Pergamon

Tetrahedron Letters 43 (2002) 2885–2888

TETRAHEDRON LETTERS

A facile synthesis of 2-substituted indoles from (2-aminobenzyl)triphenylphosphonium salts

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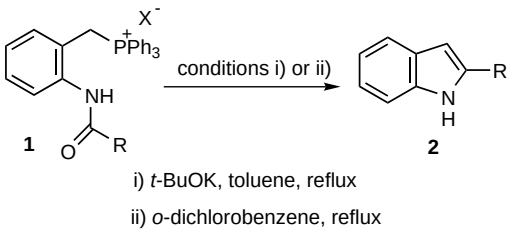
Received 7 February 2002; revised 5 March 2002; accepted 7 March 2002

Abstract—A variety of 2-substituted 1-acylindoles were obtained in yields ranging from 40 to 94% by intramolecular Wittig reaction employing (2-aminobenzyl)triphenylphosphonium derivatives and acid anhydride in the presence of triethylamine. The reaction of (2-aminobenzyl)phosphonium derivatives with various acyl chlorides in 2,6-lutidine also proceeded to give the corresponding indoles in 28–67% yields.

Although a great number of synthetic routes to the indole nucleus have already been reported, it is still significant to develop more effective methods owing to their important features in medicinal chemistry and natural product synthesis.[1,2] In recent years, intramolecular Wittig and Horner–Wadsworth–Emmons reactions were proven to be two of the most powerful strategies for the construction of various heterocycles,[3] and some of them were effectively applied to indole synthesis. In some cases, cyclization of (2-acylaminobenzyl)triphenylphosphonium salts **1** to 2-substituted indoles **2** were achieved by treatment with potassium *tert*-butoxide[4] or by heating without base[5] (Scheme 1). Although these cyclizations are considered to be useful enough even at this level, they would be more applicable to the syntheses of complex molecules if these reactions could be carried out under milder conditions.

Herein, we describe a new procedure for indole synthesis, in which (2-diacylaminobenzyl)triphenylphosphonium salts **3** were employed as active intermediates. In this protocol, salts **3** were generated in situ from (2-aminobenzyl)triphenylphosphonium bromides **4**[3a] and acylating agent in the presence of an amine base. The diacylated intermediates **3** were expected to be more reactive than monoacylated compounds **5** owing to the high electrophilicity at carbonyl carbon on nitrogen (Fig. 1). First, we planned the intramolecular Wittig reaction of the diacetate of (2-amino-6-methoxycarbonylbenzyl)triphenylphosphonium bromide (**4a**). Unfortunately, this gave only low yield of monoacetylated indole by treatment with potassium *tert*-butoxide (15% yield; reflux in toluene for 2 h). Treatment of **4a** with acetic anhydride and pyridine, however, did not lead to the isolation of diacetylated compounds, and formation of the target indole **6a** was observed (Scheme 2). This fact indicates that the amine base was effective enough to promote the intramolecular Wittig reaction of diacylate **3**. Based on these results, we tried the direct indole formation from phosphonium salts **4a–f** (Table 1).[6] The reaction was carried out with 5 equiv. of acid anhydride and 3.6 equiv. of base at 120°C for 2 h. The reaction did not proceed in the absence of base (entry 2). Improved reactivity was observed by the use of



Scheme 1.

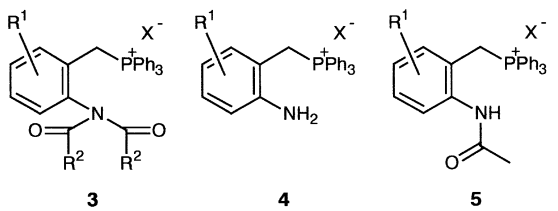


Figure 1.

