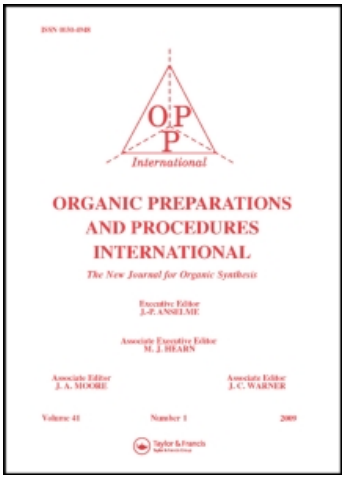


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# SYNTHESIS OF SOME SPIRO-ISOXAZOLIDINE-3,5-DIONES

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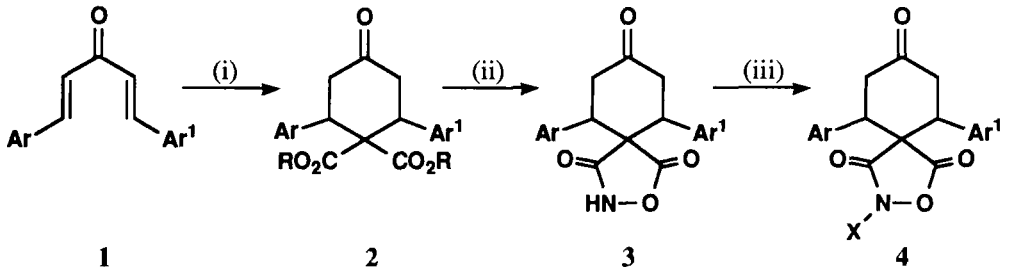
Over the years, different synthetic routes have been developed for the biologically important spiro-pyrimidines.[1a-e] Apart from these, syntheses of some spiro-pyrazolidinediones were also reported.[1c] However, we are aware of no previous reports about spiro-isoxazolidinediones. Therefore, we herein report the synthesis of 6,10-diaryl-2-oxo-3-azaspiro[4,5]decane-1,4,8-triones (**3**) by the condensation of dimethyl or diethyl-2,6-diaryl-4-ketocyclohexane-1,1-dicarboxylates (**2**) with hydroxylamine hydrochloride in presence of sodium alkoxide in relatively high yields.




**1** **2** **3** **4**

i) $CH_2(CO_2R)_2$, $RO^-$ ii) $NH_2OH{\cdot}HCl$, $RO^-$ iii) Acylation or nitrosation

a) R = Me, Ar = Ar¹ = $C_6H_5$
b) R = Me, Ar = Ar¹ = 4-$MeC_6H_4$
c) R = Me, Ar = Ar¹ = 4-$MeOC_6H_4$
d) R = Me, Ar = Ar¹ = 4-$ClC_6H_4$
e) R = Me, Ar = $C_6H_5$, Ar¹ = 4-$MeC_6H_4$
f) R = Me, Ar = $C_6H_5$, Ar¹ = 4-$ClC_6H_4$
g) R = Et, Ar = Ar¹ = $C_6H_5$
h) R = Et, Ar = Ar¹ = 4-$MeC_6H_4$
i) R = Et, Ar = Ar¹ = 4-$MeOC_6H_4$

a) X = $COC_6H_5$
b) X = COMe
c) X = $SO_2C_6H_5$
d) X = NO

The cyclohexanones **2** were prepared by the double Michael addition of dimethyl or diethyl malonate to 1,5-diaryl-1,4-pentadien-3-ones (**1**) in the presence of sodium methoxide or ethoxide.[2] Benzoylation, benzenesulfonylation, acetylation and nitrosation of **3** gave the N-substituted derivatives **4**.

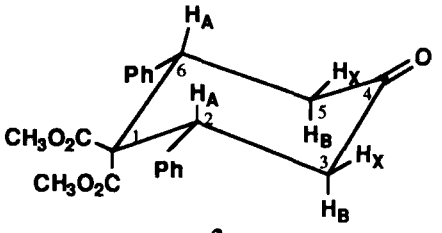
The IR spectra of **2** exhibited strong bands in the regions 1770-1740 and 1725-1690 $cm^{-1}$ for the carbonyl group of the ester and cyclohexanone moiety, respectively,[3] while those of the isoxazole and cyclohexane portions of **3** appear in the regions 1720-1700 and 1700-1685 $cm^{-1}$, respectively.[3,4] Compounds **3** exhibited medium to strong bands in the region 3390-3380 $cm^{-1}$ (NH). Compounds **4a-d** also displayed medium to strong bands in the regions 1510-1500 (NO),[4,5] 1310-1295 and 1150-1140 ($SO_2$)[6-9] and 1690-1660 (CO) $cm^{-1}$.[3,4]

