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An efficient one pot regioselective synthesis of 3,3'-spiro-phosphonylpyrazole-oxindole framework via base mediated [1,3]-dipolar cycloaddition reaction of Bestmann-Ohira reagent with methyleneindolinones

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A one pot, highly regioselective synthesis of racemic 3,3'-spiro-phosphonylpyrazole-oxindole by 1,3-dipolar cycloaddition of in situ generated anion of dialkyl 1-diazomethylphosphonate from Bestmann-Ohira reagent (BOR) & methyleneindolinones has been developed. The synthesis affords the highly functionalized pyrazole scaffolds in good yields with excellent regioselectivity under mild reaction conditions within a short reaction time.

Introduction

The 3,3'-spiro-oxindoles are valuable structural core present in many natural alkaloids and pharmacological agents. They exhibits interesting structural as well as biological properties.[1] (Fig. 1) Hence, considerable efforts have been devoted to develop new and efficient synthetic strategies to access these important structural motifs.[2] Similarly, organophosphonates also an important structural units posses remarkable biological activities[3,4] and attracts much attention due to their role as metabolic probes,[5] peptide mimetics,[6] pharmacological agents,[7] antibiotic and biomolecules. Very recently, the synthesis of natural and non-natural phosphonate analogues incorporating nucleotides, azaheterocycles and their biological activities have been reviewed.[8,9] Therefore in view of the importance of heterocycles fused with phosphonate groups, it is imperative to have a straightforward access of these versatile building blocks[3,10,11] by developing new synthetic methodologies. Among the various biologically active heterocycles, pyrazoles occupies a central stage due to its wide applications in the pharmaceutical industry, agrochemicals,[12,13], biological agents,[14] and also plays a central role in coordination chemistry.[15] Few pyrazoles such as Withasomnine,[16,17] celecoxib and Viagra exhibits important

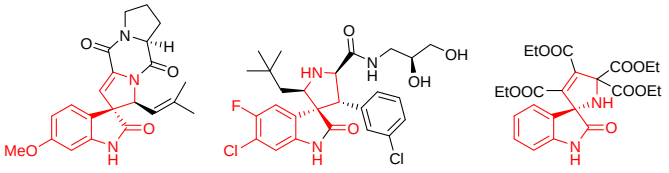

Fig.1 Biologically active compounds containing spiro-oxindole core.

therapeutic potential (Withasomnine: analgesic and CNS depressant; Celecoxib: nonsteroidal antiarthritic drug and Viagra: phosphodiesterase inhibitor). Bestmann-Ohira reagent (BOR) a modified version of Seyferth-Gilbert reagent[18] is well-known for the conversion of aldehydes into terminal alkynes under mild basic conditions. Also, phosphonylated heterocycles,[19,20] can be obtained by 1,3-dipolar cycloaddition reaction of Bestmann-Ohira reagent (BOR) with various dipolarophiles. In recent years, due to their structural complexity and high biological activity several methods for the synthesis of phosphonyl pyrazoles have been reported in the literature using Bestmann-Ohira reagent (BOR) as the cycloaddition partner.[21]

However, base mediated 1,3-dipolar cycloaddition reactions of methyleneindolinones with Bestmann-Ohira reagent has not been documented in the literature. During the course of this study, Peng and co-workers reported the synthesis of chiral spiro-phosphonylpyrazoline-oxindoles using organocatalytic enantioselective 1,3-dipolar cycloadditions between Seyferth-Gilbert reagent and isatylidene malononitriles.[22] Considering the importance of 3,3'-spiro-oxindoles and as part of our ongoing research in the development of new and efficient

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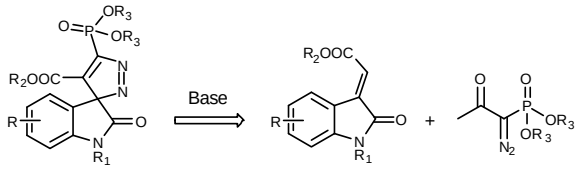
methodologies involving construction of C-C and C-N bond formation reactions,[23] we herein disclose for the first time, one pot construction of 3,3'-spiro-phosphonylpyrazole-oxindole skeleton *via* base mediated 1,3-dipolar cycloaddition reaction between Bestmann-Ohira reagent with substituted methyleneindolinones. To achieve this goal, we envisioned that 3,3'-spiro-phosphonylpyrazole-oxindole core could be constructed by 1,3-dipolar reaction between various substituted methyleneindolinones **1** and Bestmann-Ohira reagent (BOR) **2** in presence of base (Scheme 1).

