Organic LETTERS

Letter

pubs.acs.org/OrgLett

A Cascade Phosphinoylation/Cyclization/Desulfonylation Process for the Synthesis of 3-Phosphinoylindoles

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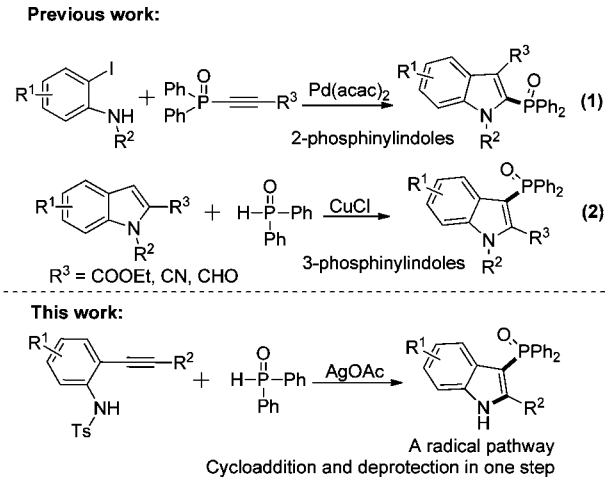
Supporting Information

ABSTRACT: 3-Phosphinoylindole derivatives play important roles as pharmaceutical drugs and ligands. A new method for the synthesis of 3-phosphinoylindole derivatives has been achieved through silver-mediated cycloaddition between N-Ts-2-alkynylaniline derivatives and H-phosphine oxides. This transformation offers a straightforward route to the formation of the C−P bond, indole ring, and desulfonylation in one step.

Indole frameworks are important structural moeities commonly found in a variety of natural products which have vital medicinal values and various biological activities.[1] Recently, it has been shown that indolyl-backbone phosphines, especially 3-phosphinoylindole derivatives, are effective in promoting metal-catalyzed cross-couplings which act as ligands fit for the direct α-arylation of carbonyl compounds.[2] Moreover, 3-phosphinoylindole frameworks represent novel second-generation NNRTIs (non-nucleoside reverse transcriptase inhibitors) which show excellent potency against HIV-1 in vitro (IDX899).[3] Because of the current interest in the pharmacologically and synthetically important indole-based derivatives, various methods have been reported for the synthesis of such heterocyclic phosphonates.[4] As for indole-based phosphine oxides, only two methods were developed. The Yorimitsu and Oshima group developed a conceptually new method for the synthesis of 2-phosphinoylindoles using 1-alkynylphosphine derivatives as key starting materials.[4f] In 2014, Yang et al. reported the copper-catalyzed cross-coupling reaction of 2-substituted indoles and diphenylphosphine oxide (Scheme 1).[4h] This breakthrough for the preparation of 3-phosphinoylindoles is highly efficient, yet only indoles bearing electron-withdrawing groups at the 2-position could give a satisfactory yield.

Herein, we report the first approach to the synthesis of 3-phosphinoylindoles using N-Ts-2-alkynylanilines[5] and P(O)H compounds. Frequently, sulfones are introduced into synthetic schemes to assist particular transformations; further progress along the synthetic route can later require the removal of a sulfone group. For the cleavage of the N-Ts group (4-methylbenzene-1-sulfonyl, Ts), reagents such as alkali metals (Li, Na, K, Mg), lithium naphthalenide, or $LiAlH_4$ in the presence of nickel compounds have been applied. The need for such drastic conditions in the deprotection step restricted the use of the Ts group to only very stable molecules.[6] In this paper, 3-phosphinoylindole derivatives were constructed using a one-step strategy via radical cascade cycloaddition−desulfonylation processes.

Scheme 1. Route to Indole-Based Phosphine Oxides



To successfully execute this difficult approach, we focused on N-Ts-2-alkynylaniline, because the Ts group can act as a radical leaving group.[7] This idea was first examined using N-Ts-2-phenylethynylaniline (**1a**) and diphenylphosphine oxide (**2a**) as reaction partners. In the beginning, some oxidants, such as $K_2S_2O_8$, TBHP, $AgNO_3$, $CuSO_4$, and $Mn(OAc)_3{\cdot}2H_2O$, were tested, but the reaction did not work well under these conditions. When AgOAc[8] was chosen as the oxidant, using dimethylformamide (DMF) as the solvent, the product **3a** was obtained in 66% yield at 100 °C under an argon atmosphere.

