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ARTICLE

Rapid and selective synthesis of spiropyrazolines and pyrazolylphthalides employing Seyferth-Gilbert reagent†

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An unexpected product-selectivity in the reaction of 2-arylideneindane-1,3-dione with dimethyl diazomethylphosphonate leading to the formation of two different types of products is reported. The reaction carried out in acetone in the presence of catalytic amount of cesium fluoride afforded spiropyrazoline phosphonates via 1,3-dipolar cycloaddition reaction, whereas the reaction in methanol yielded an interesting class of pyrazolylphthalides. This strategy provides an efficient alternative method for the construction of pyrazolylphthalides, and moreover, the process is general, works under mild conditions, and exhibits high functional group compatibility.

INTRODUCTION

Dimethyl (diazomethyl)phosphonate (Seyferth-Gilbert reagent, SGR) and its Bestmann-Ohira modification (dimethyl 1-diazo-2-oxopropylphosphonate, BOR) have been extensively employed for the convenient generation of homologated terminal and internal carbon-carbon triple bonds from aldehydes and ketones under ambient reaction conditions.[1,2] Subsequently, the 1,3-dipolar cycloaddition reaction involving diazomethylphosphonate (DAMP) anion, the key intermediate generated from these reagents, and various activated olefins has emerged as an important methodology for the synthesis of phosphonylated pyrazoles.[3] In fact, a variety of activated olefins have been reported to undergo cycloaddition reaction with the Seyferth-Gilbert reagent, and these transformations generally proceed through a pyrazoline intermediate which subsequently undergoes air-oxidation or elimination reaction to afford pyrazole derivatives. Although great progress has been achieved in the synthesis of phosphonylpyrazoles using Seyferth-Gilbert reagent, relatively a few protocols are reported for the synthesis of spiropyrazolines.[4] On the basis of the fact that this reagent has found only limited applications in the synthesis of spiropyrazolines, and inspired by the attractive features of spiropyrazolines,[5,6] we sought to explore further the possibility of employing diazophosphonate for the synthesis of spiropyrazolines. We envisioned that the use of a highly reactive 1,1-diactivated alkene such as 2-arylideneindane-1,3-dione[7] as dipolarophile would provide the spirocyclic skeleton via a formal 1,3-dipolar cycloaddition reaction. The only report on the synthesis of spiropyrazolineindane-1,3-dione relies on the cycloaddition reaction of diazoindane-1,3-dione with vinylphosphonate (Fig. 1a).[8] Herein, we report a highly effective and mild protocol for the synthesis of phosphonylspiropyrazoline derivatives and quite interestingly, further investigations revealed an attractive product selectivity switch on changing the reaction conditions, introducing a new and efficient route to pyrazolylphthalides (Fig. 1b).

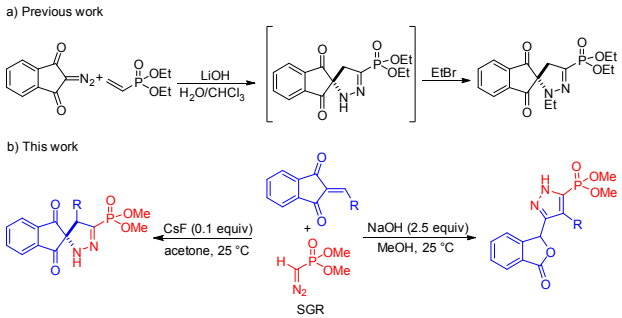

Fig. 1 Selective synthesis of spiropyrazolineindane-1,3-diones and pyrazolylphthalides.

