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Formation of indole nucleus via intramolecular cyclization of aminophenylpropenyltriphenylphosphonium salts with one-carbon degradation

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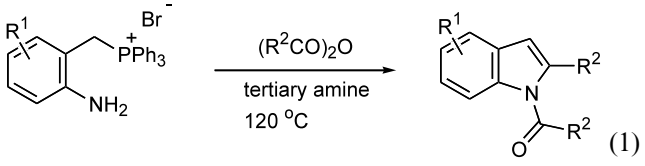
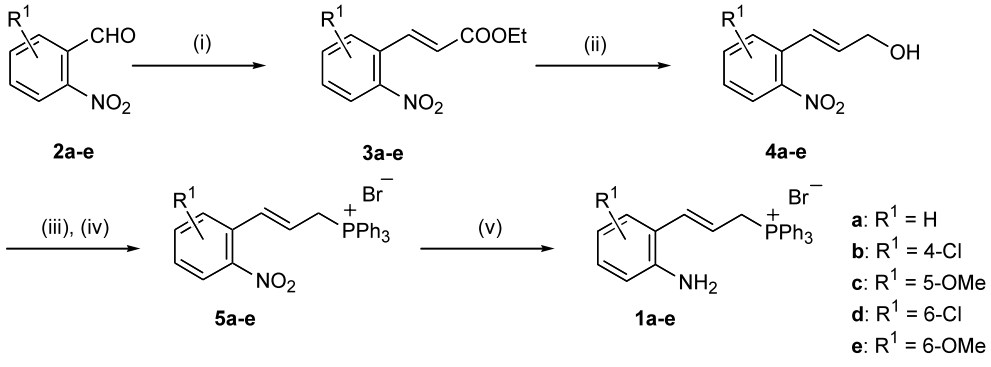
Abstract—Treatment of 3-(2-aminophenyl)-2-propenyltriphenylphosphonium bromide with acid anhydride and tertiary amine affords 1,3-diacylindoles in yields ranging from 22 to 64%. A plausible mechanism of this new cyclization reaction is described.

The Wittig and related reactions are recognized to be powerful strategies for the construction of heterocycles.[1] Recently, we described that the intramolecular Wittig reaction was effective for indole formation from (2-diacylaminobenzyl)triphenylphosphonium salts which were generated in situ by the reaction of (2-aminobenzyl)triphenylphosphonium salts with acylating agents in the presence of tertiary amines (Eq. (1)).[2]



(1)

Based on these results, we were interested in the development of this convenient synthetic route to benzoazepine derivatives from 3-(2-aminophenyl)-2-propenyltriphenylphosphonium salts under similar reaction conditions (Eq. (2)). In order to evaluate the possibility of this protocol, phosphonium salts **1** were chosen as starting materials (Scheme 1). Thus, the 2-nitrobenzaldehyde derivatives **2a–e** were treated with ethoxycarbonylmethylenetriphenylphosphorane in refluxing toluene for 3 h to give **3a–e** as mixtures of stereoisomers. The cinnamates **3a–e** were subjected to reduction by DIBAL to give alcohols **4a–e**, which were then converted into the corresponding phosphonium bromides **5a–e** by bromination and sub-



Scheme 1. *Reagents and conditions*: (i) Ph_3P=CHCOOEt, toluene, reflux, 3 h; **3a**: 84%; **3b**: 84%; **3c**: 97%; **3d**: 89%; **3e**; 93%. (ii) DIBAL, CH_2Cl_2, −78°C, 3 h; **4a**: 100%; **4b**: 100%; **4c**: 100%; **4d**: 100%; **4e**: 99%. (iii) PBr_3, Et_2O, 0°C, 1 h. (iv) PPh_3, $CHCl_3$, rt, overnight; **5a**: 81%; **5b**: 96%; **5c**: 46%; **5d**; 51%; **5e**: 67% (two steps). (v) Zn, 48% HBr, EtOH, 0°C to rt, overnight; **1a**: 87%; **1b**: 76%; **1c**: 83%; **1d**: 73%; **1e**; 95%.