**TABLE 1. Yields, mps and Analyses of Compounds 2, 3 and 4**

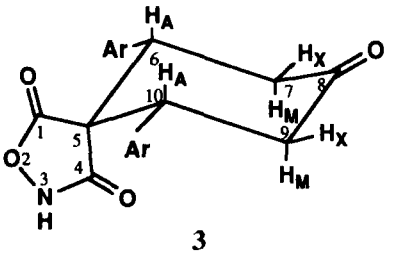
| Cmpd | Yield (%) | Obs. (lit.) mp (°C) | Elemental Analysis (Calcd.) C | H | N |
|---|---|---|---|---|---|
| **2a** | 80 | 134-136 (135-136)[a] | — — | — — | — — |
| **2b** | 78 | 176-177 | 73.26 (73.07) | 6.52 (6.64) | |
| **2c** | 76 | 195-196 (194-196)[a] | — — | — — | — — |
| **2d** | 78 | 167-168 | 60.82 (60.70) | 4.52 (4.63) | — — |
| **2e** | 70 | 168-170 | 72.48 (72.61) | 6.48 (6.36) | — — |
| **2f** | 78 | 192-193 | 66.02 (65.91) | 5.16 (5.28) | — — |
| **2g** | 70 | 77-78 (79)[a] | — — | — — | — — |
| **2h** | 68 | 116-119 | 73.72 (73.91) | 7.02 (7.16) | — — |
| **2i** | 66 | 115-116 | 68.59 (68.70) | 6.56 (6.65) | — — |
| **3a** | 74 | 172-174 | 71.83 (71.63) | 5.01 (5.11) | 4.21 (4.17) |
| **3b** | 69 | 214-216 | 72.56 (72.71) | 5.94 (5.82) | 3.91 (3.85) |
| **3c** | 70 | 218-219 | 66.65 (66.83) | 5.47 (5.35) | 3.60 (3.54) |
| **3d** | 76 | 223-224 | 59.59 (59.44) | 3.62 (3.74) | 3.51 (3.46) |
| **3e** | 65 | 196-195 | 72.00 (72.19) | 5.59 (5.48) | 4.06 (4.00) |
| **3f** | 75 | 236-237 | 64.76 (64.96) | 4.47 (4.36) | 3.84 (3.79) |
| **4a** | 80 | 154-156 | 73.61 (73.79) | 4.90 (4.36) | 3.11 (3.18) |
| **4b** | 75 | 105-107 | 69.95 (70.09) | 5.63 (5.71) | 3.33 (3.45) |
| **4c** | 68 | 122-124 | 62.66 (62.80) | 4.62 (4.70) | 2.52 (2.61) |
| **4d** | 66 | 112-114 | 55.42 (55.56) | 3.14 (3.26) | 6.38 (6.47) |

a) Ref. 2.

The $^1H$ NMR spectra of **2** and **3** may be rationalized by assuming the two aryl groups to be in the diequatorial positions, in conformity with a *cis*-1,3-arrangement of the substituents. The isoxazolidinedione moiety of **3** which itself is nearly planar, is perpendicular to the average plane of the



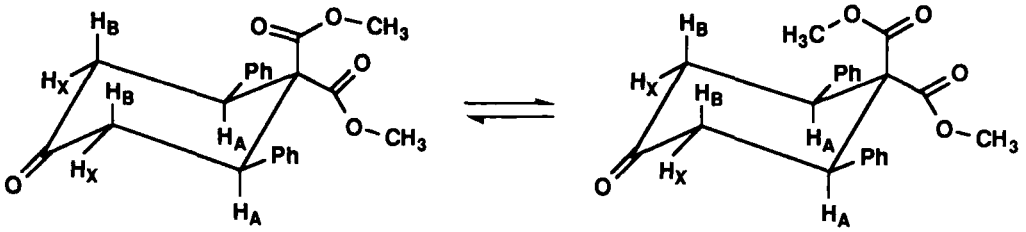
2



3

cyclohexanone ring. The methine and methylene protons of **2** constitute two identical ABX systems. The methine protons, $H_A$ should couple with the methylene protons, $H_B$ and $H_X$ and should normally appear as doublet of doublets at a downfield region.[1e] The methylene proton, $H_X$, involves both geminal and vicinal coupling and should appear as doublet of doublets in the upfield position of the spectrum. The methylene proton, $H_B$, should necessarily experience the same effect and appear as doublet of doublets in between the above mentioned two regions which are in close proximity to the downfield protons, $H_A$. However, a multiplet between 4.12-4.39 ppm is observed in the spectrum of **2** due to $H_A$ and $H_B$ protons and another multiplet in the region 3.04-3.21 ppm for $H_X$ protons. This downfield absorption of $H_B$ protons is due to the deshielding effect of the carbonyl group at position 4. The two methoxy groups at position 1 may be assumed to possess **5** and **6** orientations in the





