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Synthesis of Substituted Indoles from 2-Azidoacrylates and *ortho*-Silyl Aryltriflates†

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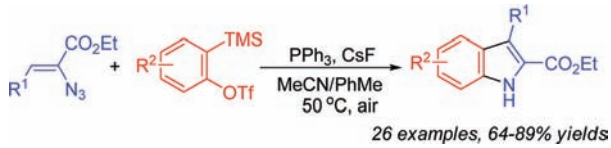
ABSTRACT



2-Azidoacrylates react with benzynes in the presence of PPh_3 and CsF to afford substituted indoles in good yields. The reaction involves the formation of iminophosphorane and benzyne and a subsequent double cyclization/hydrolysis/air-oxidation cascade. This methodology was utilized to synthesize 10*H*-indolo[1,2-a]indol-10-ones.

Indoles constitute an important class of alkaloids and are common building blocks for a number of bioactive natural products and marketed drugs.[1] Consequently, many methods have been developed for the construction of indoles,[2] including the Fischer synthesis,[3] hetero-annulations,[4] reductive cyclization,[5] and metal-catalyzed processes.[6] Still, the development of more efficient routes to substituted indoles is of great importance.

Recently, much attention has been attracted to applying *ortho*-silyl aryltriflates as the benzyne precursors in organic synthesis.[7] Additionally, aryne cyclizations have proved to be an exceptional method for gaining metal-free access to heterocyclic molecules.[8] Inspired by these works and our recent findings around the synthesis of indoles[9] and the reactions of iminophosphoranes,[10] we assumed that cycloaddition of arynes with vinyl iminophosphoranes would lead to the formation of indoles since the iminophosphorane nitrogen bears a partial negative charge and thus exhibits considerable nucleophilicity.

† Dedicated to Professor Henry N. C. Wong on the occasion of his 60th birthday.

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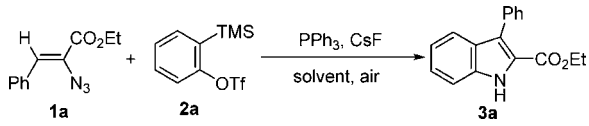
The reaction of ethyl 2-azido-3-phenylacrylate **1a** (1 equiv), 2-(trimethylsilyl)-phenyl triflate **2a** (1.5 equiv), PPh_3 (1 equiv), and CsF (3 equiv) under air was used to screen the reaction conditions (Table 1). It is noteworthy that the

Table 1. Optimization of Reaction Conditions[a]



entry	temp (°C)	solvent	t (h)	yield[b] (%)
1	50	THF	10	25
2	50	DCE	10	0
3	50	MeCN	10	0
4	50	PhMe	10	0
5	50	MeCN/PhMe (1:2)	10	73
6	50	MeCN/PhMe (2:1)	10	66
7	50	MeCN/PhMe (1:1)	10	81
8	50	MeCN/PhMe (1:1)	5	81
9	50	MeCN/PhMe (1:1)	2	50
10	80	MeCN/PhMe (1:1)	10	70
11	25	MeCN/PhMe (1:1)	10	60
12	50	MeCN/PhMe (1:1)	15	17[c]
13	50	MeCN/PhMe (1:1)	10	80[d]

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol), PPh_3 (0.5 mmol), CsF (1.5 mmol), solvent (10 mL), air. [b] Yield of the isolated product. [c] cat. PPh_3 (0.1 mmol, 0.2 equiv) was used. [d] Under N_2.

solvent system is crucial to the success of this annulation chemistry (Table 1, entries 1−7). By using MeCN/toluene as the cosolvent, we could control the release rate of benzyne,[11] consequently prevent the formation of benzotriazole, and improve the yield of product **3a**. We found that the cosolvent with a 1:1 ratio of MeCN/toluene was the most suitable solvent (Table 1, entry 7). A screening of the temperature and time of this reaction showed that 50 °C and 5 h were the best choices for this transformation (Table 1, entries 7−11). When the PPh_3 loading was reduced to 20 mol %, low yield (17%) of **3a** was obtained (Table 1, entry 12). Interestingly, when the reaction was conducted under inert conditions at 50 °C for 10 h, the product **3a** also was isolated in 80% yield (Table 1, entry 13). Thus, the most suitable reaction conditions for the formation of **3a** were established (Table 1, entry 8).

