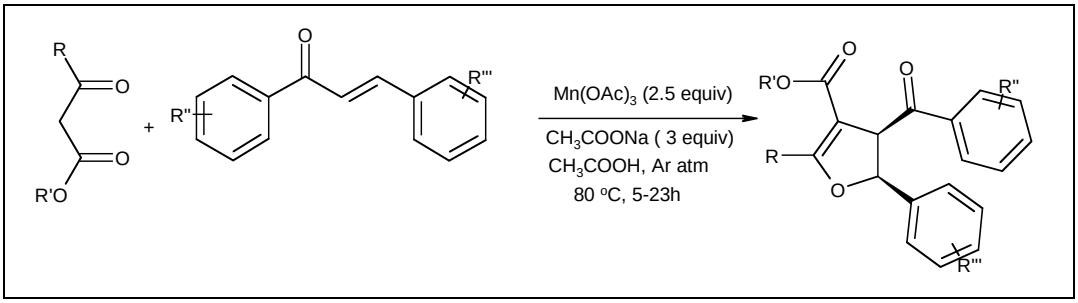

A diastereoselective synthesis of 4,5-dihydrofurans by oxidative addition of 1,3-dicarbonyl compounds with chalcones mediated by $Mn(OAc)_3$ in moderate to good yields is reported.

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INTRODUCTION

The introduction of radical chemistry to synthetic organic chemistry for the construction of complex carbocyclic as well as heterocyclic compounds has created a new methodology [1]. The versatility of this technology has encouraged great interest in the development of novel reagents and procedures for the generation of radicals [2]. Ceric ammonium nitrate (CAN) and manganese(III) acetate have been extensively used as single electron transfer agents for the construction of C-C bonds [1-4]. Furthermore, the utility of CAN in carbon-heteroatom bond forming reactions (C-N, C-S, C-Se, C-Br, C-I) was demonstrated [5].

Oxidative addition of 1,3-dicarbonyl compounds with alkenes, dienes, and exocyclic alkenes provides a straightforward synthesis of dihydrofuran and spiro-dihydrofuran derivatives [6,7]. The dihydrofuran ring is a ubiquitous motif, which is found in numerous natural products (*e.g.* polyether antibiotics, nucleosides, lignans) [8]. The CAN or Mn(III) mediated synthesis of tetra-substituted dihydrofurans by the addition of acetonyl acetone/dimedone with cinnamyl esters have been reported [8,9].

In continuation of our work on chalcones [10], we expected that 1,3-dicarbonyl compounds would add to chalcones stereo- and regio-selectively through a [3+2] oxidative addition protocol. Chalcones are easily prepared by stirring a mixture of an aldehyde and acetophenone in methanol under ice-cold conditions for 2 h at basic pH. The oxidative addition of 1,3-dicarbonyl compounds with chalcones mediated by Mn(III) was still to be explored.

In the present work, various chalcones were subjected to oxidative addition with 1,3-dicarbonyl compounds mediated by $Mn(OAc)_3$ or CAN. In a representative example, CAN mediated oxidative addition of 1,3-dicarbonyl compounds with chalcone at a low temperature (-5 to 0°C) did not afford the expected products. TLC showed more than five closely moving spots, which were difficult to separate. Recently Zhang *et al.* demonstrated a CAN-$NaHCO_3$ mediated synthesis of dihydrofurans in moderate yields [11]. However, CAN in acetonitrile was very sluggish for the reaction of (i) sulfones and chalcones (ii) 1,3-dicarbonyls and *o*-hydroxy chalcones. Hence, we considered Mn(III) acetate in acetic acid for the oxidative addition reactions [12].

RESULTS AND DISCUSSION

A typical experimental procedure involved stirring the mixture of chalcone and 1,3-dicarbonyl compound at 80 °C under an inert atmosphere. After the usual work-up and column chromatography, the reaction gave reasonable yields of the oxidative addition products (Scheme 1). The temperature was varied from room temperature to 100 °C. The reaction was very slow at room temperature and, at higher temperatures, it led to a mixture of undesired products, which were difficult to isolate.

Finally, the addition of three equivalents of NaOAc to the reaction at 80 °C resulted in the formation of only one diastereomer. Two and one half equivalents of $Mn(OAc)_3$ and 3 equivalents of NaOAc in acetic acid and stirring the reaction mixture at 80 °C under an argon atmosphere provided the optimal conditions for the synthesis of dihydrofurans **3a-f** (Table 1).