Results and Discussion

We initiated our experiments by subjecting 2-benzylideneindane-1,3-dione **1a** to a stoichiometric amount of Seyferth-Gilbert reagent **2** under reaction conditions similar to those previously reported for the synthesis of pyrazoles. Thus, the reaction carried out by treating

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† Electronic Supplementary Information (ESI) available: Detailed experimental procedures, complete characterization data, CIF for **3k** and **4q** and copies of NMR spectra. See DOI: 10.1039/x0xx00000x

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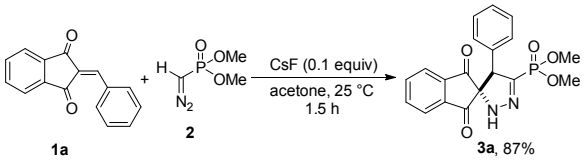
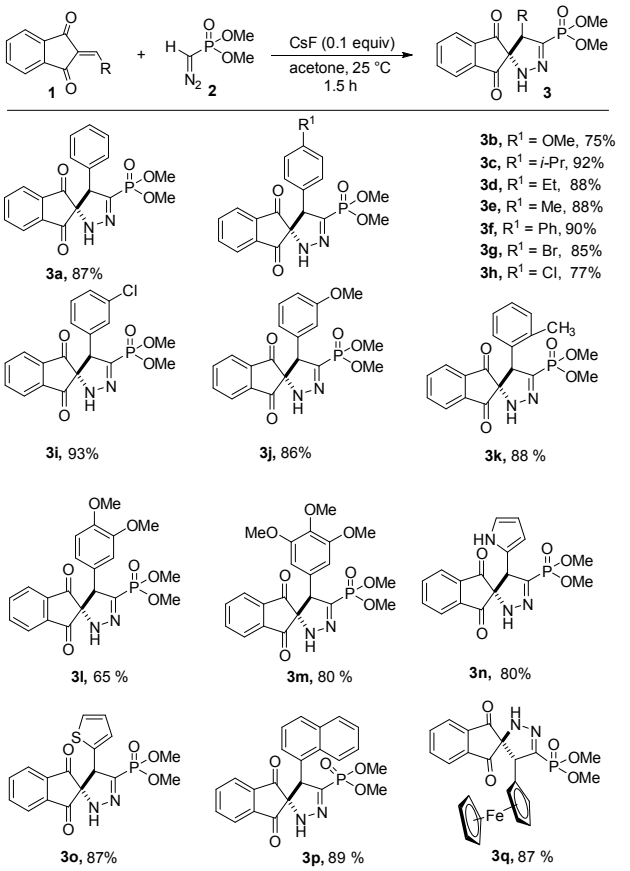
1a with Seyferth-Gilbert reagent **2** in acetonitrile using DBU as a base afforded the spiropyrazolineindane-1,3-dione **3a** in 75% yield (See the SI for details). The reaction was further evaluated under different conditions to improve the efficiency. For instance, the reaction conducted with Et_3N afforded the product in 82% yield. However, the reactions tried using alkoxide bases such as NaOEt and *t*-BuOK were unsuccessful. Upon further reaction optimizations, we found that the spiropyrazoline **3a** could be rendered catalytic by treatment of **1a** with 0.1 equivalent of CsF in acetone in 87% yield (Scheme 1). Our subsequent attempts to use other bases in catalytic amounts gave the product in lower yields.



Scheme 1 Synthesis of spiropyrazolineindane-1,3-diones.

Under the optimized conditions, we next evaluated the scope and limitations of the spiropyrazoline synthesis. It is evident from the data shown in Table 1 that the electronic nature of arylidene moiety has little influence on the efficiency of this reaction. Products from the reactions of substrates bearing electron-withdrawing and electron-donating substituents at 4-position with S-G reagent were obtained in consistently high yields (**3b**–**3h**). Arylideneindane-1,3-diones with chloro and methoxy substituents at *m*-position also participated well in this reaction to deliver the spiropyrazolines in excellent yield (**3i**, **3j**). A methyl substituent at *o*-position was also compatible for the reaction (**3k**) and the structure of the compound **3k** was unequivocally confirmed by X-ray analysis (Fig. 2).[9] Besides, the reactions of di- and trisubstituted substrates also occurred to yield the corresponding spiropyrazoline derivatives (**3l, 3m**). The reactions attempted using heteroarylideneindane-1,3-diones of pyrrole and thiophene were also successful, and the products were obtained in good yields (**3n, 3o**). Notably, the reaction tolerated substrates containing naphthyl and ferrocenyl moiety (**3p, 3q**). The selective formation of spiropyrazoline in this case may be attributed to the lack of nucleophiles in the reaction media.