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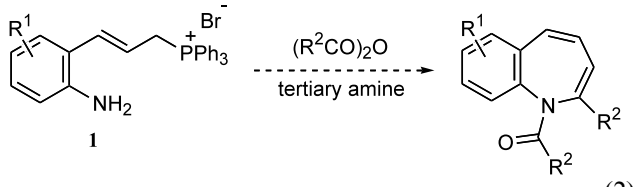
sequent substitution reaction with triphenylphosphine. The nitro group was reduced by the use of zinc powder and hydrobromic acid to afford the phosphonium salts **1a**–**e**.



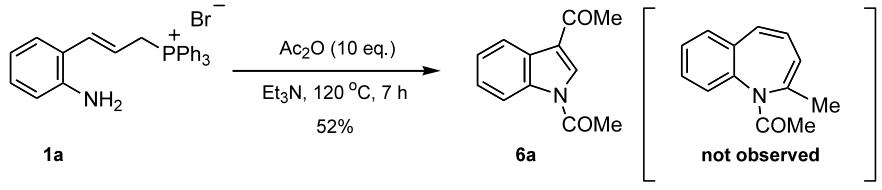
(2)

Cyclization of **1a** was carried out by treatment with acetic anhydride in the presence of triethylamine at 120°C. To our surprise, no trace of the desired benzoazepine derivatives produced. Instead, an unprecedented cyclization reaction proceeded via one-carbon degradation from the allylic moiety to form 1,3-diacylindoles **6a** (Scheme 2).

The cyclization reaction of several substrates was examined under various reaction conditions. The results are summarized in Table 1.[3] In all cases, indole formation was observed exclusively. Amine base was required for this cyclization, and relatively high yield of the indole product was obtained by the use of diisopropylethylamine (entries 4 and 5).[4] Other acid anhydrides and acyl chlorides also served as the acylating agents, although the yields of the products were moderate (entries 6–9). It is intersting to note that not only this cyclization tolerates substitution at aromatic moiety but also is applicable to construction of 3,4-disubstituted indoles, which are generally prepared with difficulty by Friedel–Crafts reaction (entries 12 and 13).

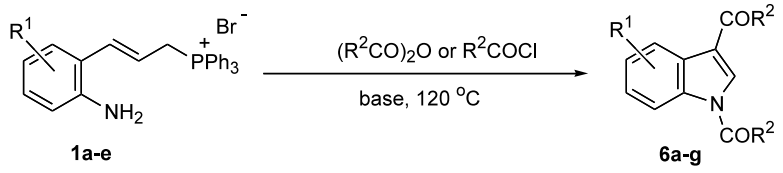
In the cyclization of **1**, some co-products were observed. When **1a** was allowed to react under the conditions described in entry 5, triphenylphosphine oxide (**7**) and triphenylphosphonium diacetylmethylide (**8**) were isolated in 49% and 5% yield, respectively (Scheme 3).[5,6] In addition, treatment of triphenylphosphonium acetylmethylide with acetic anhydride and diisopropylethylamine at 120°C provided **7** and **8** in 78% and 8% yields. These results suggest elimination of triphenylphosphonium acetylmethylide as the one-carbon unit.

The following experiments were carried out to elucidate the mechanism of this indole formation. The reaction of *N*,*N*-diacetylated phosphonium salt **9**,[7] previously prepared by acetylation of **1a**, with benzoic anhydride was performed in the presence of diisopropylethylamine at 120°C (Scheme 4). In spite of excess amount of benzoic anhydride, 3-acetylindoles **6a** and **10** were mainly produced, indicating that the acyl group on the nitrogen atom migrates intramoleculary to γ-carbon of the allylic phosphonium salt.[8]



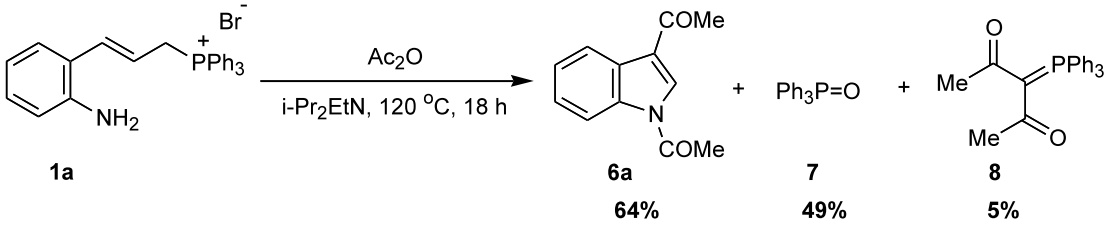
Scheme 2.

