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A Convenient Synthesis of Substituted Spiro[5.5]Undecanes Using Lewis Acid Catalysts

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Abstract

A one-pot synthesis of 3, 3-Dimethyl-7, 11-diphenyl-spiro [5, 5] undecane-1, 5, 9-triones **4a-c** has been achieved by the application of Michael reaction between dimedone (5,5-dimethylcyclohexane-1,3-dione) **1** and *trans,trans* diarylideneacetones [1,5-diaryl-1,4-pentadien-3-ones] **2a-c** (a. Ar = C_6H_5-, b. Ar = 2-Cl-C_6H_4-, c. Ar = 2- CH_3O- C_6H_4) using Lewis acid catalysts.

Key words: spiro[5.5]undecane; dimedone; *trans,trans* diarylideneacetone; Lewis acid catalyst; Michael reaction.

I. Introduction

Spiro [5. 5] undecane system has been known to be present as phytochemicals, in alkaloids, terpenoids and other natural products. Many alkaloids having spiro structures were found to be very potent nicotinic receptor antagonists[1]. Many spiro-oxindole derivatives were found to possess wide biological applications as antimicrobial, antitumor and inhibitors of human NK-1 receptor[2, 3]. Several azaspiro-compounds were reported to be tachykinin antagonists and of particular use in the treatment of depression, anxiety, pain, inflammation, migraine, emesis or postherpetic neuralgia[4]. Many natural products such as fredericamycin[5], spirovetivanes, acroanes, chamigrenes,[6] angularly fused cyclopentanoids (e.g. crinipellin-A, laurenene)[7] consist of spiro structures. The stereochemistry of spiranes with six-membered rings has been extensively studied[8]. The chirality of the parent spiro [5.5]undecane (**Figure 1**) was observed by Dodziuk[9,10], but at that time no chiral element according to the classification of Cahn, Ingold and Prelog[11,12] was found and the chirality of the spiro compounds with six-membered rings could not be satisfactorily explained. M. Alin *et al* reported[13] that in monospiranes the two enantiomeric structures exist either as A or B configuration (**Figure 1**) Iwata and co-workers[14] have reported the stereoselective synthesis of spiro [5.5] undecane systems using Lewis acid promoted spiroannulation of *bis*-acetals. A tandem reaction involving yamine was used by Ficini and co-workers[15] during the synthesis of the acoradiene. Spiroannulation *via* intramolecular 1, 4- addition has also been shown for the synthesis of the core structure of alkaloid Manzamine A.[16] As a result of the important biological activities and interesting structures the chemistry of spiro compounds has aroused intense interest in both their synthesis and chemical reactivity. From the literature [17] it is found that among many strategies, which have evolved for the synthesis of spiro structures, the acid-catalyzed cyclization of 1:1 Michael adduct has been very convenient and effective. The present work has been focused on devising a convenient route for the synthesis of spiro compounds. Due to the similarities in the structures to other reported [17] medicinally important spiro compounds, the target compounds are also expected to be potentially bioactive. In the present work, we wish to report the synthesis of 7,11-diaryl-spiro [5.5]undecane-1,5,9-triones **4a-c** from diarylideneacetones and dimedone, in which spiro rings are formed with substituted cyclohexane ring moiety.

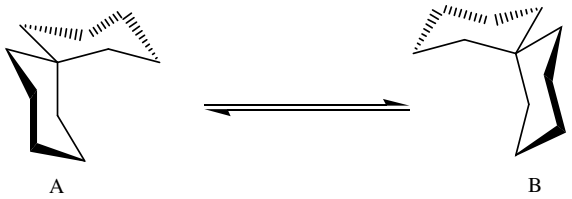


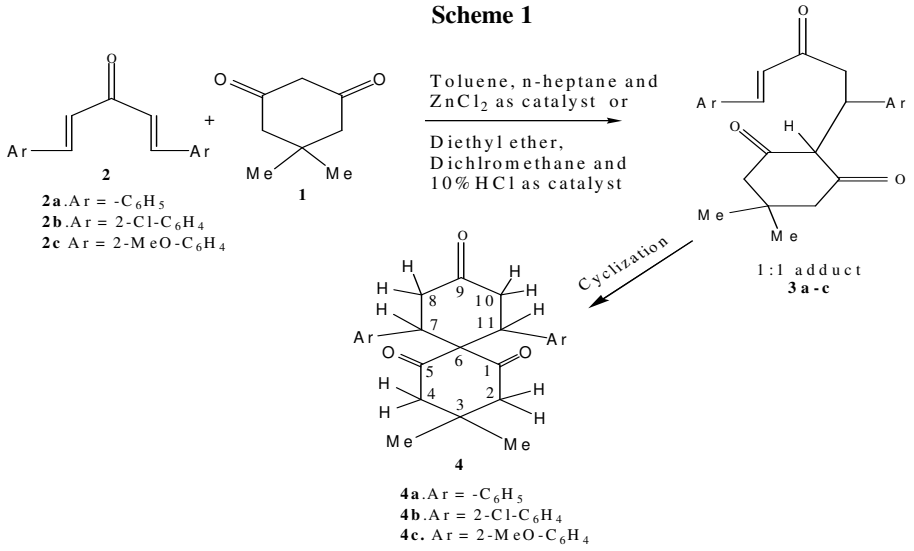
Fig. 1. Helical structure of Spiro [5,5] undecane