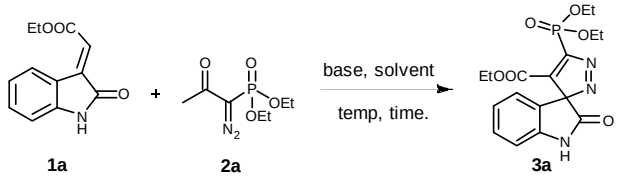


Scheme 1 One pot access to 3, 3'-spiro-phosphonylpyrazole-oxindole.

Results and discussion

To explore the feasibility of this proposed strategy shown in scheme **1**, we commenced our study by choosing methyleneindolinone **1a** and Bestmann-Ohira reagent (BOR) **2a** as model substrates to optimize the reaction conditions in the presence of various bases and solvents at room temperature (Table 1).

Table 1 Optimization of the reaction conditions for the 1,3-dipolar cycloaddition reactions of methyleneindolinone (**1a**) with Bestmann-Ohira reagent (**2a**)[a]

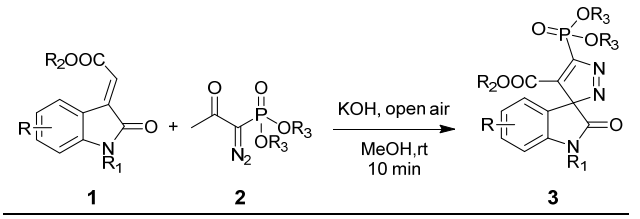


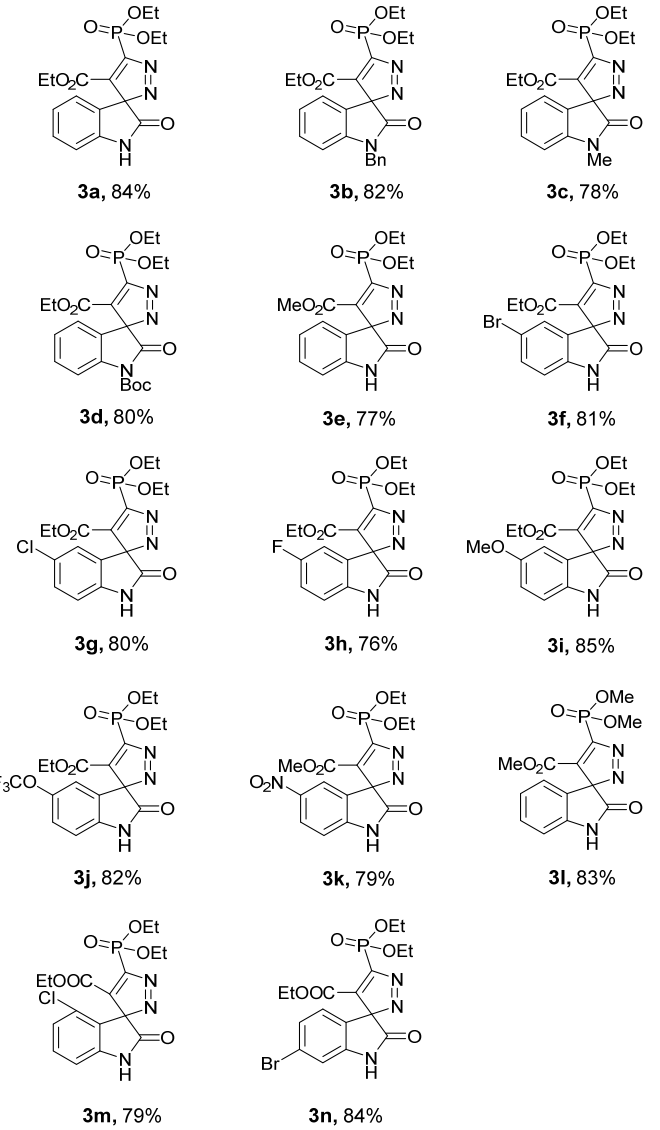
Entry	Base	Solvent	Temp (^oC)	Time	Yield[b] (%)
1	K_2CO_3	MeOH	25	12 h	40
2	-	MeOH	25	24 h	n.r.
3	-	MeOH	reflux	4 days	n.r.
4	NEt_3	MeOH	25	24 h	complex
5	DBU	MeOH	25	24 h	traces
6	NaOMe	MeOH	25	18 h	55
7	**KOH**	**MeOH**	**25**	**10 min**	**80**
8	KOH	EtOH	25	10 min	75
9	KOH	CH_3CN	25	24 h	n.r.
10	KOH	DMSO	25	24 h	n.r.
11	KOH	THF	25	24 h	30
12	NaOEt	EtOH	25	24 h	65

[a]Unless specified All reactions were performed on 0.1 mmol scale using **1a** (0.1 mmol), **2a** (0.2 mmol) and base (0.2 mmol) in anhydrous solvents at room temperature in open air. [b]Isolated yield after silica gel column chromatography.

