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# Convenient Synthesis of Triphenylphosphanylidene Spiro[cyclopentane-1,3′-indolines] and Spiro[cyclopent[2]ene-1,3′-indolines] via Three-Component Reactions

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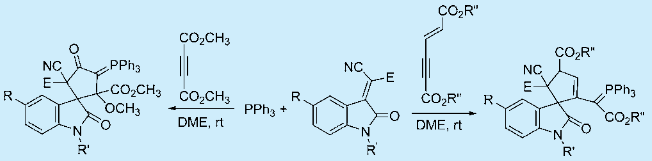
*Supporting Information*

**ABSTRACT:** Three-component reactions of triphenylphosphine, but-2-ynedioate, and isatylidene malononitrile (ethyl cyanoacetate) in dimethoxyethane resulted in triphenylphosphanylidene spiro[cyclopentane-1,3′-indolines] in satisfactory yields. Furthermore, similar three-component reactions of triphenylphosphine, hex-2-en-4-ynedioate, and isatylidene malononitrile (ethyl cyanoacetate) afforded functionalized spiro[cyclopent[2]ene-1,3′-indolines] in good yields.

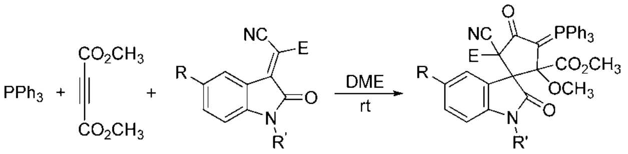


Over the past decade, nucleophilic phosphine catalyzed reactions have attracted much research effort and have emerged as highly efficient synthetic tools for diverse carbocycles and heterocycles.[1,2] In these phosphine catalyzed reactions, *in situ* generated phosphorus ylides from the addition of triphenylphosphine to electron-deficient alkenes or alkynes are key reactive 1,3-dipoles, which can be captured by suitable substrates to undergo a wide variety of cyclizations and annulations to give versatile carbocyclic and heterocyclic systems. Among these transformations, the electron-deficient alkynoates[3,4] and allenonates[5,6] are the most common substrates. In recent years, Morrita−Baylis−Hillman (MBH) acetates and carbonates have also been widely used as complementary and versatile substrates in phosphine catalyzed reactions.[7,8] Particularly, there have been increasing interest in the applications of phosphine catalyzed cyclization reactions for the construction of biologically active spiro-cyclopentane-oxindole and spiro-cyclohexane-oxindole systems.[9,10] Rammchary and co-workers described phosphine catalyzed Tomiat Zipper cyclization of methyleneoxindoles with but-3-yn-2-one for the synthesis of spiro[cyclopentane-1,3′oxindoles].[11] Marinetti and coworkers successfully developed phosphine catalyzed [3 + 2] and [4 + 2] cyclizations between allenoates and isatin-derived olefins to efficiently access spiranic oxindoles.[12] Several phosphine catalyzed diastereo- and enatioselective syntheses of spiro-cyclopentene-oxindoles via annulations of isatin-derived electron-deficient alkenes with MBH adducts have also been disclosed.[13] Against this background and with the aim of expanding our previous studies on providing multicomponent reactions for the convenient synthesis of spirooxindoles,[14,15] herein we wish to report the facile construction of triphenylphosphanylidene substituted spiro[cyclopentane-1,3′-indolines] and spiro[cyclopent[2]ene-1,3′-indolines] from three-component reactions of triphenylphosphine, electron-deficient alkynes, and isatylidene derivatives.