Scheme 1: Oxidative addition of methyl acetoacetate with chalcone mediated by $Mn(OAc)_3$

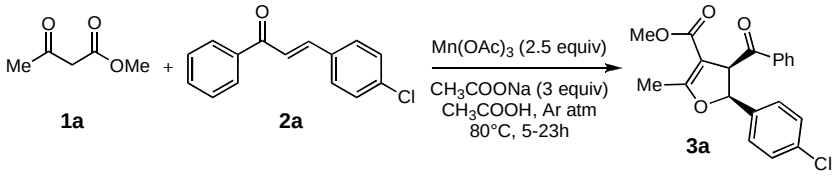
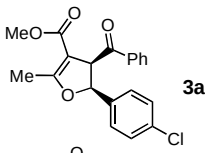
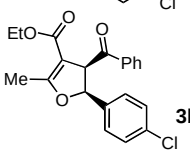
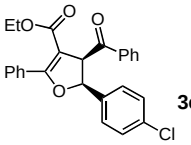
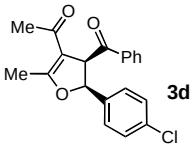
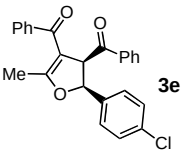
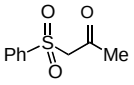
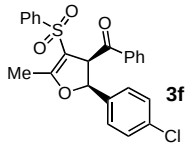


Table 1

Oxidative addition of 1,3-dicarbonylcompounds on chalcones.

Entry	$RCOCH_2COR'$ R	R'	$ArCOCHCHAr'$ Ar	Ar'	Time (h)	Product	Yield[a,b]
1	Me	OMe	Ph	4-Cl-C_6H_4	6	 **3a**	64
2	Me	OEt	Ph	4-Cl-C_6H_4	6	 **3b**	68
3	Ph	OEt	Ph	4-Cl-C_6H_4	23	 **3c**	46
4	Me	Me	Ph	4-Cl-C_6H_4	5	 **3d**	73
5	Me	Ph	Ph	4-Cl-C_6H_4	14	 **3e**	41
6			Ph	4-Cl-C_6H_4	26	 **3f**	44

[a]Isoalted yield, [b]products characterized by IR, NMR and GC-MS techniques.

The reaction was extended to different 1,3-dicarbonyl compounds, such as cyclic and acyclic ketones, and ß-keto sulphones (Table 1). The oxidative additions mediated by Mn(III) had led to the formation of tetrasubstituted dihydrofurans with two chiral centers at C-4 and C-5. To ascertain the configuration around C-4 and C-5, the J values of the two doublets resonating at δ 5-6 ppm were calculated. They were found to be 6-7 Hz which confirmed that the configuration around C-4 and C-5 carbon was *cis*. The typical J values for *cis* diastereomer of five membered compounds was around 5-7 Hz [13]. The *trans* isomer was not considered as its typical J values vary from 9 to 12 Hz [13a].

The targeted oxidative addition reaction, followed by the tandem cyclization of ortho-hydroxy chalcones was performed (Scheme 2). These compounds were subjected to coupling reaction with ethyl acetoacetate. But the reaction did not proceed beyond dihydrofuran formation. The appearance of a phenolic -OH group in ^1H NMR and IR spectra substantiated the non-progression of the expected tandem cyclization **3g-i** (Table 2).

Scheme 2. Oxidative addition of 1,3-dicarbonylcompounds on 2-hydroxychalcones.

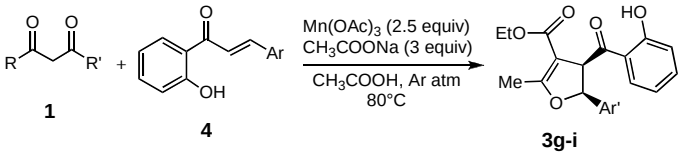
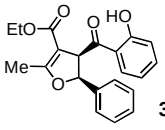
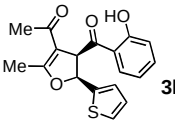
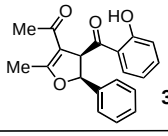


Table 2

Oxidative coupling of 1,3-dicarbonylcompounds with 2-hydroxychalcones.