To our delight, when methyleneindolinone **1a** was treated with Bestmann-Ohira reagent **2a** in the presence of 2.0 equiv. K_2CO_3 in anhydrous MeOH at room temperature in an open air, the desired 3,3'spiro-phosphonylpyrazole-oxindole **3a** was obtained in 40% yield at 25 °C after 12 h (Table 1, entry 1). The reaction was highly regioselective, with the carbon end of the dipole adding to the β-position of the methyleneindolinone **1a**

Table 2 Substrate scope for the 1,3-dipolar cycloaddition reactions between methyleneindolinones (**1**) and Bestmann-Ohira Reagent (**2**)[a]





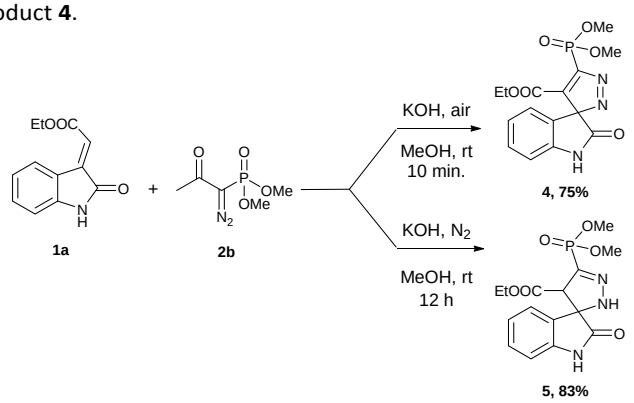
[a]All reactions were performed on 0.1 mmol scale using **1** (0.1 mmol), **2** (0.2 mmol) and KOH (0.2 mmol) in anhydrous MeOH for 10 min at room temperature. Isolated yield after silica gel column chromatography.

which was further confirmed by detailed spectroscopic analysis and X-ray crystallography. Encouraged by these results, we set out to find a compatible base for our 1,3-dipolar cycloaddition reaction. Several organic and inorganic

bases (2.0 equiv.) were screened in protic as well as aprotic solvents to promote cycloaddition reaction between methyleneindolinone **1a** and Bestmann Ohira reagent (BOR) **2a** at room temperature. Among the bases examined, potassium hydroxide (KOH) provided **3a** in the highest yield (80%) as a single regioisomer within a short reaction time (Table 1, entry 7). However, the attempts to use other weak organic bases like triethyl amine, afforded a complex reaction mixture (Table 1, entry 4). The use of the base DBU gives less yield of **3a** (Table 1, entry 5). In the presence of sodium methoxide (NaOMe), **3a** was obtained in moderate yield (Table 1, entry 6). Further attempts to improve the yield of the reaction we focused on the solvent screening. Moreover, solvents other than methanol/ethanol did not affect the 1,3-dipolar reaction even after 24 h (Table 1, entry 9, 10 and 11).

After detailed optimization of reaction condition, we confirmed the requirement of a nucleophilic base and protic solvent for 1, 3-dipolar reaction (Table 1, entry 7). Based on the results obtained, we used MeOH as the ideal solvent and KOH as the suitable base for further studies. With the optimized conditions in hand, the generality and scope of this base mediated 1,3-dipolar cycloaddition reaction was next investigated to see its functional group tolerance. Much to our satisfaction, the reaction demonstrated good compatibility and proved to be a general method to build structurally diverse 3,3'-spiro-phosphonylpyrazole-oxindoles in generally high yields (76-85%) with excellent regioselectivity. First, the influence of N-substituents of the indolinone motif was investigated by using substrates with N-H groups, N-benzyl, N-methyl, N-Boc (Table 2, **entries 3a-3d**), which revealed that both N-protected and N-unprotected methyleneindolinones **1**[24] could successfully take part in the dipolar cycloaddition reaction to afford the spiro-products **3**. As observed, the protecting groups did not affect the yield significantly and all of the corresponding 3,3'-spiro-phosphonylpyrazole-oxindoles were obtained in good yields (Table 2, **entry 3a-3d**, 78-84%). The scope of the substrates was further successfully extended to various halogenated substrates (Table 2, **entry 3f-3h**, **3m** and **3n** 76-84%) which provides the possibility for further functionalization. The results disclosed that the electronic nature and the position of the halogen substituents at C-4, C-5 as well as C-6 of methyleneindolinones **1** were seen to have little influence on the efficiency of this reaction, because all of these substrates uniformly afforded the 3,3'-spiro-phosphonylpyrazole-oxindoles with structural diversity in excellent regioselectivity with good yields. As shown in Table 2, attachment of both electron-donating substituents such as OMe, OCF_3 and electron withdrawing substituents such as NO_2 at the C-5 position on the aromatic ring of methyleneindolinones **1** was well tolerated, with the corresponding products being obtained in good yields with high regioselectivity (Table 2, **entry 3i-3k**, 79-85%). In most of the cases, 3,3'-spiro-phosphonylpyrazole-oxindole could be isolated in good yields after column chromatography.