5 ⇌ 6

preferred conformation resulting from rotation of the axial carbomethoxy group. The axial carbomethoxy group in **6** is in close proximity to the carbonyl group at position 4 and also involves the usual 1,3-diaxial interactions while **5** is devoid of these effects. Hence, the two carbomethoxy groups in 6 are in different environments and exhibit sharp signals at 3.32-3.57 and 3.53-3.55 ppm for equatorial and axial methoxy of carbomethoxy groups, respectively. The downfield absorption of axial methoxy of carbomethoxy group is due to the deshielding effect exerted by the carbonyl group at position 4.[10] In the case of **3**, the methine and methylene protons also exhibited two AMX systems. The axial protons, $H_M$ at C-7 and C-9, fall in the deshielding zone of the carbonyl group at position 8.[1e] Hence, they absorb at distinctly different position than the equatorial protons, $H_X$.[11] Moreover, the Dreiding model suggests that one of the axial protons ($H_M$) of C-7 or C-9 is in close proximity to the paramagnetic cone of the carbonyl group at position 4 and hence absorb at different fields. The

$H_A$ and $H_X$ showed doublet of doublets 3.94-4.10 and 2.73-2.82 ppm, respectively. However, two doublets of doublets are exhibited by $H_M$ at 3.04-3.18 and 2-92-2.96 ppm. The coupling constants for these compounds were found to be $J_{AM}$ = 10.20, $J_{AX}$ = 5.10 and $J_{MX}$ = 15.32 Hz. A broad singlet around 8.48-5.51 ppm is observed for the NH proton which disappeared on deuteration. The spectra for **4** are similar to those of **3** except for the absence of NH absorption in IR and a signal for NH proton in $^1$H NMR.

The $^{13}$C NMR spectrum of **2** exhibited $\delta_C$ values in the regions 43.87-43.98 (C-3 and C-5), 51.83-51.98 (C-2 and C-6), 64.08-64.42 (C-1) and 209.59-210.05 ppm (C-4).[12] In addition, the $^{13}$C chemical shift values of 168.56-169.95 and 165.72-170.14 ppm have been assigned to the axial and equatorial carbonyl carbons of carbomethoxy group, respectively. In the case of **3**, $^{13}$C chemical shift values were found at 42.77-43.30 and 43.43-44.09 (C-7 and C-9), 51.68-51.92 (C-6 and C-10), 63.99-64.57 (C-5) and 209.64-210.02 (C-8) ppm. Moreover, $\delta_C$ values at 169.70-170.08 and 169.91-170.34 ppm were assigned to the carbonyl carbons at C-1 and C-4 of isoxazolidinedione moiety.

## EXPERIMENTAL SECTION



All melting points are uncorrected. The elemental analyses were performed by the Regional Sophisticated Instrumentation Centre, Central Drug Research Institute, Lucknow. The IR spectra were measured on Perkin-Elmer Grating Infrared Spectrophotometer as KBr discs. The $^1$H NMR and $^{13}$C NMR spectra were recorded in $CDCl_3$ solution at 500 MHz on GE NMR Omega and Bruker Spectrospin Nuclear Magnetic Resonance Spectrometers operating at 500.080 and 500.135 and 125.745 and 125.759 MHz respectively, using TMS as an internal standard.

**Dimethyl or Diethyl 2,6-Diaryl-4-ketocyclohexane-1,1-dicarboxylates (2). General Procedure.**- To a solution of **1**[3] (0.234 g, 10 mmol) and 10 mmol of dimethyl (0.132 g) or diethyl (0.160 g) malonate in 20 mL of methanol/ethanol in a round bottomed flask was added a catalytic amount of 5% sodium methoxide or ethoxide. The mixture was refluxed for 2 hrs. Upon cooling and overnight refrigeration, the product **2** separated as colorless crystals which were collected and recrystallized from methanol or 2-propanol.

**6,10-Diaryl-2-oxo-3-azaspiro[4,5]decane-1,4,8-triones (3). General Procedure.**- To a mixture of 10 mmol of **2**, hydroxylamine hydrochloride (0.069 g, 10 mmol) and 10 mL of alcohol in a 100 mL round-bottomed flask fitted with a reflux condenser, was added 5 mL of 10% sodium methoxide/ethoxide. The reaction mixture was refluxed for 12-20 hrs. The progress of the reaction was monitored by thin layer chromatography. After completion of the reaction, the mixture was cooled and poured onto crushed ice containing conc. hydrochloric acid. The product (**3**) which separated as solid was recrystallized from methanol or 2-propanol to yield colorless crystals. The purity of all the products was checked by thin layer chromatography.

**Acylation of 3. General Procedure**[5].- A solution of 10 mmol of **3** in 5 mL of pyridine was treated with 10 mmol of benzoyl or benzenesulfonyl chloride (for acetylation, 10 mmol of **3** was taken in a mixture containing 5 mL of glacial acetic acid and 2 mL of acetic anhydride). The reaction mixture

was heated for 2-3 hrs and cooled. The contents were poured onto crushed ice containing conc. hydrochloric acid. The product was collected, washed with water, dried and recrystallized from methanol or ethanol. The purity was checked by thin layer chromatography.

**Nitrosation of 3. General Procedure**[5].- A well cooled solution of 10 mmol of **3** in 8 mL of 2N hydrochloric acid was treated with a cold saturated solution of sodium nitrite. The reaction mixture was cooled in an ice-bath for 1 hr. The solid that separated was collected, washed with water, dried and recrystallized from 95% ethanol.

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