In a preliminary reaction, the reaction of DMAD and isatylidene malononitrile with 20 mol % of triphenylphosphine as the catalyst was used as standard substrates to optimize the reaction conditions. The reaction can be accomplished quickly at room temperature to afford a triphenylphosphanylidene spiro[cyclopentane-1,3′-indoline]. The triphenylphosphanylidene group could not be eliminated by carriying out the reaction for a longer time or at the elevated temperature. Thus, a stoichiometry reaction was further investigated. When equivomolecular triphosphine was introduced in the reaction at room temperature, a violent reaction was observed, which resulted in the expected spiro[cyclopentane-1,3′-indoline] with significantly more byproducts. It is better to add triphenylphosphine to the mixture of dimethyl acetylenedicarboxylate and isatylidene malononitrile in DME at 0 °C. Then, the reaction mixture was carried out at room temperature for about 2 h. Under these simple conditions, the functionalized triphenylphosphanylidene spiro[cyclopentane-1,3′-indoline] **1a** was obtained in 86% yield. Various isatylidene malononitriles were used in the reaction, and the corresponding spiro[cyclopentane-1,3′-indoline] **1b−1f** were produced in satisfactory yields (Table 1, entries 2−6). The substituents on the oxindole moiety showed marginal effect on the reactions. Under similar reaction conditions, the three-component reaction containing ethyl isatylidene cyanoacetate also afforded the corresponding spiro compounds **1g−1i** in good yields. The structures of the obtained spiro[cyclopentane-1,3′-indolines] **1a−1i** were fully characterized by IR, HRMS, $^1$H, and $^{13}$C NMR spectra and were confirmed by X-ray determination of single crystal structures of compounds **1b** (Figure 1) and **1d**. It should be pointed out that several diastereoisomers can exist in each sample of product due to two or three diastereoisomeric carbon centers existing in the newly formed cyclopentyl ring of spiro[cyclopentane-1,3′-indolines] **1a−1i**. It can be seen that

**Received:** March 20, 2014
**Published:** April 18, 2014

**Table 1. Three-Component Reaction for Spiro[cyclopentane-1,3′-indolines] 1a−1i**[a]



| entry | compd | E | R | R′ | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | **1a** | CN | H | $CH_2C_6H_5$ | 86 |
| 2 | **1b** | CN | F | $CH_2C_6H_5$ | 86 |
| 3 | **1c** | CN | Cl | $CH_2C_6H_5$ | 88 |
| 4 | **1d** | CN | H | *n*-$C_4H_9$ | 81 |
| 5 | **1e** | CN | F | *n*-$C_4H_9$ | 83 |
| 6 | **1f** | CN | Cl | *n*-$C_4H_9$ | 86 |
| 7 | **1g** | $CO_2Et$ | F | $CH_2C_6H_5$ | 65 |
| 8 | **1h** | $CO_2Et$ | F | *n*-$C_4H_9$ | 62 |
| 9 | **1i** | $CO_2Et$ | Cl | *n*-$C_4H_9$ | 61 |

[a]Reaction conditions: DMAD (1.2 mmol), isatylidene malononitrile (ethyl cyanoacetate, 1.0 mmol), $PPh_3$ (1.0 mmol) in DME (10.0 mL), 0 °C−rt, 2 h. [b]Isolated yields.

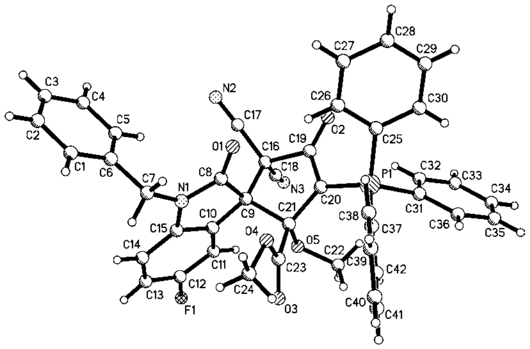
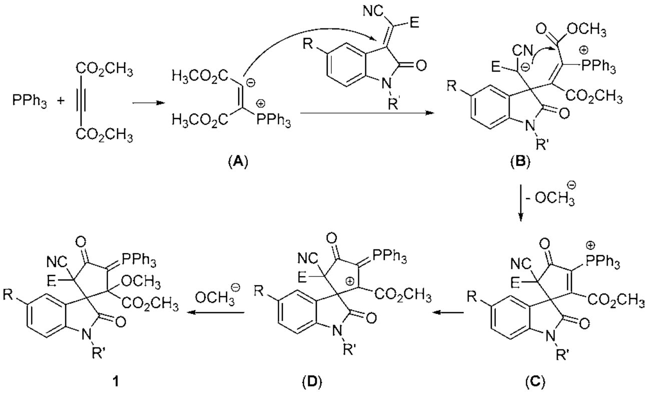


**Figure 1.** Molecular structure of spiro compound **1b**.

there are no protons directly connected to the newly formed cyclopentyl ring, which would result in very small differences of the $^1H$ NMR signs for the different diastereoisomers. In fact the $^1H$ NMR spectra of spiro compounds **1a**−**1i** clearly display one set of absorption signs for the characterized groups in the molecules. The molecular structures of **1b** and **1d** indicated that the methoxy and phenyl groups of the oxindole moiety exist in a *cis*-configuration in the newly formed cyclopentyl ring. Thus, we can conclude that the prepared spiro compounds **1a**−**1i** all have this configuration and this three-component reaction is a highly diastereoselective reaction.