In order to gain some insight into the mechanistic details of the 1,3-dipolar reaction, the following two experiments were conducted under the optimal conditions: (Scheme 2) (a) When methyleneindolinone **1a** was treated with Bestmann-Ohira reagent **2b** in the presence of potassium hydroxide in open air, within a short reaction time (10 min.) we observed the formation of desired 3,3'-spiro-phosphonylpyrazole-oxindole **4** in good yields (75%). (b) While the same reaction when we carried out in nitrogen atmosphere, even after 12 h we did not observe formation of desired product **4** instead we got unoxidized product **5** in 83% yield. Both these experiments clearly indicate that the transformation of **4** into **5** may need the assistance of air oxygen for further oxidation to get desired product **4**.



Scheme 2 Control experiments to investigate the role of air oxygen.

The structure and regioselectivity of 3,3-'spiro-phosphonylpyrazole-oxindoles were unambiguously determined by X-ray crystallography of **5** (Fig.2).

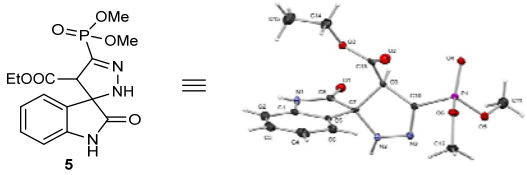
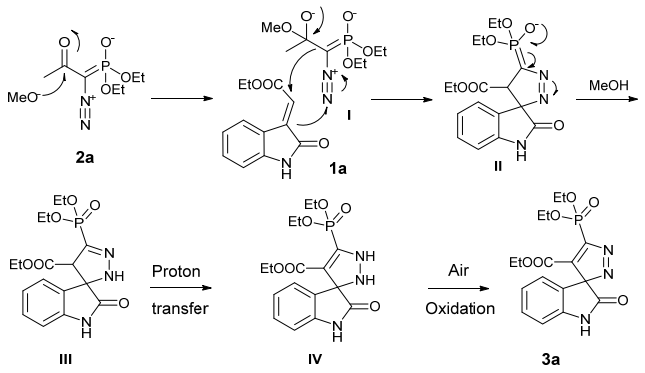


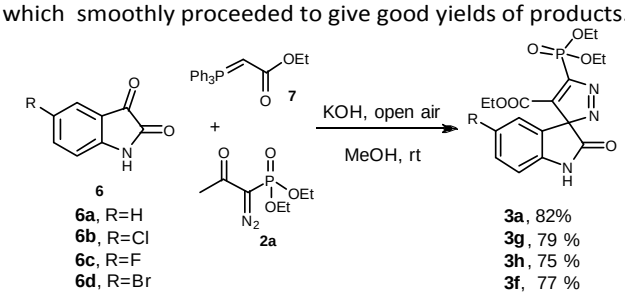
Fig. 2 ORTEP diagram of **5**.

On the basis of the above experimental results, together with the related reports of 1,3-dipolar cycloaddition reaction of Bestmann-Ohira reagent,[18] a plausible mechanism for the formation of 3,3'-spiro-phosphonylpyrazole-oxindoles is illustrated in Scheme 3. The mechanism involves deacylation of Bestmann-Ohira reagent **2a** by the nucleophilic methoxide followed by reaction of the diazo- phosphonate anion arising from I which is well known in the literature [21] with methyleneindolinone **1a** in a 1,3-dipolar fashion to afford the initial cycloadduct II (Scheme 3). Subsequent protonation of intermediate **II** in methanol to form Pyrazoline **III**, followed by proton transfer (tautomerism) gives rise to intermediate **IV**. And finally air oxidation completes the reaction giving final compound **3a**.



Scheme 3 Proposed mechanistic pathway for the formation of 3,3'-spiro-phosphonylpyrazole-oxindoles **3a** from BOR **2a** and methyleneindolinone **1a**.

To demonstrate the application of our present methodology for the efficient synthesis of 3,3'-spiro-phosphonylpyrazole-oxindole, we devised a sequential multicomponent reaction (MCR) strategy as shown in Scheme 4. Based on domino Wittig reaction/1,3-dipolar cycloaddition reaction sequence, we conducted a three-component reaction between readily available isatin **6**, phosphonium ylide **7**, and BOR reagent **2a** which smoothly proceeded to give good yields of products.



Scheme 4 Sequential multicomponent reaction of isatin, phosphonium ylide and Bestmann-Ohira reagent (BOR).

