Stereoselective Synthesis of Pyrrolo[1,2-*a*]indoles from Allenes in PEG-400 as the Reaction Medium

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Abstract: Base-catalyzed domino cyclization of allenes with 3-chloro-2-formylindoles in PEG-400 was investigated. Pyrroloindoles were formed stereoselectively as single products. The structure of the product depends on the type of allene used. Two compounds have been characterized by single crystal X-ray diffraction.

Key words: allenes, 3-chloro-2-formylindole, domino cyclization, pyrroloindoles, PEG-400

Pyrrolo[1,2-*a*]indoles are tricyclic ring compounds that have attracted much attention due to the broad range of their biological activities[1] and because of their potential as intermediates for the synthesis of polyheterocycles.[2] Although several methods are reported for the preparation of this class of compounds, they usually require several steps and expensive reagents.[3] However, to our knowledge, synthesis of this type of derivative from allenes has never been mentioned, although allenes are proven and useful precursors for a variety of targeted molecules of synthetic and biological applications.[4–6] To this end, base/phosphine catalyzed domino cyclization of allenes with substrates possessing OH/NHR and CHO groups in appropriate positions (e.g., substituted salicylaldehydes or the corresponding imines) is an important reaction.[6,7]

During our ongoing investigations into base-catalyzed domino cyclization reactions of allenes with substrates (having NH/OH and CHO groups in appropriate positions for cyclization), we surmised that 3-chloro-2-formylindole[8] is a substrate that could be used in this type of reaction to prepare pyrrolo[1,2-*a*]indole. In this letter, we wish to report the domino cyclization reactions of 3-chloro-2-formylindole with allenes catalyzed by potassium carbonate in PEG-400 medium leading to the corresponding pyrroloindoles in moderate to good yields. Initially, we used the inexpensive and readily accessible allenylphosphonates **1a–g**,[9,10] then extended the reaction to include the allenyl ester **2**[11a,b] and allenylsulfones **3a** and **3b** (Figure 1).[10,11c]

Initially, we treated the allenylphosphonate **1a** with 3-chloro-2-formylindole **4** in the presence of potassium carbonate in dimethylsulfoxide (DMSO) at 90 °C for four hours, leading to the formation of phosphono-pyrroloindole **5** (Scheme 1) in low yield; only 50% of the allene was consumed in the reaction. Increasing the reaction time led to the formation of a mixture of products. Hence, we optimized the reaction conditions by assessing the reaction in a number of different bases/solvents. The results are summarized in the Table 1. Using potassium carbonate as a base in different solvents (DMSO, EtOH, MeCN, DMF, PEG-400; Table 1, entries 1–5 and 11), it was found that the corresponding pyrroloindole **5** was formed in 14–82% yield; an *E*-configuration around double bond is tentatively assigned. In some cases, a mixture of isomers (Table 1, entries 4 and 5) was obtained. Both 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and potassium carbonate in PEG-400 (a green solvent) gave excellent yields and, in our case, potassium carbonate posed no problems.[7] The ^{31}P NMR evidence showed that only one stereoisomer of **5** was formed.

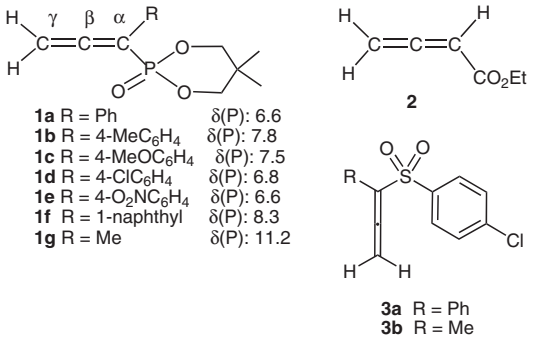
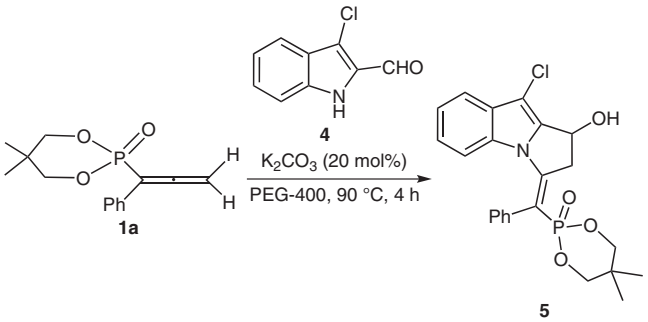