Table 1 Scope of the spiropyrazoline synthesis: Variation of 2-arylideneindane-1,3-diones[a]



[a]**General conditions: 1 (0.30 mmol), 2 (0.33 mmol), CsF (0.03 mmol), acetone (5.0 mL), 1.5 h. Isolated yield after silica gel column chromatography.**

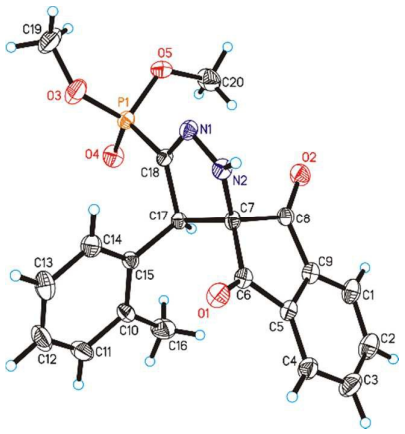


Fig. 2 ORTEP diagram of **3k** drawn with 30% ellipsoid probability.

During the course of reaction optimization for the synthesis of spiropyrazolineindane-1,3-diones, we observed an unusual product selectivity switch when the reaction of **1a** with SGR was carried out in methanol under basic conditions. The reaction proceeded

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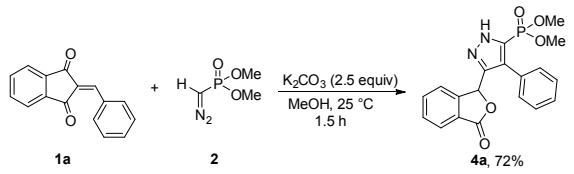
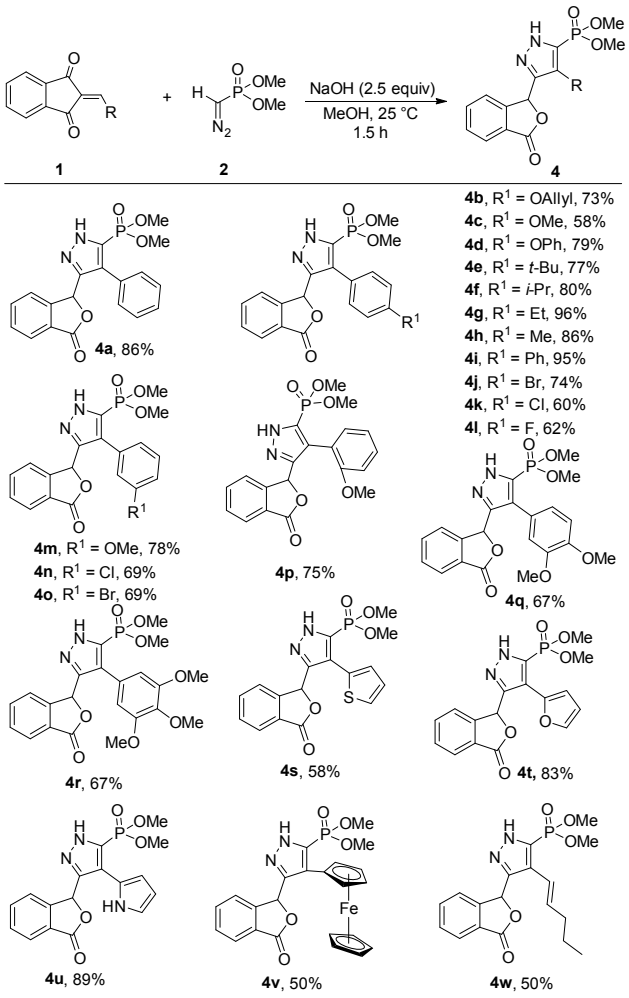
smoothly to afford structurally and biologically relevant phthalide in 72% yield (Scheme 2). Phthalides, an interesting class of compound frequently found in nature, exhibit an exceptionally broad spectrum of biological activities.[10] *n*-Butylphthalide,[11] a marketed antiplatelet drug and Mycophenolic acid[12] are some of the examples of pharmaceutically important phthalide-containing natural products. They also serve as versatile building blocks for the synthesis of polyaryl natural products.[13] As a consequence, the development of novel strategies for the synthesis of C3 substituted phthalides remains an attractive area for chemists.