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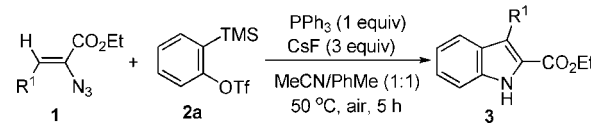
Since ethyl 2-azidoacrylates are readily available,[12] the prospect of vinyl iminophosphorane generation from them is highly appealing. We, therefore, extended the substrate scope to various ethyl 2-azidoacrylates **1** using the optimized reaction conditions. As shown in Table 1, aryl-substituted vinylazides **1a**∼**1i** (Table 2, enties 1−9) and aryl-substituted

Table 2. Azidoacrylate Scope in Indole Synthesis[a]



entry	R^1	product	yield[b] (%)
1	Ph (**1a**)	**3a**	81
2	4-MeC_6H_4 (**1b**)	**3b**	79
3	4-ClC_6H_4 (**1c**)	**3c**	84
4	4-BrC_6H_4 (**1d**)	**3d**	82
5	4-$MeOC_6H_4$ (**1e**)	**3e**	76
6	3-$NO_2C_6H_4$ (**1f**)	**3f**	89
7	4-PhC_6H_4 (**1g**)	**3g**	82
8	4-$PhCH_2OC_6H_4$ (**1h**)	**3h**	74
9	2-naphthyl (**1i**)	**3i**	80
10	PhCH=CH (**1j**)	**3j**	72
11	2-ClC_6H_4CH=CH (**1k**)	**3k**	73
12	2-$MeOC_6H_4CH$=CH (**1l**)	**3l**	70
13	2-$NO_2C_6H_4CH$=CH (**1m**)	**3m**	76

[a] Reaction conditions: **1** (0.5 mmol), **2a** (0.75 mmol), PPh_3 (0.5 mmol), CsF (1.5 mmol), toluene/CH_3CN (1:1, 10 mL), 50 °C, air, 5 h. [b] Yield of the isolated product.

dienyl azides **1j**−**1m** (Table 2, entries 10−13) afforded indoles **3** in good yields (70−89%). Furthermore, the structure of compound **3g** was unambiguously confirmed by single-crystal X-ray analysis (Figure 1).

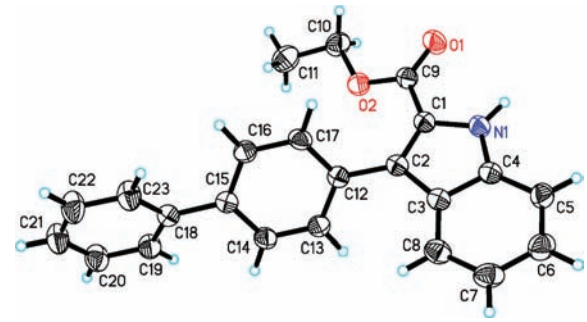
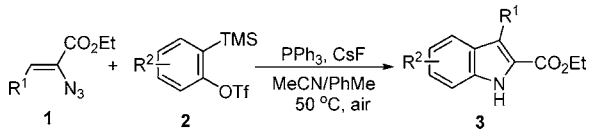
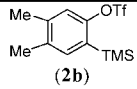
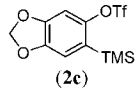
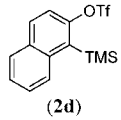
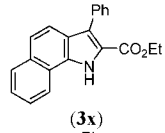
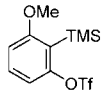
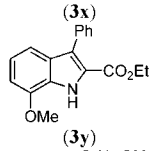
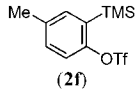
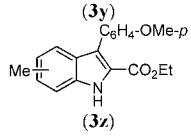


Figure 1. Crystal structure of compound **3g**.