Experimental Section

General information

Solvents were purified and dried by standard procedures before use; petroleum ether of boiling range 60–80 °C was used. Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR were recorded on 200, 400, 500 MHz NMR spectrometers. ^{31}P NMR was recorded on 202.4 MHz NMR spectrometer. HRMS data for new compounds were recorded using Orbitrap mass analyzer associated with Accela 1250 pump. Column chromatography was carried out by using silica gel of the selected particle size of 100-200 mesh or 230-400 mesh. Unless otherwise specified, all reactions were carried out under air atmosphere in oven-dried round-bottom flasks. Dimethyl-2-oxopropylphosphonate and Diethyl-2-oxopropylphosphonate were purchased from commercial sources and used for the synthesis of the Bestmann-Ohira reagent **2**.[26, 27] the reactions were monitored by TLC visualized by UV (254 nm) and/or with iodine. Coupling constants are given in hertz (Hz) and the classical abbreviations are used to describe the signal multiplicities. All commercially available reagents were used as received.

A general experimental procedure for 1,3-dipolar cycloaddition reaction of Bestmann-Ohira reagent 1 with methyleneindolinones 2

To an oven-dried round bottom flask was added methyleneindolinones 1 (0.1 mmol, 1.0 equiv.) dissolved in 3 mL of MeOH. Subsequently, a solution of Bestmann-Ohira reagent 2 (0.2 mmol, 2.0 equiv.) in 2 mL of MeOH was added to the reaction mixture with constant stirring. After the addition of potassium hydroxide (0.2 mmol, 2.0 equiv.), the reaction mixture was stirred at 25 °C for 10 min. The solvent was evaporated and the crude reaction mixture was extracted using ethyl acetate. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was then purified using column chromatography (100–200 mesh silica gel) using pet ether-ethyl acetate as the eluent.

A general experimental procedure for sequential multicomponent reaction of isatin 6, phosphonium ylide 7, and BOR reagent 2a

To a solution of the corresponding substituted isatin **6** (5 mmol, 1equiv.) in methanol (30 mL) was added phosphonium ylide **7** (5 mmol, 1.1 equiv) and the mixture was stirred at room temperature for 12 h. Then a solution of Bestmann-Ohira reagent **2a** in 2 ml of MeOH was added to the reaction mixture. After the completion of reaction, as indicated by TLC, the solvent was evaporated and the crude reaction mixture was 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 pet ether-ethyl acetate as the eluent.

Ethyl 5'-(diethoxyphosphoryl)-2-oxospiro[indoline-3,3'-pyrazole]-4'-carboxylate (3a)

Yield: 84%; White solid; mp: 120-122 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.36-1.39 (m, 6H), 1.46 (t, *J* = 7.6 Hz, 3H), 4.28- 4.34 (m, 4H), 4.45 (q, *J* = 7.6 Hz, 1H), 7.19-7.21 (m, 1H), 7.46 (m, 2H), 8.76-8.77 (m, 1H), 11.4 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.6, 16.9 (d, J_{C-P} = 6.4 Hz), 17.0 (d, J_{C-P} = 6.4 Hz), 62.6, 64.3 (d, J_{C-P} = 5.9 Hz), 64.4 (d, J_{C-P} = 5.9 Hz), 112.3, 117.1, 124.5, 127.2, 132.5, 135.5, 145.1, 150.4, 163.3; ^{31}P NMR (202.4 MHz, $CDCl_3$) δ: 6.59; HRMS (ESI) calcd for $C_{17}H_{20}N_3O_6NaP$ $[M+Na]^+$ 416.0982; found 416.0979.

Ethyl 1-benzyl-5'-(diethoxyphosphoryl)-2-oxospiro[indoline-3,3'-pyrazole]-4'-carboxylate (3b)

Yield: 82%; White solid; mp: 168-170 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.41-1.51 (m, 9H), 4.29-4.37 (m, 4H), 4.48 (q, *J* = 7.5 Hz, 2H), 5.59 (s, 2H), 7.28-7.36 (m, 2H), 7.48-7.53 (m, 1H), 9.01- 9.03 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.3, 15.6 (d, J_{C-P} = 6.6 Hz), 15.8 (d, J_{C-P} = 6.6 Hz),, 47.5, 61.5, 63.0 (d, J_{C-P} = 6.0 Hz), 63.1(d, J_{C-P} = 6.0 Hz), 112.1, 114.9, 123.5, 125.9, 127.1 (d, J_{C-P} = 12.5 Hz), 127.3 (d, J_{C-P} = 12.5 Hz), 128.4, 131.5, 134.1, 135.0, 144.5, 162.2; ^{31}P NMR (202.4 MHz, $CDCl_3$) δ: 6.12; HRMS (ESI) calcd for $C_{24}H_{26}N_3O_6NaP$ $[M+Na]^+$ 506.1451; found 506.1451.