Figure 1



Scheme 1

Under the above optimized reaction conditions, we assessed the scope of the reaction with allenylphosphonates **1a–f** with 3-chloro-2-formylindole **4**, leading to the for-

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Table 1 Optimizing the Yield of **5** in the Reaction of Allene **1a** with **4**

Entry	Base	Solvent	Time (h)	Temp (°C)	Yield (%)[a]
1	K_2CO_3	DMSO	4	90	50
2	K_2CO_3	DMSO	24	90	14
3	K_2CO_3	MeCN	12	90	46
4	K_2CO_3	EtOH	12	90	37
5	K_2CO_3	DMF	4	90	36
6	Ph_3P	PEG-400	12	90	N.R.
7	DABCO	PEG-400	12	90	N.R.
8	NaOAc	PEG-400	4	90	53
9	K_3PO_4	PEG-400	4	90	75
10	DBU	PEG-400	6	90	80
11	K_2CO_3	PEG-400	4	90	82[b]

[a] Yields were calculated by using $^1H/^{31}P$ NMR spectroscopy.
[b] Yield of isolated product was 74%.

mation of phosphono-pyrroloindoles **5**–**10** (Scheme 2, Table 2).[12] In most of the cases, the yields of the isolated products were good and, except for **10**, a single stereoisomer (*E*, based on compound **12**) was formed in each case. All the reactions led to the formation of β,γ-cyclized products.

In contrast to the reactions of α-aryl allenylphosphonates **1a**–**f** discussed above, the α-methyl allenylphosphonate **1g** afforded the β,α-cyclized product **11** (Scheme 3) as the only product, although approximately 50% of the allene **1g** remained unreacted. The yield was not increased by adding more base or by increasing the reaction time. The structure of this compound was confirmed by X-ray crystallographic analysis (Figure 2).[13]

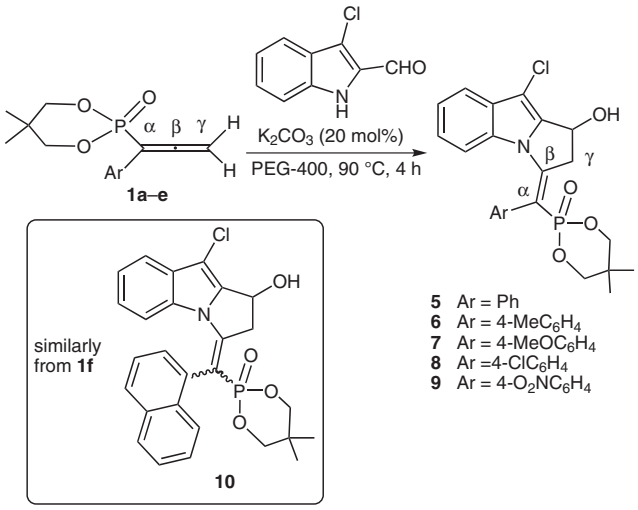
The reaction of ester allene **2** with **4** leads to the formation of pyrroloindole (*E*)-**12**, which is a β,γ-cyclized product