Scheme 2 Synthesis of 3-Pyrazolylphthalides.

The selective formation of pyrazolylphthalides was particularly interesting, and a brief optimization study carried out using various bases showed that NaOH provided the product in 86% yield (See the SI for details). Subsequently, a range of arylideneindane-1,3-diones was used to evaluate the scope of pyrazolylphthalides synthesis as shown in Table 2. A series of substrates bearing electron-donating and electron-withdrawing substituents at *p*-position of the aryl group was employed for the reaction and the phthalide derivatives were obtained in reasonable to excellent yields (**4b**–**4l**). The reaction was feasible with alkoxy, alkyl, bromo, chloro and fluoro substituted aryilideneindane-1,3-diones. Similar results were observed with *m*-substituted arylidenes affording the products in good yields (**4m**-**4o**). The reactions of *ortho*-, di- and trisubstituted aryilideneindane-1,3-diones also occurred to form the products **4p**–**4r** in reasonable yields. The structure of **4q** was further confirmed by X-ray analysis (Fig. 3).[9] The reaction was compatible with substrates bearing heteroaryl groups such as thiophene, furan, and pyrrole (**4s**–**4u**) and comparably high yields were obtained in all cases. Furthermore, when ferrocene-substituted olefin was subjected to the reaction conditions the desired product was generated, albeit in a lower yield (**4v**). The reaction is not limited to arylidenes, and our attempt using alkylideneindane-1,3-dione, though less efficient, afforded the product **4w** in 50% yield.

Table 2 Scope of 3-pyrazolylphthalide synthesis: Variation of 2-arylideneindane-1,3-diones[a]



[a]**General conditions: 1 (0.30 mmol), 2 (0.45 mmol), NaOH (0.75 mmol), MeOH (5.0 mL), 1.5 h. Isolated yield after silica gel column chromatography**.

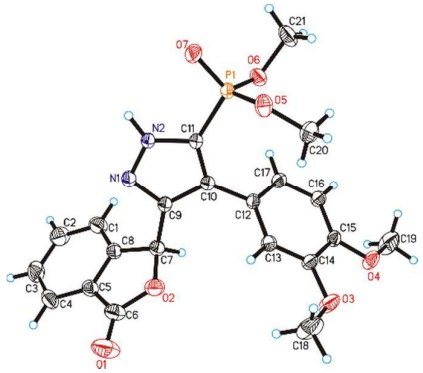


Fig. 3 ORTEP diagram of **4q** drawn with 30% ellipsoid probability.

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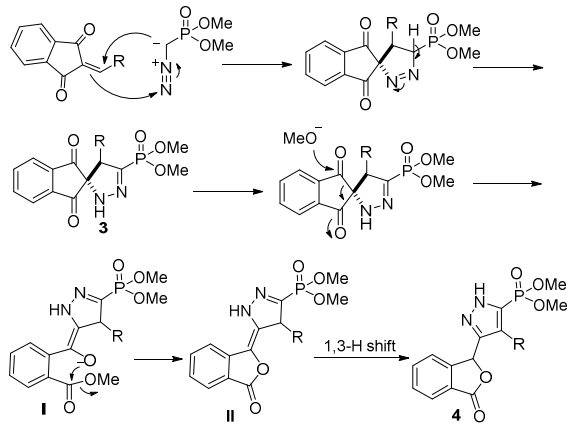
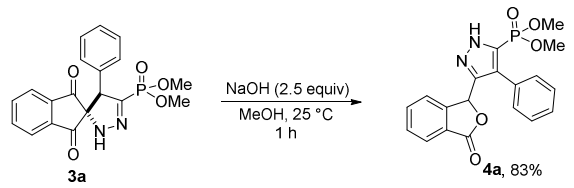
In analogy to the related reactions involving S-G and BOR reagents, the following mechanistic pathway is proposed (Scheme 3). The 1,3-dipolar cycloaddition reaction of dimethyl (diazomethyl)phosphonate (DAMP) anion generated in situ with 2-arylideneindane-1,3-dione would take place first to afford the spiropyrazoline derivative **3**. The formation of phthalide **4** would involve the generation of spiropyrazoline **3.** Subsequently, the nucleophilic attack of methoxide ion at one of the carbonyl moieties would result in the ring opening of the spirocyclic 1,3-dione to afford the enolate intermediate **I**. Intermediate **I** cyclizes to afford the arylidenephthalide derivative **II** which spontaneously generates the pyrazolylphthalides derivative **4** through a 1,3-H shift**.**