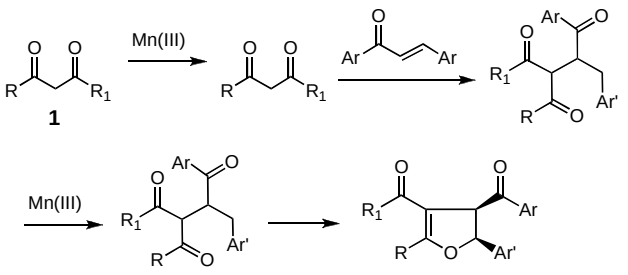
Entry	$RCOCH_2COR'$ R	R'	$ArCOCHCHAr'$ Ar	Ar'	Time (h)	Product	Yield
1	CH_3	OEt		Ph-	6	 **3g**	61
2	CH_3	CH_3			24	 **3h**	54
3	CH_3	CH_3		Ph	14	 **3i**	63

[a]Isolated yield, [b]products characterized by IR, NMR and GC-MS techniques.

The probable mechanism of the reaction is expected to proceed *via* oxidation of 1,3-dicarbonyl compounds to

electrophilic radical followed by addition cyclization (Scheme 3) similar to previous reports.[8,9,14].

Scheme 3: A plausible mechanism for the formation of dihydrofurans.



In summary we have reported a novel and efficient diasteroselective synthesis of tetrasubstituted *cis* 4,5-dihydrofurans by employing Manganese (III) acetate.

EXPERIMENTAL

Melting points were determined in capillary tubes and are uncorrected. Analytical TLC was performed on pre-coated plastic sheets of silica gel G/UV-254 of 0.2 mm thickness (Machery-Nagel, Germany). IR spectra were taken as KBr pellets on a Perkin Elmer RXI FT-IR spectrometer. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded in $CDCl_3$ solutions with TMS as internal standard on a JEOL instrument. Mass spectra were recorded using JEOL DX-303 in EI ionization mode at 70eV. Elemental analysis data were recorded using Thermo Finnigan FLASH EA 1112 CHN analyzer.

General experimental procedure for the oxidative addition of 1,3-dicarbonyl compounds. A mixture of chalcone (1 mmol) and 1,3-dicarbonyl compound (1.2 mmol), $Mn(OAc)_3$ (2.5 mmol) and NaOAc (3 mmol) in acetic acid under Ar atmosphere was stirred over oil-bath at 80 °C. After stirring the reaction mixture for appropriate time (Table 1 and Table 2), it was neutralized with $NaHCO_3$ and extracted with $CHCl_3$ (3 x 30 mL). The organic layer was dried with Na_2SO_4 and the compound was separated by column chromatography using 5 % ethyl acetate and petroleum ether. The reaction afforded *cis* dihydrofurans.

Methyl *cis*-4-benzoyl-5-(4-chlorophenyl)-2-methyl-4,5-dihydrofuran-3-carboxylate (3a). Viscous liquid; IR ($CHCl_3$): 1649, 1684, 2950 cm^{-1}; ^{1}H NMR: δ 2.38 (s, 3H), 3.54 (s, 3H), 5.11 (d, J = 6.9 Hz, 1H), 5.55 (d, J = 6.8 Hz, 1H), 7.18 (d, J = 8.6 Hz, 2H), 7.32 (d, J = 9.15 Hz, 2H), 7.41 (q, J = 7.45 Hz, 1H), 7.55 (t, J = 7.45 Hz, 2H), 7.84 (d, J = 6.85 Hz, 2H); ^{13}C NMR: δ 14.34, 51.06, 57.71, 86.43, 103.78, 127.19, 128.77, 128.82, 129.29, 133.6, 136.15, 138.59, 165.22, 170.17, 177.66, 200.05; MS (EI, m/z): 356 (M+); *Anal*. calcd for $C_{20}H_{17}ClO_4$: C, 67.32; H, 4.80. Found: C, 67.11; H, 4.62.

Ethyl *cis*-4-benzoyl-5-(4-chlorophenyl)-2-methyl-4,5-dihydrofuran-3-carboxylate (3b). Viscous liquid; IR ($CHCl_3$): 1630, 1700, 1720 cm^{-1}; ^{1}H NMR: δ 0.94 (t, J = 7.5Hz, 3H), 2.38 (s, 3H), 3.95 (q, J = 7.5 Hz, 2H), 5.00 (d, J = 6.85 Hz, 1H), 5.56 (d, J = 6.8 Hz, 1H), 7.18 (d, J = 8 Hz, 2H), 7.32 (d, J = 8.6 Hz, 2H), 7.40 (t, J = 7.45 & 8.0 Hz, 3H), 7.54 (t, J = 7.45 Hz, 1H), 7.85 (d, J = 7.45 Hz, 1H); ^{13}C NMR: δ 13.95, 14.29, 57.57, 59.92, 86.57, 104.12, 127.12, 127.50 128.74, 128.80, 129.27, 133.65, 134.67, 136.78, 138.69, 164.67, 200.43.MS (EI, m/z): 370 (M+); Anal. calcd for $C_{21}H_{19}ClO_4$: C, 68.02; H, 5.16. Found: C, 67.85; H, 5.05.