Table 2 Yields and ^{31}P NMR Data for Compounds **5**–**10**

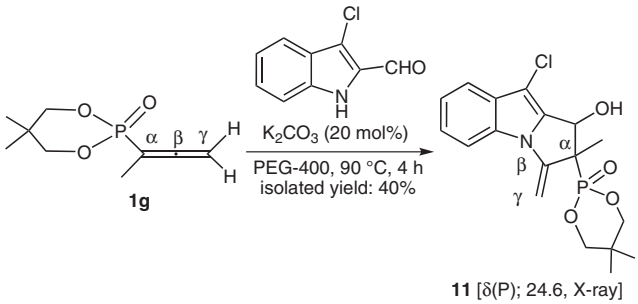
Entry	Product	Ar	δ (P)	Yield (isolated, %)
1	**5**	Ph	15.1	74
2	**6**	4-MeC_6H_4	15.6	70
3	**7**	4-$MeOC_6H_4$	15.9	69
4	**8**	4-ClC_6H_4	15.2	71
5	**9**	4-$O_2NC_6H_4$	14.8	75
6	**10**	1-naphthyl	13.7, 14.7	68

[a] Analysis of the crude reaction mixture ($^{31}P/^1H$ NMR) suggested that yields were in the range of 85–90%.

(Scheme 4). Spectroscopic and analytical data are consistent with the proposed structure. The *E*-configuration was established by X-ray crystallography (Figure 3).[13]



Scheme 2



Scheme 3

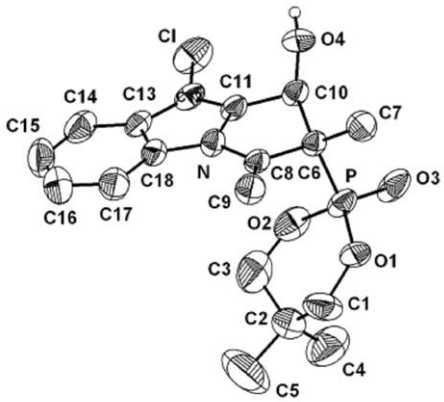
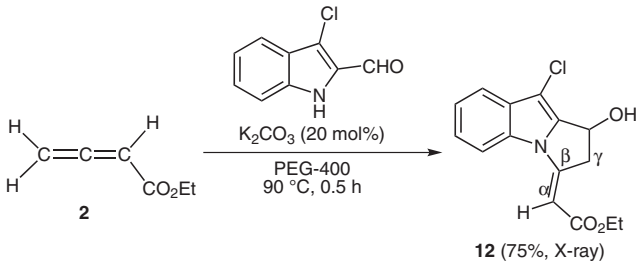


Figure 2 ORTEP diagram of compound **11**. Hydrogen atoms except at the OH group are omitted for clarity. Selected bond lengths [Å] with esd's in parentheses: P–C(6), 1.816(2); C(6)–C(8), 1.522(3); C(8)–C(9), 1.314(3); C(6)–C(10), 1.580(3); N–C(8), 1.403(3); O(4)–C(10), 1.413(2) [hydrogen bond parameters: O(4)–H(4)···O(1), 0.82, 1.94, 2.752(3), 170.6°; symmetry code: 1-x, 1/2+y, 1.5-z].[13]



Scheme 4

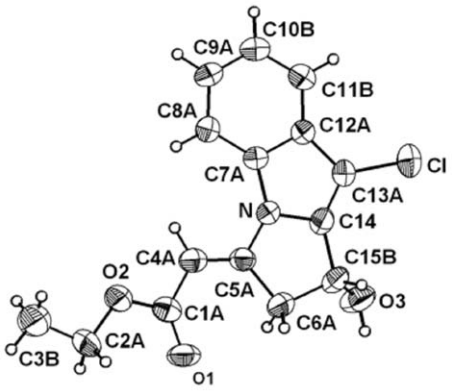
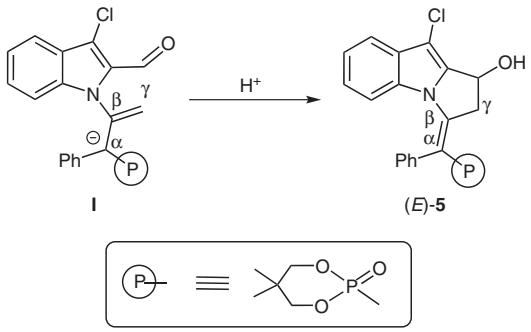