Scheme 3 Reaction mechanism.

To get more insight into the mechanism of the phthalide formation, we carried out an experiment subjecting spiropyrazoline **3a** to the reaction conditions used for phthalide synthesis (NaOH, MeOH) and pleasingly, the reaction proceeded smoothly to afford the phthalide derivative **4a** in 83% yield (Scheme 4). This experiment confirms that the formation of phthalides **4** proceeds through the intermediacy of spiropyrazoline **3a** via methanol-induced rearrangement**.**



Scheme 4 Mechanistic studies.

Conclusions

In summary, we have uncovered an efficient protocol for the synthesis of spiropyrazoline phosphonates and pyrazolylphthalides employing the Seyferth-Gilbert reagent. The reaction of 2-arylideneindane-1,3-dione conducted with dimethyl diazomethylphosphonate in acetone gave spiropyrazolineindane-1,3-dione, while the use of basic methanol provided hitherto unknown pyrazolylphthalide derivatives. The strategy was explored for the synthesis of various functionalized spiropyrazolines and pyrazolylphthalides and was found to be tolerant to a wide range of electron-rich, electron-deficient and heterocyclic moieties. Furthermore, the mechanistic studies proved that pyrazolylphthalide is formed by a methanol-mediated rearrangement of spiropyrazoline phosphonates. The mild reaction conditions allowed the incorporation of a wide range of synthetically useful functional groups in the substrates. Further studies on the applications of diazomethylphosphonate in the synthesis of heterocycles are currently underway in our laboratory.

Experimental Section

Unless otherwise specified, all reactions were carried out under air atmosphere in oven dried round-bottom flasks. Dimethyl 2-oxopropylphosphonate and 1,3-Indanedione were purchased from commercial sources and were used without further purification. The reactions were monitored by TLC visualized by UV (254 nm) and/or with iodine. Flash chromatography was performed on 100-200 mesh silica gel using the gradient system ethyl acetate-hexane (0-50%)/Acetone-Dichloromethane (0-30%). NMR data were recorded at Bruker AV 400 MHz in DMSO-d_6/$CDCl_3$ using as internal standards the residual DMSO signal for ^{1}H NMR (δ = 2.50 ppm), $CHCl_3$ (δ = 7.26 ppm) respectively. The corresponding deuterated solvent signal for ^{13}C NMR were assigned as DMSO (δ = 39.51 ppm), $CDCl_3$ (77.16). Coupling constants are given in Hertz (Hz) and the classical abbreviations are used to describe the signal multiplicities. Melting points were measured with a Büchi B-540 apparatus and are uncorrected. High resolution mass spectra were obtained using Q-TOF mass spectrometer. All commercially available reagents were used as received.