Ethyl *cis*-4-benzoyl-5-(4-chlorophenyl)-2-phenyl-4,5-dihydrofuran-3-carboxylate (3c). Viscous liquid; IR ($CHCl_3$): 1630, 1700, 1720 cm^{-1}; ^{1}H NMR: δ 0.81 (t, J = 7.5Hz, 3H), 3.93 (m, 2H), 5.22 (d, J = 6.85Hz, 1H), 5.6 (d, J = 7.45Hz, 1H), 7.28 (d, J = 8.6Hz, 2H), 7.36 (d, J = 8.6Hz, 2H), 7.42-7.47 (m, 6H), 7.45 (t, J = 7.45Hz, 1H), 7.90 (d, J = 7.45Hz, 1H), 7.92 (d, J = 8.55Hz, 2H); ^{13}C NMR: δ 14.91, 59.61, 62.34, 86.29, 106.51, 114.16, 114.25, 115.38, 127.19, 127.85, 128.82, 129.34, 129.74, 136.86, 143.51, 144.67, 155.91, 163.67, 171.41, 201.08; MS (EI, m/z): 432 (M+); *Anal*. calcd for $C_{26}H_{21}ClO_4$ C, 72.14; H, 4.89. Found: C, 72.36; H, 4.62.

1-[*cis*-4-benzoyl-5-(4-chlorophenyl)-2-methyl-4,5-dihydrofuran-3-yl]ethanone (3d). Viscous liquid; IR ($CHCl_3$): 1612, 1693, 1731 cm-1; ^{1}H NMR: δ 2.25 (s, 3H), 2.42 (s, 3H), 5.11 (d, J = 6.9 Hz, 1H), 5.47 (d, J = 6.85 Hz, 1H), 7.25 (dd, J = 5.35 & 2.3 Hz, 2H), 7.36 (d, J = 6.9 Hz, 2H), 7.39 (d, J = 7.65 Hz, 2H), 7.51 (q, J = 6.9 Hz, 1H), 7.85 (d, J = 6.8 Hz, 2H); ^{13}C NMR: δ 15.50, 29.79, 58.56, 86.84, 116.51, 125.86, 128.73, 128.88, 129.03, 129.12, 130.99, 133.53, 136.71, 139.83, 168.55, 200.32; 340 (M+); *Anal*. calcd for $C_{20}H_{17}ClO_3$: C, 70.49; H, 5.03. Found: C, 70.09; H, 4.82.

***cis*-4-(3,4-Dibenzoyl)-2-methyl-5-(4-chlorophenyl)-4,5-dihydrofuran (3e).** Viscous liquid; IR ($CHCl_3$): 1645, 2959 cm^{-1}; ^{1}H NMR: δ 2.26 (s, 3H), 5.12 (d, J = 6.9Hz, 1H), 5.61 (d, J = 6.9 Hz, 1H), 7.23 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.60 Hz, 2H), 7.41-7.48 (m, 6H), 7.49 (t, J = 7.45Hz, 1H), 7.92 (d, J = 7.45 Hz, 1H), 7.94 (d, J = 8.4 Hz, 2H); ^{13}C NMR: δ 16.12, 68.51, 86.13, 107.12, 114.23, 114.58, 115.64, 127.23, 127.83, 128.79, 129.31, 129.58, 136.92, 143.53, 144.77, 155.08, 163.27, 171.49, 200.13; MS (EI, m/z): 402 (M+); *Anal*. calcd for $C_{25}H_{19}ClO_3$: C, 74.53; H, 4.75. Found: C, 74.40; H, 4.70.