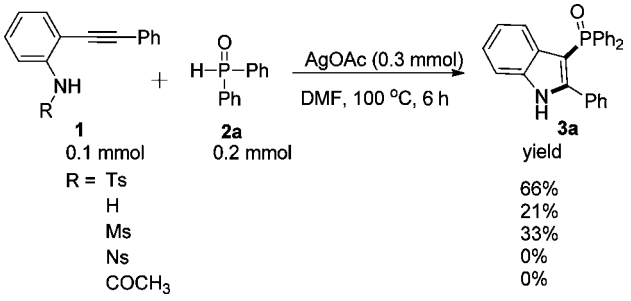
Received: January 7, 2016
Published: February 29, 2016

DOI: 10.1021/acs.orglett.6b00056
Org. Lett. 2016, 18, 1242−1245

Examination of various silver salts indicated that AgOAc is optimal, and solvent screening showed that dimethylformamide (DMF) is also optimal. However, the yield of product **3a** decreased when the temperature was lowered to 80 °C or raised to 120 °C indicating that the choice of temperature is also crucial for the reaction. However, the reaction yield was not improved by variation the AgOAc concentration. The reaction did not occur at all in the absence of AgOAc. After optimization of the reaction conditions, we established an efficient route to formation of 3-phosphinoylindoles. The optimal reaction conditions are **1a** (0.1 mmol), **2a** (0.2 mmol), AgOAc (0.3 mmol), and DMF (1 mL) at 100 °C for 6 h under an argon atmosphere. Under these optimal reaction conditions, about 30% of **1a** was recovered and **2a** was not detected.

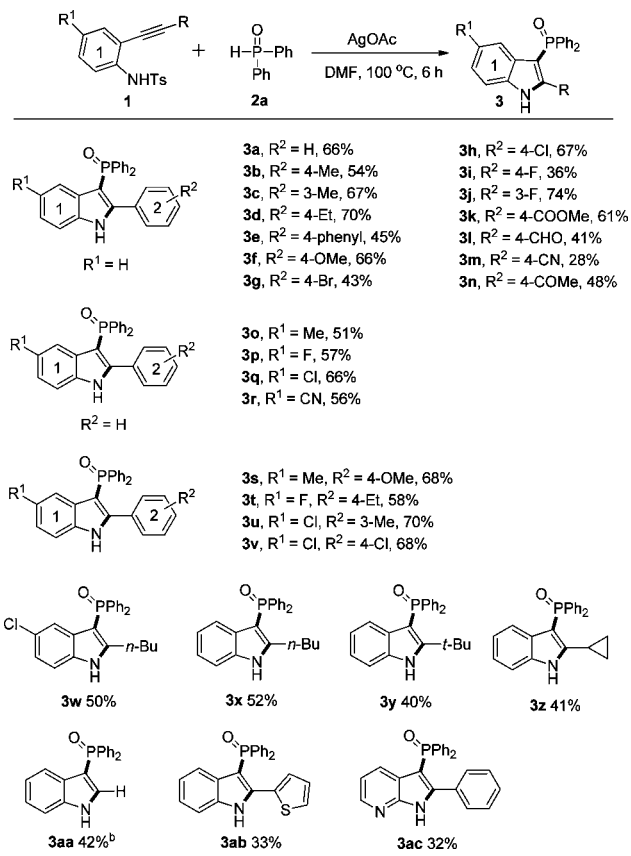
Then, we turned our attention to examining the effect of N-protecting groups in this reaction (Scheme 2). Significant differences in yield of **3a** were observed between the substituents 4-methylbenzene-1-sulfonyl (Ts, 66%), hydrogen (H, 21%), methanesulfonyl (Ms, 33%), 4-nitrobenzene-1-sulfonyl (Ns, 0%), and acetyl (0%), indicating that the species of protecting group at the nitrogen atom of 2-alkynylaniline has a big influence on the reaction.