Ethyl 5'-(diethoxyphosphoryl)-1-methyl-2-oxospiro [indoline-3,3'-pyrazole]-4'-carboxylate (3c)

Yield: 78%; White solid; mp: 210-212 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.40-1.53 (m, 9H), 3.84 (s, 3H), 3.92- 4.40 (m, 6H), 7.59-7.67 (m, 1H), 8.94- 8.98 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.8, 16.1(d, J_{C-}

$_P$ = 6.4 Hz), 16.3 (d, J_{C-P} = 6.4 Hz), 31.4, 61.8, 63.3 (d, J_{C-P} = 6.1 Hz), 63.4 (d, J_{C-P} = 6.1 Hz), 112.3, 113.7, 114.4, 123.8, 127.3, 132.0, 136.1, 140.3, 144.4, 150.1, 162.6; ^{31}P NMR (202.4 MHz, $CDCl_3$) δ: 6.17; HRMS (ESI) calcd for $C_{18}H_{22}N_3O_6NaP$ $[M+Na]^+$ 430.1138; found 430.1137.

1-(tert-butyl)4'-ethyl 5'-(diethoxyphosphoryl)-2-oxospiro[indoline-3,3'-pyrazole]-1,4'-dicarboxylate (3d)

Yield: 80%; White solid; mp: 155-157 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.17 (t, *J* = 7.6 Hz, 3H), 1.32-1.41 (m, 6H), 1.46 (s, 9H), 4.18- 4.35 (m, 6H), 7.05-7.09 (m, 1H), 7.30-7.40 (m, 1H), 7.55-7.67 (m, 1H), 7.99-8.01 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.8, 16.32 (d, J_{C-P} = 6.6 Hz), 16.39 (d, J_{C-P} = 6.6 Hz), 28.3, 61.0, 63.7 (d, J_{C-P} = 6.0 Hz), 63.8 (d, J_{C-P} = 6.0 Hz), 80.4, 122.8, 128.3, 130.0, 130.9, 136.7, 153.2, 162.3; ^{31}P NMR (202.4 MHz, $CDCl_3$) δ: 5.03; HRMS (ESI) calcd for $C_{22}H_{28}N_3O_8NaP$ $[M+Na]^+$ 516.1512; found 516.1515.

Methyl 5'-(diethoxyphosphoryl)-2-oxospiro [indoline-3,3'-pyrazole]-4'-carboxylate (3e)

Yield: 77%; Yellow orange powder; mp: 178-180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.34-1.42 (m, 6H), 4.0 (s, 3H), 4.28-4.35 (m, 4H), 7.36-7.43 (m, 2H), 7.50-7.56 (m, 1H), 8.78-8.85 (m, 1H), 11.0 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.3 (d, J_{C-P} = 6.9 Hz), 16.4 (d, J_{C-P} = 6.9 Hz), 52.5, 63.82 (d, J_{C-P} = 6.4 Hz), 63.87 (d, J_{C-P} = 6.4 Hz), 117.7, 116.3, 124.2, 126.8, 132.1, 134.6, 144.5, 163.0; ^{31}P NMR (202.4 MHz, $CDCl_3$) δ: 6.26; HRMS (ESI) calcd for $C_{16}H_{18}N_3O_6NaP$ $[M+Na]^+$ 402.0825; found 402.0846.

Ethyl 5-bromo-5'-(diethoxyphosphoryl)-2-oxospiro[indoline-3,3'-pyrazole]-4'-carboxylate (3f)

Yield: 81%; White solid; mp: 175-177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.35-1.50 (m, 9H), 4.29-4.33 (m, 4H), 4.46-4.50 (q, *J* = 7.2 Hz, 2H), 7.39-7.55 (m, 2H), 9.00-9.03 (m, 1H), 11.6 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0, 16.34 (d, J_{C-P} = 5.4 Hz), 16.39 (d, J_{C-P} = 5.4 Hz), 62.1, 63.80 (d, J_{C-P} = 6.1 Hz), 63.85 (d, J_{C-P} = 6.1 Hz), 113.1, 116.6, 118.2, 129.2, 131.9, 134.1 (d, J_{C-P} = 16.4 Hz), 134.8 (d, J_{C-P} = 16.4 Hz), 140.8, 143.9, 148.7, 162.2; ^{31}P NMR (202.4 MHz, $CDCl_3$) δ: 6.52; HRMS (ESI) calcd for $C_{17}H_{20}N_3O_6BrP$ $[M+H]^+$ 472.0268; found 472.0265.