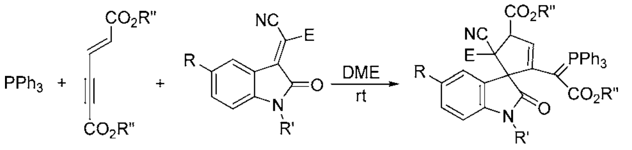
In order to explain the formation mechanism of the spiro[cyclopentane-1,3′-indolines] **1a**−**1i**, a domino reaction path is proposed in Scheme 1 based on the known 1,4-dipolar addition reactions of triphenylphosphine with electron-deficient alkynes.[3,4,11] The first reaction is the formation of the 1,3-dipolar intermediate (**A**) from the addition of triphenylphosphine to acetylenedicarboxylate. The second reaction is the addition of the 1,3-dipole (**A**) to isatinylidene malononitrile resulting in an adduct intermediate (**B**). Third, the intramolecular nucleophilic substitution of the carbanion to alkoxide in the ester affords the cyclic intermediate (**C**). Then, a carbonium (**D**) was formed by the 1,3-arrangement of the triphenylphosphanyl cation in cyclic intermediate **C**. Finally, the coupling of carbonium **D** with the methoxide in solution produces triphenylphosphanylidene spiro[cyclopentyl-1,3′-indoline] **1** as the separated product.

**Scheme 1. Formation Mechanism of Spiro[cyclopentane-1,3′-indolines]**



The scope and limitation of this three-component reaction were explored by using other electron-deficient alkynes in the reaction. Under similar reaction conditions, another widely used electron-deficient alkyne, methyl propiolate, cannot yield any separated product in the three-component reaction. It is known that methyl propiolate can easily dimerize to give dimethyl hex-2-en-4-ynedioate in the presence of DABCO.[16] Thus, the three-component reactions containing dialkyl hex-2-en-4-ynedioate, triphenylphosphine, and isatylidene malononitrile (ethyl cyanoacetate) were investigated. After workup, the functionalized spiro[cyclopent[2]ene-1,3′-indolines] **2a**−**2k** were produced in good yields. The results are summarized in Table 2. The structures of the spiro compounds **2a**−**2k** were established using spectroscopic methods. The single crystal structure of **2g** was also determined by the X-ray diffraction method (Figure 2). The most unusual feature of the structure of spiro[cyclopent[2]ene-1,3′-indolines] **2a**−**2k** to that of spiro[cyclopentane-1,3′-indolines] **1a**−**1i** is the fact that the triphenylphosphanylidene group did not connect to the

**Table 2. Synthesis of Spiro[cyclopent[2]ene-1,3′-indolines] 2a−2k from Three-Component Reaction**[a]



| entry | compd | E | R | R′ | R″ | yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | **2a** | CN | H | $CH_2C_6H_5$ | $CH_3$ | 80 |
| 2 | **2b** | CN | $CH_3$ | $CH_2C_6H_5$ | $CH_3$ | 75 |
| 3 | **2c** | CN | F | $CH_2C_6H_5$ | $CH_3$ | 80 |
| 4 | **2d** | CN | Cl | $CH_2C_6H_5$ | $CH_3$ | 77 |
| 5 | **2e** | CN | Cl | *n*-$C_4H_9$ | $CH_3$ | 77 |
| 6 | **2f** | $CO_2Et$ | H | $CH_2C_6H_5$ | $CH_3$ | 67 |
| 7 | **2g** | $CO_2Et$ | F | $CH_2C_6H_5$ | $CH_3$ | 65 |
| 8 | **2h** | $CO_2Et$ | F | *n*-$C_4H_9$ | $CH_3$ | 68 |
| 9 | **2i** | $CO_2Et$ | Cl | *n*-$C_4H_9$ | $CH_3$ | 65 |
| 10 | **2j** | CN | H | $CH_2C_6H_5$ | $CH_2CH_3$ | 64 |
| 11 | **2k** | CN | F | $CH_2C_6H_5$ | $CH_2CH_3$ | 66 |

[a]Reaction conditions: dialkyl hex-2-en-4-ynedioate (1.2 mmol), isatylidene malononitrile (ethyl cyanoacetate, 1.0 mmol), $PPh_3$ (1.0 mmol) in DME (10.0 mL), 0 °C−rt, 2 h. [b]Isolated yields.