Scheme 2. Effect of the N-Protecting Groups



With the optimal conditions in hand, the generality of the method was explored, and the results are summarized in Scheme 3. First, various functional groups on the benzene ring **2** were examined and most of the functional groups were tolerated under the optimized conditions. With methyl substituted on benzene **2**, such as *meta*- and *para*-methyl groups, these compounds reacted efficiently to give the desired products **3b** and **3c** in 54% and 67% yields. Some electron-donating (ethyl, phenyl, and methoxy) groups were investigated and gave the corresponding products **3d**–**3f** in 70–45% yields. Halogen atoms such as fluorine, chlorine, and bromine have little influence under the optimized reaction conditions to afford the corresponding products **3g**–**3j** in moderate to good yields, which could allow for further synthetic transformations. The structure of **3h** was confirmed by single-crystal X-ray analysis (see SI). Various electron-withdrawing (COOMe, CHO, CN, and COMe) groups on the benzene ring **2** were also investigated and smoothly converted into products **3k**–**3n** in 61–28% yields. Functional groups on the benzene ring **1**, methyl, fluoro, chloro, and cyano groups, were examined and gave the corresponding products **3o**–**3r** in 66–51% yields. When benzene rings **1** and **2** were both substituted, the corresponding products **3s**–**3v** were obtained in good yields (70–58%). Aliphatic alkynes were also examined, and the desired products were obtained (**3w**–**3z**) in lower yields (50–40%). Interestingly, we could not obtain the desired product when **1aa** was introduced into this reaction; instead, **3aa** was obtained in 42% yield. In addition, heterocyclic compounds could also provide the expected products **3ab** and **3ac** in relatively lower yields.

Scheme 3. Synthesis of 3-(Diphenylphosphinoyl)indole Derivatives[a]



[a]Reaction conditions: **1** (0.3 mmol), **2a** (0.6 mmol), AgOAc (0.9 mmol) in DMF (3 mL) stirring under argon at 100 °C for 6 h. [b] **1aa** = 4-methyl-*N*-(2-((trimethylsilyl)ethynyl)phenyl)benzenesulfonamide.

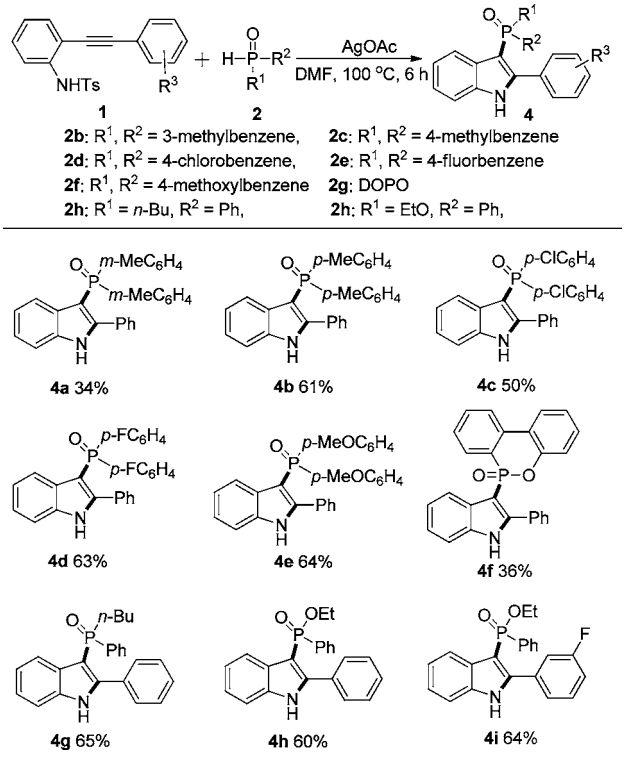
Next, the reactions of variously substituted phenylphosphine oxides with **1** were examined (Scheme 4). Diarylphosphine oxides **2a**–**2e** reacted with **1a** to give the products **4a**–**4e** in 64–34% yields. 9,10-Dihydro-9-oxa-10-phosphaphenanthrene 10-oxide (DOPO, **2f**) reacted with **1a**, giving the expected product **4f** in 36% yield. Alkyl(phenyl)phosphine oxide **2g** also underwent coupling with **1a** to produce the corresponding product **4g** in 65% yield. Moreover, ethyl phenylphosphinate (**2h**) could be used in the annulation giving products **4h** and **4i**, respectively, in 60% and 64% yields.

There have been a number of recent reports concerning the synthesis of β-ketophosphonates from the reaction of terminal alkynes with *H*-phosphonates.[9] We were therefore interested in discovering what products would be obtained when terminal 2-alkynylaniline was introduced in this reaction; we synthesized **5** to investigate this reaction (Scheme 5).[10] Contrary to expectation, product **6** was not observed inspective of whether the reaction was conducted under argon or air. Instead, **3aa** was afforded in 40% yield under argon and 31% yield under air.