Figure 3 An ORTEP diagram of compound (*E*)-**12**. Selected bond lengths [Å] with esd's in parentheses. C(4A)–C(5A), 1.343(4); C(5A)–C(6A), 1.500(3); C(6A)–C(15B), 1.536(4); N(1)–C(5A), 1.378(3); O(3)–C(15B), 1.415(3). [Hydrogen bond parameters: O(3)–H(3)···O(1), 0.82, 2.01, 2.813(3), 165.6°; symmetry code: 1-x, -y, -z].[13]

The sulfonyl moiety ($ArSO_2$-), as an electron-withdrawing group, is comparable to the phosphoryl [$(RO)_2P(O)$] or the ester group. Hence, we preferred to compare the reactivity of allenes bearing these groups. Thus, we treated the allenylsulfones **3a** and **3b** with 3-chloro-2-formylindole (**4**) and obtained sulfonated pyrroloindoles **13** and **14** in good yields (Scheme 5). Consistent with the results discussed above, the α-phenyl substituted allenylsulfone **3a** gave β,γ-cyclized product **13**, while the α-methyl substituted allenylsulfone **3b** gave the β,α-cyclized product **14**. A distinction between the two types of products can be readily made on the basis of ^{1}H NMR analysis by looking at the presence or absence of signals due to the olefinic (=CH_2) protons.

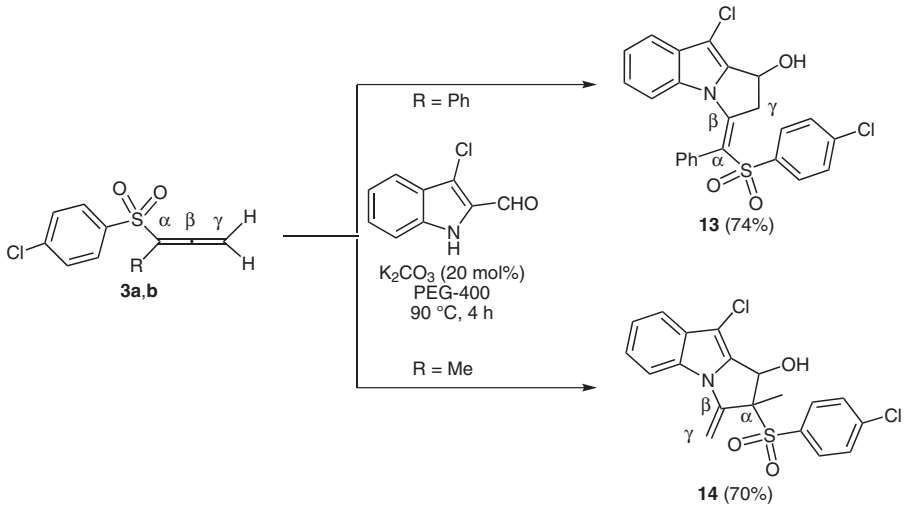
A brief outline of the mechanistic pathway for the formation pyrroloindoles is shown in Scheme 6.[7] First, the base (K_2CO_3) abstracts a proton from 3-chloro-2-formylindole (pK_a of 2-formylindole is 14;[3i] which is expected to be lower with Cl substitution[14]) to generate an anion that attacks **1a** at the β-position to give resonance-stabilized intermediate **I**, which undergoes intramolecular aldol reaction followed by protonation to afford the final product (*E*)-**5**. In the reaction using the allenylphosphonate (**1g**), which has a methyl group at the α-carbon, cyclization occurs via an anion similar to **I**, leading to product **11** (not shown in Scheme 6). A rationalization for the formation of other pyrroloindoles can be made in a similar manner.