Table 1. Cyclization of aminophenylpropenyltriphenylphosphonium bromides using acid anhydrides or acyl chlorides

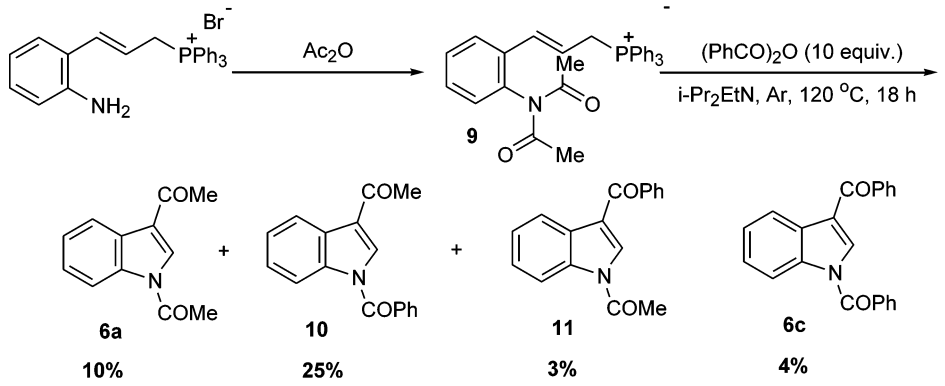


Entry	Substrate	$(R^2CO)_2O$ or R^2COCl	Base	Time (h)	Product	Yield (%)
1	**1a** (R^1 = H)	Ac_2O	None	7	**6a**	–
2[a]	**1a** (R^1 = H)	Ac_2O	Et_3N	7	**6a**	52
3[a]	**1a** (R^1 = H)	Ac_2O	Pyridine	7	**6a**	13
4[a]	**1a** (R^1 = H)	Ac_2O	*i*-Pr_2EtN	7	**6a**	53
5[a]	**1a** (R^1 = H)	Ac_2O	*i*-Pr_2EtN	18	**6a**	64
6[a]	**1a** (R^1 = H)	$(EtCO)_2O$	*i*-Pr_2EtN	18	**6b**	31
7[a]	**1a** (R^1 = H)	$(PhCO)_2O$	*i*-Pr_2EtN	18	**6c**	49
8[b]	**1a** (R^1 = H)	AcCl	2,6-Lutidine	18	**6a**	32
9[b]	**1a** (R^1 = H)	PhCOCl	2,6-Lutidine	18	**6c**	32
10[a]	**1b** (R^1 = 4-Cl)	Ac_2O	*i*-Pr_2EtN	18	**6d**	53
11[a]	**1c** (R^1 = 5-OMe)	Ac_2O	*i*-Pr_2EtN	18	**6e**	62
12[a]	**1d** (R^1 = 6-Cl)	Ac_2O	*i*-Pr_2EtN	18	**6f**	29
13[a]	**1e** (R^1 = 6-OMe)	Ac_2O	*i*-Pr_2EtN	18	**6g**	22

[a] Molar ratio: phosphonium salt/acid anhydride/*i*-Pr_2EtN = 1/10/3.6.
[b] Molar ratio: phosphonium salt/acyl chloride/2,6-lutidine = 1/10/15.



Scheme 3.