Ethyl 5-chloro-5'-(diethoxyphosphoryl)-2-oxospiro[indoline-3,3'-pyrazole]-4'-carboxylate (3g)

Yield: 80%; White solid; mp: 190-192 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.35-1.50 (m, 9H), 4.27-4.33 (m, 4H), 4.45-4.50 (q, *J* = 7.2 Hz, 2H), 7.37-7.47 (m, 2H), 8.86 (d, *J* = 2.0 Hz ,1H), 11.6 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0, 16.32 (d, J_{C-P} = 6.4 Hz), 16.38 (d, J_{C-P} = 6.4 Hz), 62.0, 63.83 (d, J_{C-P} = 5.7 Hz), 63.89 (d, J_{C-P} = 5.7 Hz), 112.7, 118.0, 126.2, 129.2, 132.0 (d, J_{C-P} = 22.6 Hz), 133.7 (d, J_{C-P} = 22.6 Hz), 140.9, 143.7, 146.5, 148.8, 162.2; ^{31}P NMR (202.4 MHz, $CDCl_3$) δ: 6.45; HRMS (ESI) calcd for $C_{17}H_{20}N_3O_6ClP$ $[M+H]^+$ 428.0775; found 428.0773.

Ethyl 5'-(diethoxyphosphoryl)-5-fluoro-2-oxospiro[indoline-3,3'-pyrazole]-4'-carboxylate (3h)

Yield: 76%; White solid; mp: 194-196 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.35-1.49 (m, 9H), 4.29-4.33 (m, 4H), 4.44- 4.50 (q, *J* = 7.0 Hz, 2H), 7.19-7.23 (m, 1H), 7.49-7.52 (m, 1H), 8.60-8.63 (m, 1H), 11.6 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0, 16.30 (d, J_{C-P} = 6.1 Hz), 16.37 (d, J_{C-P} = 6.1 Hz), 62.0, 63.7 (d, J_{C-P} = 6.5 Hz), 63.8 (d, J_{C-P} = 6.5 Hz), 112.6, 118.3, 120.0, 131.6, 141.4, 143.9, 146.2, 148.8, 157.2, 159.6, 162.3; ^{31}P NMR (202.4 MHz, $CDCl_3$) δ: 5.50; HRMS (ESI) calcd for $C_{17}H_{20}N_3O_6FP$ $[M+H]^+$ 412.1068; found 412.1065.

Ethyl 5'-(diethoxyphosphoryl)-5-methoxy-2-oxospiro[indoline-3,3'-pyrazole]-4'-carboxylate (3i)

Yield: 85%; White solid; mp: 212-214 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.37-1.49 (m, 9H), 3.84 (s, 3H), 4.29- 4.48 (m, 6H), 7.03 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 8.48 (s, 1H),11.1 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.0, 14.3, 16.4, 55.6, 61.9, 63.7 (d, J_{C-P} = 6.4 Hz), 63.8 (d, J_{C-P} = 6.4 Hz), 108.7, 112.4, 114.0, 114.2, 117.6, 121.1, 128.7, 142.3, 144.3, 156.0, 162.6; ^{31}P NMR (202.4 MHz, $CDCl_3$) δ: 6.52; HRMS (ESI) calcd for $C_{18}H_{22}N_3O_7PNa$ $[M+Na]^+$ 446.1088; found 446.1106.

Ethyl5'(diethoxyphosphoryl)2oxo5(trifluoromethoxy)spiro[indoline-3,3'-pyrazole]-4'-carboxylate (3j)

Yield: 82%; White solid; mp: 164-166 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.37-1.49 (m, 9H), 3.84 (s, 3H), 4.29-4.48 (m, 6H), 7.03 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 8.48 (s, 1H),11.1 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0, 16.4 (d, J_{C-P} = 6.6 Hz), 16.5 (d, J_{C-P} = 6.6 Hz), 62.1 (d, J_{C-P} = 5.8 Hz), 62.2 (d, J_{C-P} = 5.8 Hz), 64.3, 112.6, 117.8, 118.4, 118.9, 119.3 (d, J_{C-P} = 25.4 Hz), 119.5 (d, J_{C-P} = 25.4 Hz), 121.8, 125.3, 144.9, 153.3, 162.0; ^{31}P NMR (202.4 MHz, $CDCl_3$) δ: 6.54; HRMS (ESI) calcd for $C_{18}H_{19}N_3O_7F_3PNa$ $[M+Na]^+$ 500.0805; found 500.0824.