For the investigation, Michael reaction was carried out between dimedone (5,5-dimethylcyclohexane-1,3-dione) **1** and *trans,trans* diarylideneacetones [1,5-diaryl-1,4-pentadien-3-one] **2a-c** in molar proportion in a mixture of boiling toluene and n-heptane in presence of $ZnCl_2$ as well as 10% HCl solution in a mixture of diethyl ether and dichloromethane (DCM) as catalysts. *trans,trans* Diarylideneacetones **2a-c** were prepared according to the procedure reported in the literature[18] with modifications as needed.

II. Experimental Section

Melting points were determined on an Electrothermal micro melting point (MEL-TEMPII, laboratories devices USA) apparatus and uncorrected. IR spectra were recorded using Shimadzu IR-470A infrared spectrophotometer. The ^{1}H-NMR and ^{13}C-NMR spectra were run in $CDCl_3$ with TMS as an internal standard in Bruker 400 MHz NMR spectrometer. Mass spectra were recorded using JEOL JMS-HX 110A.

Scheme 1



2a.Ar = -C_6H_5
2b.Ar = 2-Cl-C_6H_4
2c Ar = 2-MeO-C_6H_4

4a.Ar = -C_6H_5
4b.Ar = 2-Cl-C_6H_4
4c. Ar = 2-MeO-C_6H_4

General procedure for the synthesis of 4a-c: Michael reaction was carried out between dimedone (5,5-dimethylcyclohexane-1,3-dione) **1**, and *trans*, *trans*-diarylideneacetone **2a-c** in molar proportion in a mixture of boiling toluene and n-heptane in presence of anhydrous $ZnCl_2$ as well as 10% HCl in a mixture of diethyl ether and dichloromethane(DCM) as catalysts under refluxing condition for 15-30 hr (depending on the reaction). The water formed in the reaction was removed by using a Dean-Stark attachment. The reaction mixture was cooled, reduced to one- fourth of its volume, neutralized with saturated aqueous $NaHCO_3$ and extracted with ether. The ether extract was dried over anhydrous Na_2SO_4 and the gummy mass obtained from the ether extract was purified by recrystallization from suitable solvents. The compounds **4a-c** obtained were characterized by IR, ^1H and ^{13}C NMR including DEPT, MS and elemental analysis.

Table. 1. Reaction conditions

Entry	Reactant	Reactant	Medium	Catalyst	Time(hr)	Yield %
4a	**2a** (2.34g , 10 mmol)	**1** (1.4g, 10 mmol)	n-heptane (30mL) + toluene(30mL)	20 mmol% $ZnCl_2$	15	43
4b	**2b** (1.20 g, 4 mmol)	**1** (3.36g, 24 mmol)	Diethyl ether (30mL) + DCM (30mL)	10% HCl	30	40
4c	**2c** (2.94g, 10mmol)	**1** (1.12g, 10mmol)	Diethyl ether (30mL) + DCM (30mL)	10% HCl	19	58

3, 3-Dimethyl-7, 11-diphenyl-spiro [5, 5] undecane-1, 5, 9-trione 4a: R_f 0.5 (neat $CHCl_3$), mp 120°-122°C, Yield 43 %; **IR** spectrum (υ max in cm^{-1}) 1445, 1490, 1595, 1670, 1700 cm^{-1}; **^1H NMR** (δ value) 0.08 (s, 6H, 2xMe -3), 1.60 (s, 2H, H-4), 2.01 (s, 2H, H-2), 2.45 (dd, 2H, H_{eq}-8, H_{eq}-10, $J_{8\text{-H gem}}$ = 14.80 Hz, $J_{10\text{-H gem}}$ = 14.80 Hz, $J_{ae\ (7,\ 11\text{-Hax and 8, 10-Heq})}$ = 3.60 Hz), 3.20 (dd, 2H, H_{ax}-8, H_{ax}-10, $J_{8\text{-H gem}}$ = 14.80 Hz, $J_{10\text{-H gem}}$ = 14.80 Hz, $J_{aa\ (7,11\text{-Hax and 8,10-Hax})}$ = 14.60 Hz), 3.73 (dd, 2H, H_{ax}-7, H_{ax}-11, $J_{ae\ (7,\ 11\text{-Hax and 8, 10-Heq})}$ = 3.60 Hz, $J_{aa\ (7,11\text{-Hax and 8,10-Hax})}$ = 14.60 Hz), 7.12-7.19 (m, 5H, H-Ar); Mass spectra: *m/z* (M^+) 374.22, Calculated M^+= 374.19. Anal. Calcd for $C_{25}H_{26}O_3$ (374.19): C, 80.18; H, 7.00. Found : C, 80.04; H, 6.95.