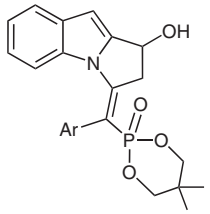
Scheme 6

In the absence of chloro-substitution, under the above conditions, only allenyl phosphonates **1a–d** gave the expected products **15–18** in 50–60% yield (Figure 4). We are investigating this aspect further with other substrates.

Under the green, base-catalyzed domino cyclization reaction conditions developed here, the order of reactivity of



Scheme 5



15 Ar = Ph δ(P): 15.7
16 Ar = 4-MeC$_6$H$_4$ δ(P): 15.9
17 Ar = 4-MeOC$_6$H$_4$ δ(P): 16.0
18 Ar = 4-ClC$_6$H$_4$ δ(P): 15.9

Figure 4

allenes with 3-chloro-2-formylindole is: allenylphosphonates (~4 h under heating) < allenyl sulfones (~2 h under heating) < ester allene (~30 min under heating). In the case of α-aryl substituted allenes **1a–f** and **3a**, the β,γ-product is the major or exclusive product, whereas in the case of α-methyl substituted allenes **1g** and **3b**, β,α-attack is favored. Ester allene **2** gave the β,γ-product, although this allene does not have α-substitution.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(10) Allenes **1d–f**, **3a** and **3b** are new, but were prepared by using described procedures.[9,11] See also: Phani Pavan, M. *Dissertation*; University of Hyderabad: India, **2010**.

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(12) Representative procedure for the preparation of pyrroloindole **5**: To the allene (0.200 g, 0.76 mmol), 3-chloro-2-formylindole[4] (**4**; 0.176 g, 98 mmol) and K_2CO_3 (0.021 g, 0.15 mmol) in a 25 mL round-bottomed flask, was added PEG-400 (2 mL) and the contents were heated at 90 °C for 4 h. The reaction mixture was quenched with H_2O (5 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The whole organic layer was washed with H_2O (3 × 25 mL), dried (Na_2SO_4), filtered, concentrated, and the products were isolated by column chromatography (hexane–EtOAc, 1:4) on silica gel. Yield: 0.25 g (74%); mp 210–214 °C. IR (KBr): 3316, 1634, 1601, 1443, 1327, 1308, 1061 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.68 (s, 3 H), 0.97 (s, 3 H), 3.53–3.56 (m, 1 H), 3.67–3.70 (m, 1 H), 3.95–4.00 (m, 2 H), 4.07–4.16 (m, 2 H), 5.43–5.47 (2 H), 6.64–7.45 (m, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$ + 5%MeOH): δ = 20.7, 21.3, 32.1, 62.4, 75.7, 76.1, 105.3 (d, $J_{P–C}$ = 190.4 Hz), 114.5, 118.0, 122.3, 123.5, 128.2, 128.7, 131.0, 131.3, 131.7, 135.6, 142.0, 150.9 (d, $J_{P–C}$ = 27.3 Hz). ^{31}P NMR (160 MHz, $CDCl_3$): δ = 15.1. LC/MS: *m/z* = 442 $[M – 2]^+$, 444 $[M]^+$. Anal. Calcd for $C_{23}H_{23}ClNO_4P$: C, 62.24; H, 5.22; N, 3.16. Found: C, 62.35; H, 5.28; N, 3.22. Spectroscopic and analytical data for the remaining pyrroloindoles **6**–**14** are given in the Supporting Information

(13) X-ray data for compounds **11** (CCDC 806280) and **12** (CCDC 806281) were collected on OXFORD diffractometer using Mo-K_α (λ = 0.71073 Å) radiation. The structures were solved and refined by standard methods, see: (a) Sheldrick, G. M. *SADABS, Siemens Area Detector Absorption Correction*; University of Göttingen: Germany, **1996**. (b) Sheldrick, G. M. *SHELX-97: A program for crystal structure solution and refinement*; University of Göttingen: Germany, **1997**. (c) Sheldrick, G. M. *SHELXTL NT Crystal Structure Analysis Package*, Version 5; Bruker AXS Analytical X-ray System: WI (USA), **1999**.

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