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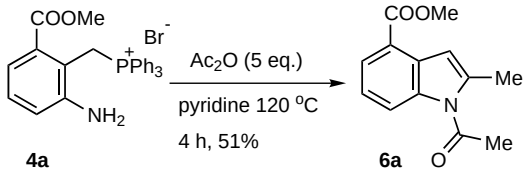
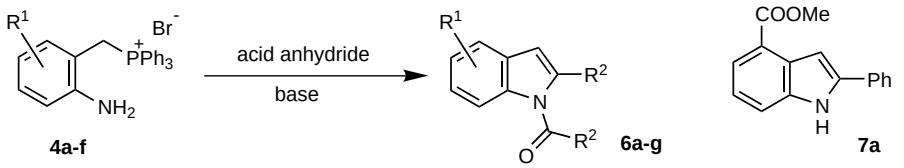


Scheme 2.

trialkylamine as the base (entries 3–5). Diisopropylethylamine and DBU gave 65 and 57% yields, respectively, and the best result (79% yield) was obtained when triethylamine was employed. The reaction run at lower temperature (80°C) caused the yield of indole to drop (entry 6, 52% yield). Slightly lower reactivity was also observed when 2.5 equiv. of acetic anhydride was employed (entry 7, 64% yield).[7] The use of propionic and benzoyl anhydrides gave the corresponding 2-substituted indoles in 59 and 40% yield (entries 8 and 9). The phosphonium salts bearing various substituents at benzene ring were reactive enough under these reaction conditions (entries 10–14). The introduction of electron withdrawing and electron donating groups at 6-position of benzene ring only showed marginal effect on the reactivity (entries 5, 10–12).

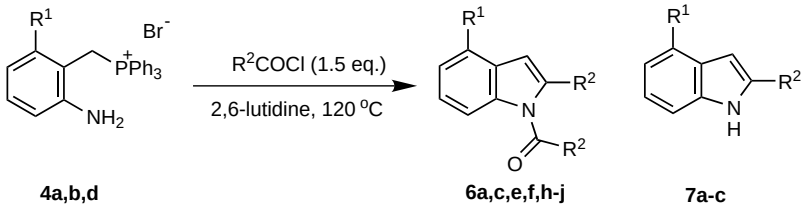
Table 1. Cyclization of (2-aminobenzyl)triphenylphosphonium bromides and acid anhydrides



Entry	R^1	$(R^2CO)_2O$ (5 equiv.)	Base (3.6 equiv.)	Temp. (°C)	Time (h)	Product	Yield (%)
1	6-COOMe (**4a**)	Ac_2O	Pyridine	120	2	**6a**	39
2	6-COOMe (**4a**)	Ac_2O	None	120	2	–	0
3	6-COOMe (**4a**)	Ac_2O	*i*-Pr_2EtN	120	2	**6a**	65
4	6-COOMe (**4a**)	Ac_2O	DBU	120	2	**6a**	57
5	6-COOMe (**4a**)	Ac_2O	Et_3N	120	2	**6a**	79
6	6-COOMe (**4a**)	Ac_2O	Et_3N	80	2	**6a**	52
7	6-COOMe (**4a**)	Ac_2O[a]	Et_3N	120	2	**6a**	64
8	6-COOMe (**4a**)	$(EtCO_2)O$	Et_3N	120	12	**6b**	59
9	6-COOMe (**4a**)	$(PhCO_2)O$	Et_3N	120	12	**7a**	40[b]
10	6-OMe (**4b**)	Ac_2O	Et_3N	120	2	**6c**	57
11	6-H (**4c**)	Ac_2O	Et_3N	120	2	**6d**	73
12	6-Cl (**4d**)	Ac_2O	Et_3N	120	2	**6e**	88
13	5-Cl (**4e**)	Ac_2O	Et_3N	120	2	**6f**	94
14	4-Cl (**4f**)	Ac_2O	Et_3N	120	2	**6g**	76

[a] 2.5 equiv. of Ac_2O was used.
[b] Product was isolated as **7a** after removal of the benzoyl moiety using K_2CO_3–MeOH.