To extend this protocol, several substituted *ortho*-silyl aryltriflates **2b**−**2f** were used as the substrates to perform the reaction (Table 3). We were delighted to find that the substituted arynes could also furnish the desired indoles **3n**−**3z** in good yields (64−88%). It is noteworthy that 1,2-naphthalyne (from **2d**) and *ortho*-methoxy benzyne (from

Table 3. Aryne Scope in Indole Synthesis[a]



entry	azide	aryne precursor	product	yield[b] (%)
1	**1a**	 (**2b**)	**3n**	80
2	**1b**	**2b**	**3o**	79
3	**1d**	**2b**	**3p**	81
4	**1e**	**2b**	**3q**	75
5	**1f**	**2b**	**3r**	88
6	**1a**	 (**2c**)	**3s**	78
7	**1b**	**2c**	**3t**	77
8	**1d**	**2c**	**3u**	79
9	**1e**	**2c**	**3v**	72
10	**1f**	**2c**	**3w**	82
11	**1a**	 (**2d**)	 (**3x**)	80
12	**1a**	 (**2e**)	 (**3y**)	64
13	**1e**	 (**2f**)	 (**3z**)	84[c]

[a] **1** (0.5 mmol), **2** (0.75 mmol), PPh_3 (0.5 mmol), CsF (1.5 mmol), toluene/CH_3CN (1:1, 10 mL), 50 °C, air, 5 h. [b] Isolated yield refers to azide. [c] Mixture of *meta*- and *para*-regioisomers (2.5:1).

2e) provided a single product, respectively (Table 3, entries 11 and 12). Furthermore, the complete regioselectivity of the products **3x** (Figure 2) and **3y** (Figure 3) was unambiguously confirmed by X-ray analysis. In the case of *meta*-methyl benzyne (from **2f**), the product **3z** was observed as a mixture of two isomers (2.5:1) in 84% yield (Table 3, entry 13).

On the basis of these results and the known chemistry of arynes,[13] a possible mechanism for this cascade process is proposed (Scheme 1). First, azide **1a** reacts with PPh_3 to form vinyl iminophosphorane **A** via the Staudinger−Meyer reaction. **A** subsequently reacts with the in situ generated benzyne to yield intermediate **B** by a nucleophilic double cyclization. The reactive **B** is easily hydrolyzed to dihy-

(12) The 2-azidoacrylates employed herein were synthesized by the condensation of an aromatic or cinnamic aldehyde with ethyl azidoacetate. Indoles were produced by thermolysis or Rh_2(II)-catalyzed decomposition of 2-azidoacrylates. See: (a) Stokes, B. J.; Dong, H.; Leslie, B. E.; Pumphrey, A. L.; Driver, T. G. *J. Am. Chem. Soc.* **2007**, *129*, 7500. (b) Hemetsberger, H.; Knittel, D.; Weidmann, H. *Monatsh. Chem.* **1970**, *101*, 16.

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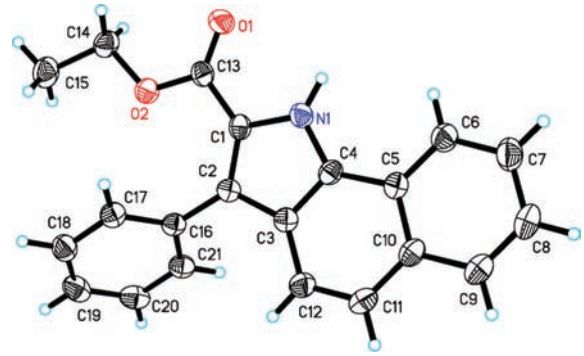


Figure 2. Crystal structure of compound **3x**.