Ethyl 5'-(diethoxyphosphoryl)-5-nitro-2-oxospiro[indoline-3,3'-pyrazole]-4'-carboxylate (3k)

Yield: 79%; Brown solid; mp: 185-187 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.32-1.44 (m, 9H), 3.87 (q, *J* = 7.2 Hz, 2H), 4.13 (m, 4H), 7.68 (s, 1H), 8.02 (d, *J* = 2.0 Hz, 1H), 8.16 (dd, *J* = 2.0, 7.2 Hz, 1H), 9.91 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.7, 16.3 (d, J_{C-P} = 6.5 Hz), 16.4 (d, J_{C-P} = 6.5 Hz), 61.9, 63.4 (d, J_{C-P} = 5.7 Hz), 63.6 (d, J_{C-P} = 5.7 Hz), 111.0, 121.1, 137.1, 139.5, 143.2, 148.1, 165.9, 177.6; ^{31}P NMR (202.4 MHz, $CDCl_3$) δ: 6.27; HRMS (ESI) calcd for $C_{17}H_{19}N_4O_8PNa$ $[M+Na]^+$ 461.0838; found 461.0842.

Methyl 5'-(dimethoxyphosphoryl)-2-oxospiro[indoline-3,3'pyrazole]-4'-carboxylate (3l)

Yield: 83%; White solid; mp: 202-204 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.93 (s, 3H), 3.99 (s, 3H), 4.04 (s, 3H), 7.30-7.37 (m, 1H), 7.41-7.60 (m, 2H), 8.85 (d, *J* = 7.2 Hz, 1H), 11.1 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 52.5, 54.13 (d, J_{C-P} = 5.0 Hz), 54.17 (d, J_{C-P} = 5.0 Hz), 111.8, 114.2, 116.3, 124.2, 127.0, 132.1, 134.8, 142.4, 144.5, 146.5, 162.8; ^{31}P NMR (202.4 MHz, $CDCl_3$) δ: 6.01; HRMS (ESI) calcd for $C_{14}H_{14}N_3O_6PNa$ $[M+Na]^+$ 374.0512; found 374.0893.

Ethyl 4-chloro-5'-(diethoxyphosphoryl)-2-oxospiro[indoline-3,3'-pyrazole]-4'-carboxylate (3m)

Yield: 79%; White solid; mp: 180-182 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.34-1.52 (m, 9H), 4.24- 4.55 (m, 6H), 7.39-7.63 (m, 3H), 11.4 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.9, 16.2 (d, J_{C-P} = 6.2 Hz), 16.3 (d, J_{C-P} = 6.2 Hz), 62.0, 63.7 (d, J_{C-P} = 5.2 Hz), 63.8 (d, J_{C-P} = 5.2 Hz), 112.5, 112.6, 112.8, 114.4 (d, J_{C-P} = 28.2 Hz) , 114.6 (d, J_{C-P} = 28.2 Hz), 118.2, 119.7, 120.0, 131.6, 141.3, 143.8, 146.5, 148.7, 157.1, 159.5, 162.2; ^{31}P NMR (202.4 MHz, $CDCl_3$) δ: 5.50; HRMS (ESI) calcd for $C_{17}H_{20}N_3O_6ClP$ $[M+H]^+$ 428.0775; found 428.0774.

Ethyl 6-bromo-5'-(diethoxyphosphoryl)-2-oxospiro[indoline-3,3'-pyrazole]-4'-carboxylate (3n)

Yield: 84%; White solid; mp: 168-170 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.36-1.54 (m, 9H), 4.25-4.57 (m, 6H), 7.41-7.74 (m, 2H), 8.99 (d, *J* = 8.0 Hz, 1H), 10.5 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.6, 15.9 (d, J_{C-P} = 6.3 Hz), 16.0 (d, J_{C-P} = 6.3 Hz), 61.7, 63.4 (d, J_{C-P} = 5.3 Hz), 63.5 (d, J_{C-P} = 5.3 Hz), 112.2, 112.3, 112.5, 114.1 (d, J_{C-P} = 22.5 Hz), 114.3 (d, J_{C-P} = 22.5 Hz), 117.9, 119.5, 119.7, 131.3, 141.0, 143.6, 146.2, 148.4, 156.8, 159.3, 161.9; ^{31}P NMR (202.4 MHz, $CDCl_3$) δ: 6.26; HRMS (ESI) calcd for $C_{17}H_{20}N_3O_6BrP$ $[M+H]^+$ 472.0268; found 472.0266.

Conclusion

In summary, we have developed a simple one pot highly efficient and completely regioselective synthesis of 3,3'-spiro-phosphonylpyrazole-oxindoles in good yields via base mediated 1,3-dipolar cycloaddition reaction between methyleneindolinones and Bestmann-Ohira reagent. Attractive features of this process are 1) its versatility, mild reaction condition, short reaction time, high yield and the efficiency in creating a complex core in a single operation. 2) Provides an efficient access to series of biologically important 3,3'-spiro-phosphonylpyrazole-oxindole in good yield with excellent regioselectivity. The scope of the reaction was expanded with the development of multicomponent reaction sequence in single step. This methodology is fascinating because it provides a quick and easy access to libraries of molecules of pharmaceutical interests under mild reaction condition.

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