Table 2. Cyclization of (2-aminobenzyl)triphenylphosphonium bromides and acyl chlorides



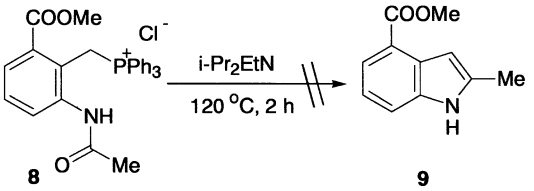
Entry	R^1	R^2COCl	Time (h)	Product	Yield (%)
1	COOMe (**4a**)	AcCl	3	**6a**	57
2	COOMe (**4a**)	AcCl	12	**6a**	62
3	OMe (**4b**)	AcCl	12	**6c**	49
4	Cl (**4d**)	AcCl	12	**6e**	67
5	Cl (**4d**)	PhCOCl	12	**6h**	66
6	COOMe (**4a**)	PhCOCl	12	**7a**	47[a]
7	Cl (**4d**)	*n*-C_3H_7COCl	12	**6i**	63
8	Cl (**4d**)	PhCH=CHCOCl	12	**6j**	28
9	COOMe (**4a**)	EtOCOCOCl	12	**7b**	53
10	Cl (**4d**)	EtOCOCOCl	12	**7c**	59

[a] Product was isolated as **7a** after removal of benzoyl moiety using K_2CO_3–MeOH.

In another set of experiments, acid chlorides were tested as the acylating reagents (Table 2).[8] The ring closure failed to occur in the presence of either diisopropylethylamine, triethylamine, or pyridine as the base. Use of 2,6-lutidine, however, afforded the desired indole in reasonable yield. Acetyl chloride was reacted with each substrate to give **6a**,**c**,**e** in 62, 49, and 67% yield, respectively (entries 2–4). Other acyl chlorides also produced successful results (entries 5–10). Especially, 2-ethoxycarbonylindole **7b**,**c** could be obtained by using ethyl oxalyl chloride as the acylating agent (entries 9 and 10).

The following three experiments were carried out in order to prove our working hypothesis that the formation of the indole nucleus from (2-aminobenzyl)-triphenylphosphonium salts indeed proceeded through *N*,*N*-diacyl intermediate. Firstly, monoacylate **8** was treated with diisopropylethylamine without acylation agent at 120°C for 2 h, and we observed only the starting phosphonium salt with no detectable amount of cyclization product **9** (Scheme 3). Secondly, *N*,*N*-diacetyl derivative **10**,[9] generated by the reaction of **4a** with acetic anhydride, was allowed to react with diisopropylethylamine at 120°C for 2 h. In this case cyclization product **6a** was obtained in moderate yield (Scheme 4). Finally, a couple of crossover reactions were examined by using *N*-acetyl derivative **8** and *N*-propionyl derivative **14**. In both cases products **12** and **13** were produced in almost the same ratio (Scheme 5).[10] These results clearly indicate that both reactions proceed through the same intermediate **15**. All the experimental facts mentioned above are reasonably interpreted by considering that (2-aminobenzyl)-triphenylphosphonium salts are subjected to *N*,*N*-diacylation and the resulting reactive diacyl derivatives undergo intramolecular Wittig reaction to afford 1-acyl indole derivatives.

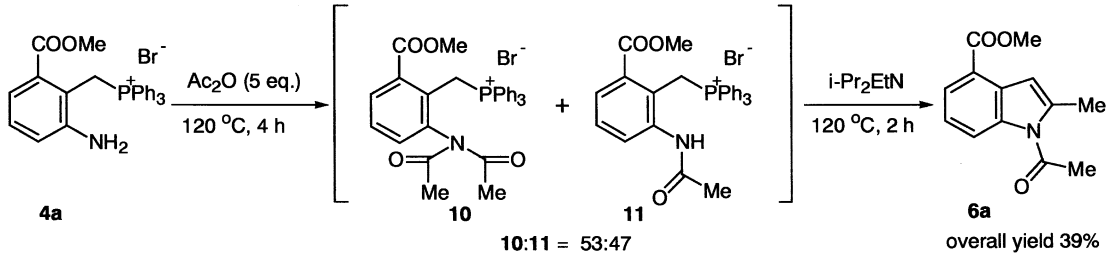
In conclusion, we have developed a convenient procedure for the synthesis of functionalized indole derivatives by employing intramolecular Wittig reaction of (2-diacylaminobenzyl)triphenylphosphonium salts generated in situ from (2-aminobenzyl)triphenylphosphonium salt and various acylating agents in the presence of amine as a base.