General procedure for the synthesis of spiropyrazolines 3

To an oven-dried round bottom flask was added 2-(benzylidene)-1H-indene-1,3(2H)-dione **1a** (50 mg, 0.21 mmol) and dissolved in 3 mL of acetone. Subsequently, a solution of Seyferth Gilbert reagent (33 mg, 0.24 mmol) in 2 mL of acetone was added to the reaction mixture and kept stirring. After addition of cesium fluoride (3.0 mg, 0.021 mmol), the reaction mixture was stirred at 25 °C for 1.5 h. After the completion of reaction, as indicated by TLC, solvent was evaporated off and extracted using ethyl acetate. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified using column chromatography (100-200 mesh silica gel) using acetone/dichloromethane as the eluent to afford the corresponding spiropyrazoline **3a** as a white solid (70 mg) in 87% yield. $\mathbf{R_f}$ (Acetone/Dichloromethane: 1/9) = 0.29. **Mp** 178-180 °C. **^{13}C NMR** (100 MHz, ppm/$CDCl_3$): 197.1 (C), 195.4 (C), 142.6 (d, J_{C-P} = 227.0 Hz, C), 141.6 (C), 140.1 (C), 136.6 (CH), 136.4 (CH), 131.8 (C), 129.5 (CH), 129.5 (CH), 128.7 (CH), 128.5 (CH), 128.5 (CH), 124.1 (CH), 123.5 (CH), 79.1 (d, J_{C-P} = 23.8 Hz, C), 65.3 (d, J_{C-P} = 23.8 Hz, CH), 53.6 (d, J_{C-P} = 5.5 Hz, CH_3), 53.4 (d, J_{C-P} = 5.9 Hz, CH_3). **^{1}H NMR** (400 MHz, ppm/$CDCl_3$): 7.98 (d, *J* = 7.6 Hz, 1H), 7.82 (t, *J* = 7.6 Hz, 1H), 7.73 (t, *J* = 7.4 Hz, 1H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.16-7.15 (m, 3H), 6.93-6.91 (m, 3H), 4.72 (s, 1H), 3.62 (d, *J* = 11.6 Hz, 3H), 3.58 (d, *J* = 11.2 Hz, 3H). **^{31}P NMR** (161.9 MHz, $CDCl_3$): 8.95. **HRMS** for $C_{19}H_{18}N_2O_5P^+$: calcd. $[M+H]^+$: 385.0948, found: 385.0949.

General procedure for the synthesis of pyrazolylphthalides 4

To an oven-dried round bottom flask was added 2-(benzylidene)-1H-indene-1,3(2H)-dione **1a** (50 mg, 0.21 mmol) and dissolved in 3 mL of MeOH. Subsequently, Seyferth Gilbert reagent (48 mg, 0.33 mmol) in 2 mL of MeOH was added to the reaction mixture and kept stirring. After addition of Sodium hydroxide (21.0 mg, 0.53 mmol), the reaction mixture was stirred at 25 °C for 1.5 h. After the completion of reaction, as indicated by TLC, solvent was evaporated off and extracted using ethyl acetate. The organic layer was dried

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over Na_2SO_4 and evaporated under reduced pressure. The residue was purified using column chromatography (100-200 mesh silica gel) using acetone/dichloromethane as the eluent to afford pyrazolylphthalides **4a** as a white solid (69 mg) in 86 % yield. $\mathbf{R_f}$ (Acetone/Dichloromethane: 2/8) = 0.42. **Mp** 162-164 °C. **^{13}C NMR** (100 MHz, ppm/$CDCl_3$): 170.3 (C), 148.1 (C), 146.0 (C), 134.1 (CH), 130.0 (CH), 130.0 (CH), 129.9 (C), 129.3 (CH), 128.5 (C), 128.3 (C), 128.2 (CH), 128.2 (CH), 128.2 (CH), 126.3 (C), 125.4 (CH), 123.1 (CH), 76.0 (CH), 53.4 (CH_3), 53.4 (CH_3). **^{1}H NMR** (400 MHz, ppm/$CDCl_3$): 12.70 (s, 1H), 7.76 (d, *J* = 7.6 Hz, 1H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.33-7.27 (m, 6H), 6.53 (s, 1H), 3.67 (d, *J* = 11.6 Hz, 3H), 3.58 (d, *J* = 11.6 Hz, 3H). **^{31}P NMR** (161.9 MHz, $CDCl_3$): 8.52. **HRMS** for $C_{19}H_{18}N_2O_5P^+$: calcd. $[M+H]^+$: 385.0948, found: 385.0944.

Acknowledgements

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Rapid and selective synthesis of spiropyrazolines and pyrazolylphthalides employing Seyferth-Gilbert reagent

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An efficient protocol for the selective synthesis of spiropyrazoline phosphonates and pyrazolylphthalides employing Seyferth-Gilbert reagent is reported.