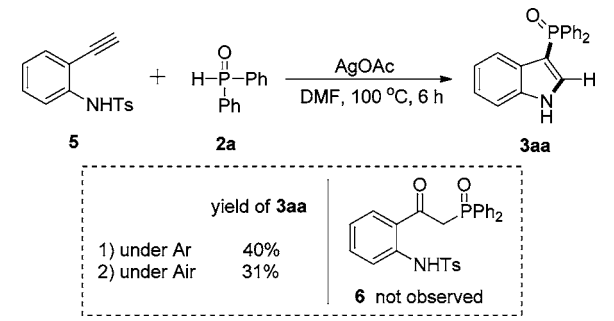
Additionally, to validate the original design of the present radical tandem process involving a silver-initiated single-electron transfer, radical trapping experiments were also conducted by employing 2,6-di-*tert*-butyl-4-methylphenol (BHT), benzoquinone (BQ), and 2,2,6,6-tetramethyl-

DOI: 10.1021/acs.orglett.6b00056
Org. Lett. 2016, 18, 1242–1245

Scheme 4. Reaction of P(O)−H Compounds with 2-Alkynylaniline Derivatives



Scheme 5. Reaction of Terminal Alkyne with 2a

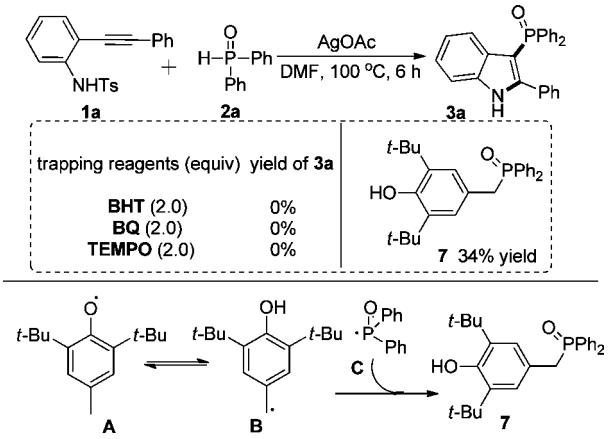


piperidinooxy (TEMPO). No desired product was obtained when these radical trapping reagents were added in the reaction under the optimal conditions. Interestingly, product **7** was obtained in 34% yield when 2 equiv of BHT were added to the reaction (Scheme 6). According to Hamashima et al.,[11] we assume that BHT could produce phenoxyl radical **A** under the reaction conditions and **A** abstracts a hydrogen atom through an intramolecular transfer affording intermediate **B** which could react with phosphoryl radical **C** to afford **7**. The product **7** suggests that a radical pathway is involved in this reaction.

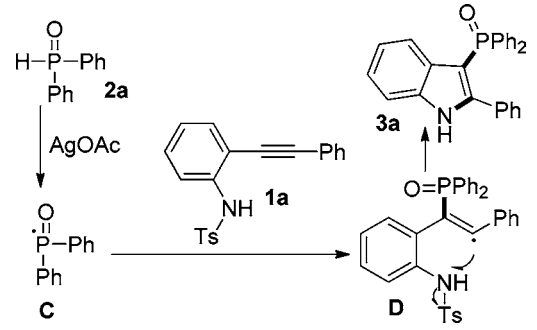
On the basis of the above-mentioned experiments, we propose a tentative pathway for this transformation (Scheme 7). First, diphenylphosphine oxide **2a** reacts with AgOAc to form the phosphoryl radical **C**, which then adds to **1a** to give the alkenyl radical **D**. The resulting alkenyl radical **D** participates in an intramolecular radical substitution reaction to generate the product **3a**.[7]

In summary, we have developed an efficient protocol for the preparation of various 3-phosphinoylindoles via phosphinoylation− cyclization−desulfonylation of various 2-alkynyl-

Scheme 6. Radical Trapping Experiments



Scheme 7. A Tentative Mechanistic Pathway



aniline derivatives with secondary phosphine oxides involving C−P and C−N bonds formation. Given that a wide range of substrates can be utilized for the cascade annulation, this simple protocol may provide a general approach to 3-phosphinoylindole frameworks of importance in medicinal and synthetic chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00056.

Copies of ^{1}H and ^{13}C NMR spectra of compounds **3a**−**3ac**, **4a**−**4i**, and **7**; single-crystal X-ray spectrum of compound **3h** (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank NSFC (21173178, 21232005, 21375113), the National Basic Research Program of China (2012CB821600), and the Fundamental Research Funds for the Central Universities (No. 20720160030). We are grateful to Prof. Dr D. M. J. Lilley from University of Dundee for valuable discussions on this paper.

DOI: 10.1021/acs.orglett.6b00056
Org. Lett. 2016, 18, 1242−1245

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DOI: 10.1021/acs.orglett.6b00056
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