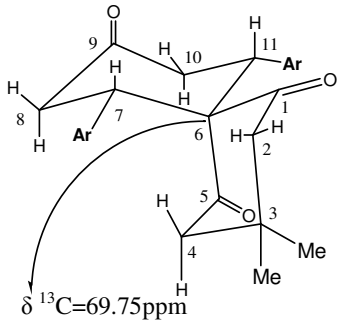
3,3-Dimethyl-7,11-bis-(2'-chlorophenyl)-spiro[5,5]undecane-1,5,9-trione 4b: R_f 0.68 (neat $CHCl_3$), mp 176-177°C, Yield 40 %; **IR** spectrum (υ max in cm^{-1}) 1580, 1620, 1660, 1700; **^1H NMR** (δ value) 0.93 (s, 6H, 2xMe-3), 2.17 (s, 2H, H-2), 2.48 (dd, 2H, H_{eq}-8, H_{eq}-10, $J_{8\text{-H gem}}$ = 14.30 Hz, $J_{10\text{-H gem}}$ = 14.30 Hz, $J_{ae\ (7,\ 11\text{-Hax and 8, 10-Heq})}$ = 3.60 Hz), 3.20 (dd, 2H, H_{ax}-8, H_{ax}-10, $J_{8\text{-H gem}}$ = 14.30 Hz, $J_{10\text{-H gem}}$ = 14.30 Hz, $J_{aa\ (7,11\text{-Hax and 8,10-Hax})}$ = 13.0 Hz), 3.42 (dd, 2H, H_{ax}-7, H_{ax}-11, $J_{ae\ (7,\ 11\text{-Hax and 8, 10-Heq})}$ = 3.60 Hz, $J_{aa\ (7,11\text{-Hax and 8,10-Hax})}$ = 13.0 Hz), 6.74 (dd, *J* =8 Hz, 1H, H-3'), 6.87 (dd, *J* =8 Hz, *J* =9 Hz, 1H, H-4'), 7.25 (t, *J*= 7 Hz, 1H, H-5'), 7.09 (d, *J*=7Hz, 1H, H-6'). Mass spectra: *m/z* (M^+) =442.11, Calculated M^+=*442.17* .Anal. Calcd for $C_{25}H_{24}Cl_2O_3$ (442.17): C, 67.73; H, 5.46. Found: C, 67.63; H, 5.40.

3,3-Dimethyl-7,11-bis-(2'-methoxyphenyl)-spiro[5,5]undecane-1,5,9-trione 4c: R_f 0.64 (neat $CHCl_3$), mp 220-221°C , Yield 58% ; **IR** spectrum (υ max in cm^{-1}) 1580, 1615, 1670, 1700; **^1H NMR** (δ value) 0.25 (s, 3H, Me), 2.14 (s, 2H, H-2), 2.41 (dd, 2H, H_{eq}-8, H_{eq}-10, $J_{8\text{-H gem}}$

= 13.0 Hz, $J_{10\text{-H gem}}$ = 13.0 Hz, $J_{ae\ (7,\ 11\text{-Hax and }8,\ 10\text{-Heq})}$ = 4 Hz), 3.25 (dd, 2H, H_{ax}-8, H_{ax}-10, $J_{8\text{-H gem}}$ = 13.0 Hz, $J_{10\text{-H gem}}$= 13.0 Hz, $J_{aa\ (7,11\text{-Hax and }8,10\text{-Hax})}$ = 13.0 Hz), 3.72 (dd, 2H, H_{ax}-7, H_{ax}-11, $J_{ae\ (7,\ 11\text{-Hax and }8,\ 10\text{-Heq})}$ = 4 Hz, $J_{aa\ (7,11\text{-Hax and }8,10\text{-Hax})}$ = 13 Hz), 3.78 (s, 3H, OMe), 6.77 (dd, *J*=8, 1H, H-3'), 6.87 (dd, *J*=8 Hz, *J*=9 Hz, 1H, H-4'), 7.18 (t, *J* = 7Hz, 1H, H-5'), 7.2 (d, *J* = 7 Hz, 1H, H-6'). Mass spectra: *m/z* (M^+) =434.27, Calculated M^+=*434.21*. Anal. Calcd for $C_{27}H_{30}O_5$ (434.21): C, 74.63; H, 6.96. Found: C, 74.35; H, 6.92.