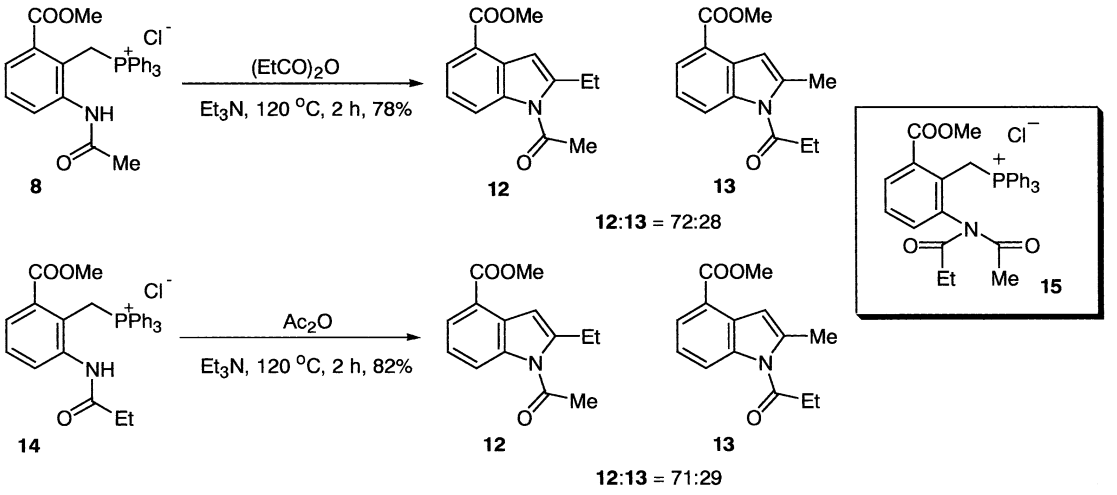
Scheme 3.

Acknowledgements

This work was supported by the Grant-in-Aid from the Ministry of Education, Science, Culture and Sports, Japan.



Scheme 4.



Scheme 5.

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6. *Typical procedure of acid anhydride–triethylamine system*: A mixture of (2-amino-6-methoxycarbonylbenzyl)-triphenylphoshonium bromide (**4a**) (1 mmol, 506 mg), acetic anhydride (10 mmol, 0.94 mL) and triethylamine (3.6 mmol, 0.5 mL) was heated at 120°C for 2 h. After dilution with H_2O, the mixture was neutralized with $NaHCO_3$ and extracted with ethyl acetate. The combined organic layer was washed with H_2O, dil. HCl and brine, and dried over Na_2SO_4. After removal of solvent in vacuo, purification by column chromatography (*n*-hexane/ethyl acetate, 5/1) afforded methyl 1-acetyl-2-methylindole-4-carboxylate (**6a**) (182 mg, 79%) as a pale yellow powder.
7. The reaction was examined at 120°C employing **3a** and base (3.6 equiv.), varying the amount of acetic anhydride. Representative data from this study: 1.5 equiv. of Ac_2O and *i*-Pr_2EtN, 12 h, 60%; 1.5 equiv. of Ac_2O and Et_3N, 12 h, 28%; 2.5 equiv. of Ac_2O and *i*-Pr_2EtN, 2 h, 64%.
8. *Typical procedure of acyl choride-2,6-lutidine system*: Acetyl chloride (3 mmol, 0.21 mL) was added at 0°C to a suspension of (2-amino-6-methoxycarbonylbenzyl)-triphenylphoshonium bromide (**4a**) (1 mmol, 506 mg) and 2,6-lutidine (1 mL), and the mixture was heated at 120°C for 12 h. After dilution with H_2O, the mixture was neutralized with $NaHCO_3$ and extracted with ethyl acetate. The combined organic layer was washed with H_2O, dil. HCl and brine, and dried over Na_2SO_4. After removal of solvent in vacuo, purification by column chromatography (*n*-hexane/ethyl acetate, 5/1) afforded methyl 1-acetyl-2-methylindole-4-carboxylate (**6a**) (144 mg, 62%) as a pale yellow powder.
9. We failed to isolate pure **10**, because this compound was extremely moisture sensitive and readily decomposed. The ratio of **10** and **11** was determined by ^1H NMR.
10. The ratios of two products were determined by ^1H NMR.