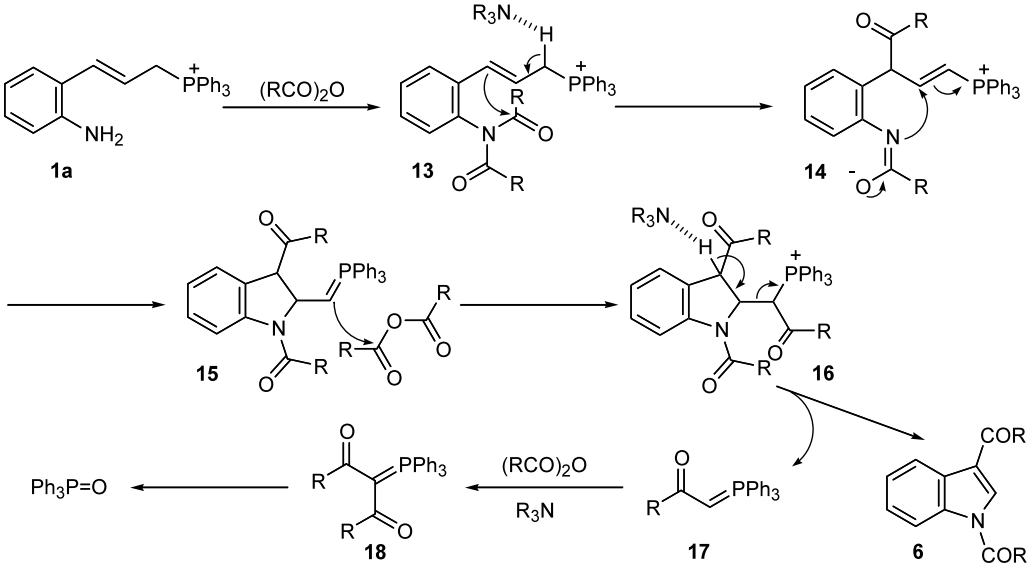
Scheme 4.

From these results, the following reaction mechanism is proposed (Scheme 5). Diacylated phosphonium salt **13** is converted into twitterionic intermediate **14** via intramolecular migration of an acyl group. Cyclization of **14** results in the formation of ylide **15**.

The interaction of intermediate **16** with tertiary amine facilitates carbon–carbon bond fission to yield 1,3-diacylindole derivative **6**. It is noted that the formation of the stabilized ylide, triphenylphosphonium acylmethylide **17**, is one of the driving forces of this elimination. The generated ylide **17** reacts with the acylating agent to give triphenylphosphonium diacylmethylide **18**, most of which is converted into triphenylphosphine oxide under these conditions.[6]

In summary, we found that 1,3-diacylindole derivatives are produced by the reaction of 3-(2-aminophenyl)-2-propenyltriphenylphosphonium bromides with acylating agents in the presence of tertiary amines.

Further work to clarify the scope and limitation of this new indole formation and its detailed reaction mechanism are now in progress.



Scheme 5. Plausible reaction mechanism.

Acknowledgements

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3. *Typical procedure for the synthesis of compound* ***6a***: A mixture of 3-(2-aminophenyl)-2-propenyltriphenylphosphonium bromide (**1a**) (474 mg, 1 mmol), acetic anhydride (0.94 mL, 10 mmol) and diisopropylethylamine (0.63 mL, 3.6 mmol) was heated at 120°C for 18 h. After dilution with H_2O, the mixture was neutralized with $NaHCO_3$ and extracted with ethyl acetate. The organic extracts were washed with H_2O, dil. HCl and brine, and dried over Na_2SO_4. Removal of solvent in vacuo, and purification by column chromatography (*n*-hexane/ethyl acetate, 1/1) afforded 1,3-diacetylindole (**6a**)[9] (128 mg, 64%) as a yellow powder: Mp 151–152°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.3–8.4 (m, 2H), 8.01 (s, 1H), 7.3–7.5 (m, 2H), 2.71 (s, 3H), 2.57 (s, 3H); IR (KBr) 1715, 1660, 1547, 1449, 1389, 1263, 1223, 1165 cm^{-1}. Anal. calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.57; H, 5.56; N, 6.96.
4. The reaction was examined at 120°C using **1a** and acetic anhydride (10 equiv.) with varying amount of *i*-Pr_2EtN. Representative results are as follows: 5.5 equiv. of *i*-Pr_2EtN, 18 h, 65% yield; 8.8 equiv. of *i*-Pr_2EtN, 18 h, 62% yield.
5. The structure of triphenylphosphonium diacylmethylide (**8**) was confirmed by ^{1}H, ^{13}C and ^{31}P NMR spectroscopy. These data were in accord with those of the authentic sample prepared by the reported procedure.[6] ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.28 (s, 6H), 7.4–7.5 (m, 15H); ^{13}C NMR (99 MHz, $CDCl_3$): δ 30.5, 126.1, 127.0, 128.5, 128.6, 131.5, 132.8, 132.9, 193.2, 193.3; ^{31}P NMR (162 MHz, $CDCl_3$): δ 16.86.
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7. *N*,*N*-Diacetylated phosphonium salt **9** was extremely moisture sensitive and readily decomposed.
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