III. Results and Discussion

A report on NMR data of a similar compound triethyl spiro[5,5]undecane-7-ene-1-yloxy) silane is available in the literature [19]. The ^{13}C chemical shifts (δ ^{13}C 68-70ppm) of the spirocarbons C-6 in compounds **4a-c** are not far from the spiro carbon chemical shift value of the reported data triethyl spiro[5, 5]undecane-7-ene-1-yloxy) silane (δ ^{13}C 75.96ppm)[19]. It is evident from the aforementioned literature report that the ^{13}C NMR chemical shifts of the spirocarbons of compounds **4a-c** are typical for a *cis* structure (**Fig.2**) [20].



H_{eq}-8, H_{eq}-10 (2.45, dd, $J_{8\text{-H gem}}$= 14.8Hz, $J_{10\text{-H gem}}$= 14.8Hz, $J_{ae\ (7,\ 11\text{-Hax and }8,\ 10\text{-Heq})}$ = 3.6Hz) H_{ax}-8, H_{ax}-10 (3.20, dd, $J_{8\text{-H gem}}$= 14.8Hz, $J_{10\text{-H gem}}$= 14.8Hz, $J_{aa\ (7,11\text{-Hax and }8,10\text{-Hax})}$= 14.6Hz) H_{ax}-7, H_{ax}-11 (3.73, dd, $J_{ae\ (7,\ 11\text{-Hax and }8,\ 10\text{-Heq})}$ = 3.6Hz, $J_{aa\ (7,11\text{-Hax and }8,10\text{-Hax})}$= 14.6Hz)

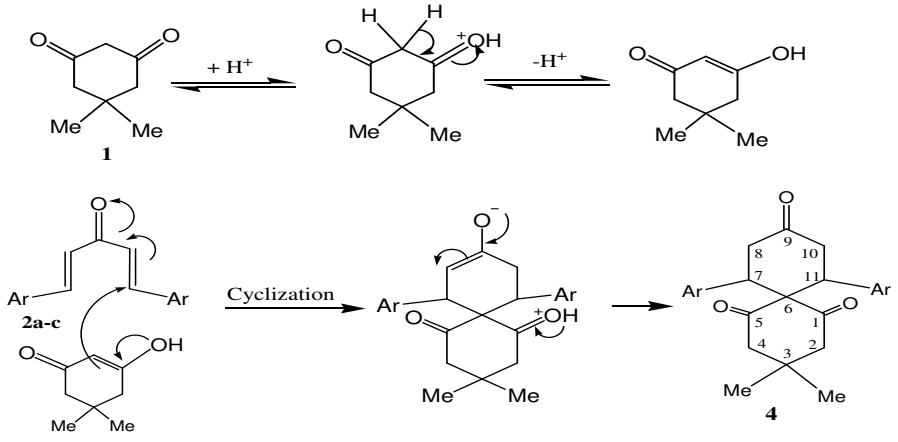
Fig. 2. Spiro ring skeleton **4** (Ar= -C_6H_5)

Table. 2. ^{13}C-NMR spectral data

Carbon atoms	Compounds (δ value in ppm)		
	4a	4b	4c
C-1of C=O	211.72	211.70	211.28
C-5 of C=O	213.16	212.85	209.21
C-9 of C=O	208.6	209.01	207.07
Aromatic Carbons	138.89-128.80	129.19-118.20	156.90 - 111.50
C-6 spiro carbon	69.75	68.52	68.033
-OMe	-	-	55.66
C-2 & C-4	56.3	56.3	53.90
C-8 & C-10	43.9	44.01	42.94
C-7 & C-11	51.01	50.9	40.84
C-3	29.57	29.53	29.26
Me	28.78	28.8	28.70

The formation of the six membered carbocyclic rings of spiro compounds **4a-c** may be explained by the initial formation a Michael 1:1 adduct **3** which underwent cyclization (**Scheme 2**). In this mechanistic pathway dimedone **1** is converted to its enol form in the presence of Lewis acid which reacts with diarylideneacetones **2** to form a Michael 1:1 adduct **3**. The procedure followed in the present research provides a route for an efficient one-pot facile synthesis of spiro compounds. It also provides an option for functionalization of the reduced ring by starting from dimedone as well as the substituted aryl groups at the 7 and 11-position.

Scheme 2



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