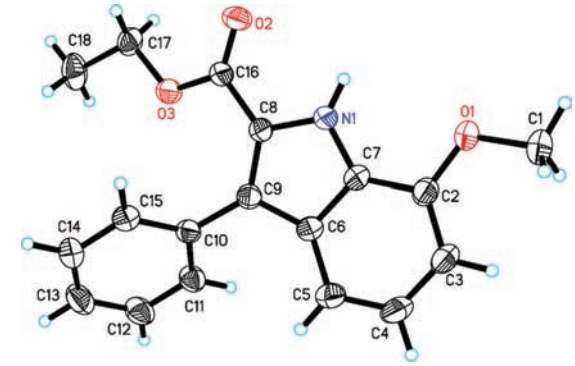
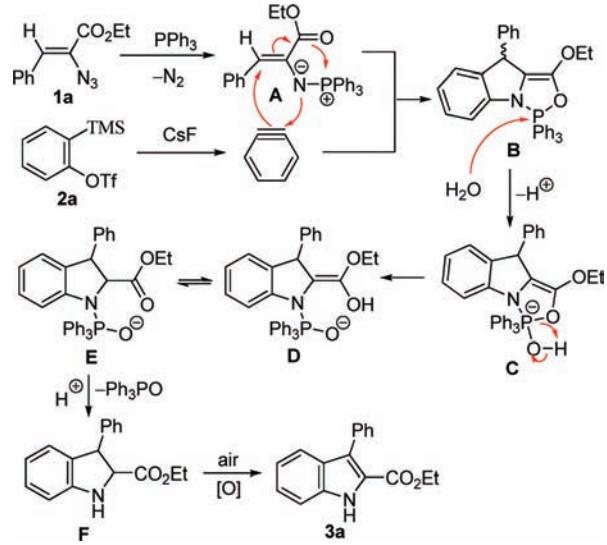


Figure 3. Crystal structure of compound **3y**.

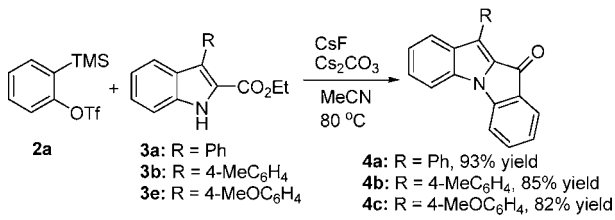
Scheme 1. Possible Mechanism for the Formation of **3**



droindole **F** and releases Ph_3PO during the conventional workup. Finally, the resulting **F** is immediately oxidized by air to afford indole **3a**. In our reactions, we isolated Ph_3PO as a byproduct. The reactive intermediate **B** was detected by both HRMS (ESI) and ^{31}P NMR trapping experiments under N_2 (see Supporting Information).

A demonstration of the synthetic utility for this method was shown in Scheme 2. Thus, treatment of indoles **3a**, **3b**, and **3e** with benzyne **2a** in the presence of Cs_2CO_3 under mild conditions afforded 10*H*-indolo[1,2-a]indol-10-ones **4a** (93% yield), **4b** (85% yield), and **4c** (82% yield), respectively. The reaction is believed to proceed via a [3 + 2] annulation of aryne and ethyl indole-2-carboxylates.[14] This two-step strategy for access to 10*H*-indolo[1,2-a]indol-10-ones, which are useful scaffolds for the synthesis of biologically active compounds, is concise and highly efficient.

Scheme 2. Synthesis of Indole-indolone **4**



In conclusion, we demonstrated a mild and efficient procedure for the synthesis of substituted indoles. In the presence of CsF and PPh_3, 2-azidoacrylates reacted with *ortho*-silyl aryltriflates to afford the corresponding indole derivatives in good yields. The reaction involves the formation of iminophosphorane and benzyne intermediates and a subsequent double cyclization/hydrolysis/air-oxidation cascade. Furthermore, the indole products could be easily converted into 10*H*-indolo[1,2-a]indol-10-ones. The further synthetic application of this methodology in more complex settings is currently in progress.

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Supporting Information Available: Detailed experimental procedures, characterizaton data, copies of ^1H, ^{13}C, and ^{31}P NMR spectra, and crystallographic information file (CIF) for compounds **3g**, **3x**, and **3y**. This material is available free of charge via the Internet at http://pubs.acs.org.

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