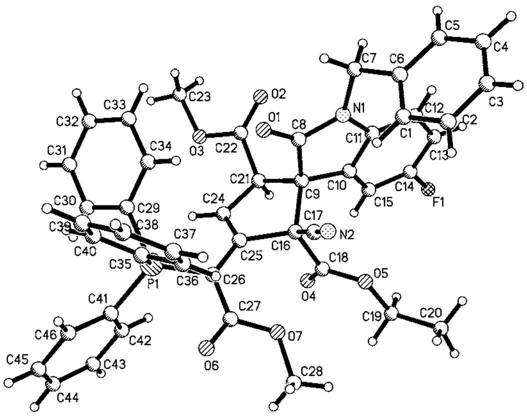
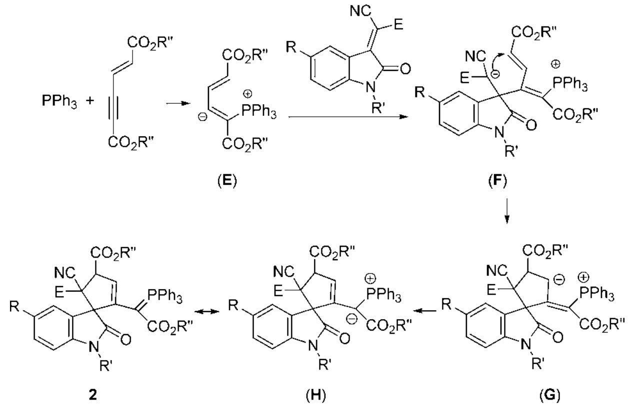


**Figure 2.** Molecular structure of spiro compound **2g**.

cyclopentyl ring, while connecting to the open acetyl chain in the molecule.

An adjusted reaction mechanism for the formation of spiro[cyclopent[2]ene-1,3′-indolines] is proposed in Scheme 2 on the basis of reported reactions.[17] At first, the addition of triphenylphosphine to hex-2-en-4-ynedioate gives intermediate **E**. Second, the addition of a 1,3-dipolar zwitterionate (**E**) to isatinylidene malononitrile produces adduct **F**. Third, the intramolecular Michael addition of the carbanion to the 1,3-diene bearing a stronger electron-withdrawing triphenylphosphanyl cation in adduct **F** affords a cyclized intermediate (**G**), which in turn transfers to a phosphorus ylide intermediate (**H**) by allylic arrangement of the carbanion. Finally, the phosphorus ylide transfers to the triphenylphosphanylidene spiro[cyclopent[2]ene-1,3′-indoline] **2**.

**Scheme 2. Formation Mechanism of Spiro[cyclopent[2]ene-1,3′-indolines]**



In summary, we have successfully developed a one-pot three-component reaction of triphenylphosphine, electron-deficient alkynes, and isatylidene malononitrile (ethyl isatylidene cyanoacetate). This reaction provided a convenient protocol for the synthesis of the functionalized triphenylphosphanylidene spiro[cyclopentane-1,3′-indoline] and spiro[cyclopent[2]-ene-1,3′-indoline] in satisfactory yields. Furthermore, the formation mechanisms for the two kinds of spirooindoles are rationally proposed. The short reaction time, readily variable substrates, ease in handling, and high yields render this multicomponent reaction applicable to the synthesis of structurally diverse spirooxindoles. The potential uses of this reaction in synthetic and medicinal chemistry might be quite significant.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Experimental procedures and spectral data for all new compounds including crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This work was financially supported by the National Natural Science Foundation of China (Grant No. 21172189) and the Priority Academic Program Development of Jiangsu Higher Education Institutions. We also thank the Analysis and Test Center of Yangzhou University for providing necessary instruments for analysis.

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## ■ NOTE ADDED AFTER ASAP PUBLICATION

The Acknowledgment was updated and reference 17 was added on April 28, 2014.