[*cis*-2-(4-Chlorophenyl)-5-methyl-4-(phenylsulfonyl)-2,3-dihydrofuran-3-yl]-phenyl-methanone (3f). Mp. 63 °C; IR (KBr) : 1070, 1291, 1325, 1422, 1692 cm^{-1}; ^{1}H NMR: δ 2.45 (s, 3H), 5.27 (d, J = 6.1 Hz, 1H), 5.62 (d, *J* = 6.1 Hz, 1H), 7.24 (d, J = 8.0 Hz, 2H), 7.35-7.40 (m, 6H), 7.55 (m, 4H), 7.76 (d, J = 8.0 Hz, 2H); ^{13}C NMR: δ 13.87, 57.04, 87.65, 110.66, 125.61, 125.86, 126.42, 128.73, 128.88, 129.03, 129.12, 130.99, 131.20, 133.53, 136.71, 139.83, 172.43, 199.38. MS (EI, m/z): 438 (M+); *Anal*. calcd for $C_{24}H_{19}ClO_4S$: C, 65.67; H, 4.36. Found: C, 65.54; H, 4.22.

Ethyl *cis*-4-(2-Hydroxybenzoyl)-2-methyl-5-phenyl-4,5-dihydrofuran-3-carboxylate (3g). Viscous liquid; IR ($CHCl_3$): 1630, 1700, 1721, 3400 cm^{-1}; ^{1}H NMR: δ 0.94 (t, J = 6.85 Hz, 3H), 2.33 (s, 3H), 3.83 (q, J = 7.45 Hz, 2H), 5.25 (d, J = 6.9Hz, 1H), 5.82 (d, J = 6.9Hz, 1H), 6.88 (t, J = 6.9Hz, 1H), 7.10-7.23 (m, 7H), 7.88 (d, J = 6.8Hz, 1H) 11.75 (s, 1H); ^{13}C NMR: δ 13.03, 15.88, 54.65, 62.15, 86.13, 115.46, 118.73, 118.94, 119.22, 121.55, 123.48, 126.29, 127.18, 131.37, 132.56, 132.93, 137.08, 163.75, 199.95; MS (EI, m/z): 352 (M+); *Anal*. calcd for $C_{21}H_{20}O_5$: C, 71.58; H, 5.72. Found: C, 71.21; H, 5.53.

1-[*cis*-4-(2-hydroxybenzoyl)-2-methyl-5-thien-2-yl-4,5-dihydrofuran-3-yl]-ethanone (3h). Viscous liquid; IR ($CHCl_3$): 1612, 1693, 1731, 3250, 3400 cm^{-1}; ^{1}H NMR: δ 2.29 (s, 3H), 2.38 (s, 3H), 5.24 (d, J = 6.1 Hz, 1H), 5.70 (d, J = 6.1 Hz, 1H), 6.80 (t, J = 6.9 & 8.4 Hz, 1H), 6.85 (t, J = 4.55 Hz, 1H), 6.89 (d, J = 5.35 Hz, 1H), 6.93 (d, J = 3.85 Hz, 1H), 7.04 (d, J = 3.05 Hz,

1H), 7.47 (t, J = 8.4 Hz, 1H), 7.65 (d, J = 7.65 Hz, 1H), 11.91 (s, 1H); ^{13}C NMR: δ 15.55, 28.92, 58.06, 82.18, 115.62, 119.14, 119.17, 119.24, 125.65, 125.89, 126.84, 127.14, 130.57, 131.15, 137.18, 141.83, 168.15, 204.54; MS (EI, m/z): 328 (M+); Anal. calcd for C_{18} $H_{16}O_4S$: C, 65.84; H, 4.91. Found: C, 65.40; H, 4.90.

1-[*cis*-4-(2-Hydroxybenzoyl)-2-methyl-5-phenyl-4,5-dihydrofuran-3-yl]-ethanone (3i). Viscous liquid; IR ($CHCl_3$): 1610, 1695, 1730, 3255, 3397 cm^{-1}; ^{1}H NMR: δ 2.28 (s, 3H), 2.30 (s, 3H), 5.14 (d, J = 6.9Hz, 1H), 5.93 (d, J = 6.9Hz, 1H), 6.9 (t, J = 6.9Hz, 1H), 7.08-7.25 (m, 7H), 7.85 (d, J = 6.8Hz, 1H), 12.06(s, 1H); ^{13}C NMR: δ 15.61, 28.71, 54.73, 85.42, 114.46, 118.59, 118.87, 119.18, 121.30, 123.50, 126.82, 127.06, 131.19, 132.47, 132.95, 137.38, 163.22, 199.84. MS (EI, m/z): 322 (M^+); Anal. calcd for $C_{20}H_{18}$ O_4: C, 74.52; H, 5.63. Found: 74.41; H, 5.53.

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