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A NEW APPROACH TO THE EFFICIENT INDOLE SYNTHESIS BY ALLENE INTRAMOLECULAR CYCLOADDITION

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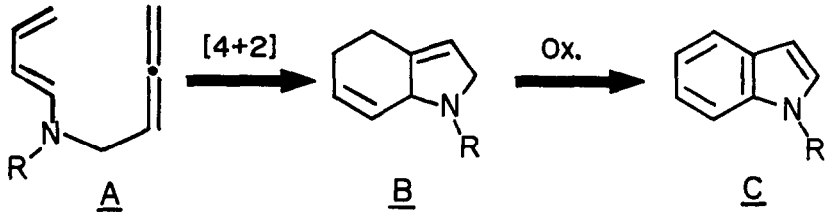
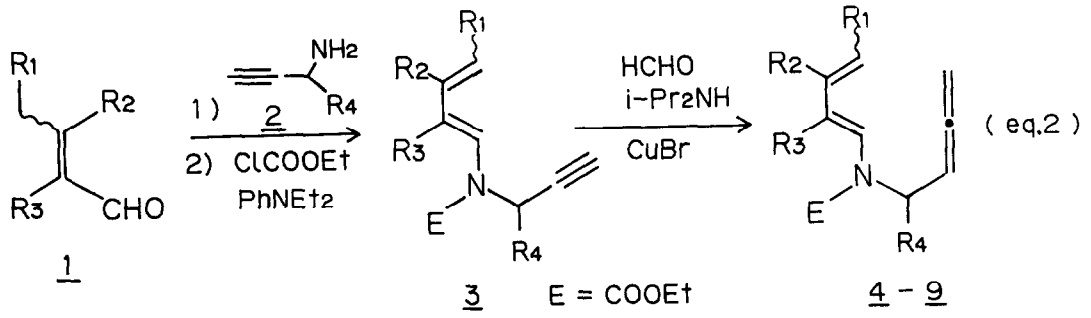
Abstract: A new development of efficient indole synthesis via allene intramolecular cycloaddition strategy is described.

Indole is one of the most important heterocyclic ring systems which constitutes the fundamental skeleton of many natural products, ex., indole alkaloids.[1] Due to the varied and useful biological acitivity as well as potential utility in organic synthesis[2] this versatile heterocyclic compound has continued to attract considerable interest[3] and hence a large number of synthetic methods have been developed for a century.[2] However, essentially all approaches utilize the substitued benzenes and only differ in the type and sequence of reactions used in forming the pyrrole ring.[2] Herein, we wish to report on a new versatile indole synthesis based on the intramolecular Diels-Alder reaction of allenic dienamide (A) and dehydrogenation of the adduct (B) as outlined in eq 1. The synthesis is characterized by the efficient one-step construction of the tetrahydroindole ring system via the allene intramolecular cycloaddition strategy.[4]



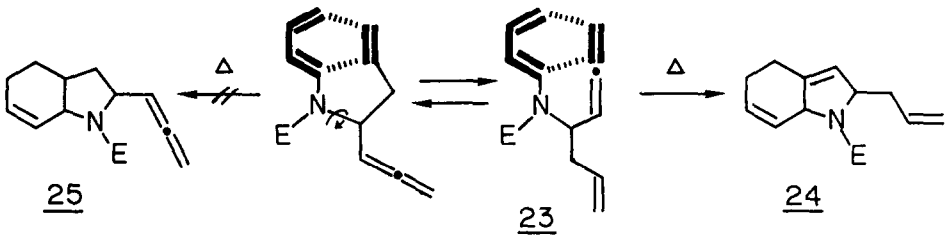
(eq.1)

The requisite allenic dienamides (4-9) were readily prepared from the appropriately substituted aldehydes 1 and propargyl amines 2 via the dienamide formation[5] followed by the homologation to allenes[6] (eq 2). As shown in Table I, these allenic compounds underwent the intramolecular Diels-Alder reaction with remarkable facility to give the corresponding adducts in almost quantita-



(eq.2)

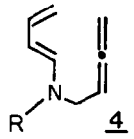
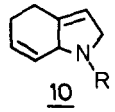
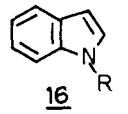
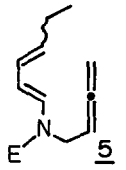
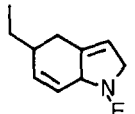
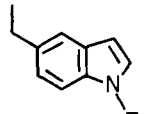
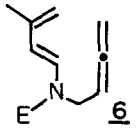
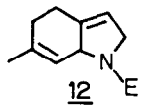
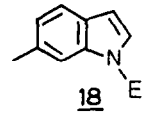
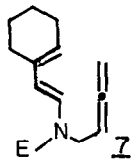
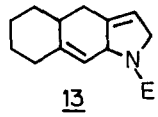
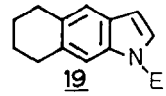
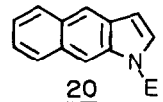
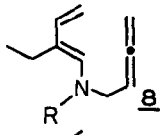
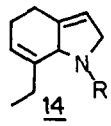
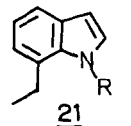
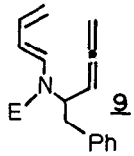
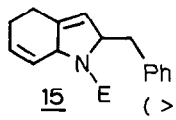
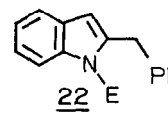
tive yields.[7] The reaction was somewhat retarded by the C_5-substituent and required slightly drastic reaction conditions (entry 3,4). In sharp contrast, the C_2 and C_7-substituents markedly facilitated the intramolecular cycloaddition, and thus the allenes formed in situ underwent spontaneously the Diels-Alder reaction to give the bicyclic products directly (entry 7-9). Structural assingment of these adducts was made on the basis of the spectroscopic data[8] as well as the chemical transformations. For example, a catalytic hydrogenation of 10 over 10% Pd/C in ethanol gave the corresponding cis-indolidine in a quantitative yield. On the other hand, treatment of the Diels-Alder adducts with DDQ (method A) or activated MnO_2 (method B) in benzene at the ambient temperature resulted in a smooth dehydrogenation to give the corresponding indole derivatives (Table I). In the case of 13, oxidation by method A led to the over-dehydrogenation to give 20,[9] while method B afforded the indole 19[9] in a moderate yield.



(eq.3)

The key to the development of a new sequence for the effective indole synthesis was the use of allene as the intramolecular dienophile, which remarkably facilitated not only cycloaddition[4] but also dehydrogenation of the adducts due to the presence of an additional double bond in the five-membered ring forming in the cycloaddition. A superiority of the allenic dienophile to the olefinic one[10] was clearly demonstrated by the thermal reaction (100 °C, 5 h) of 23 which underwent the Diels-Alder reaction only at the allenic double bond to give adduct 24[8] exclusively (in 75% overall yield from the corresponding propargyl amide) (eq 3). This is apparently due to the favorable geometry of allenes for the π-overlap in the transition states.[4]

Table I. Indole Syntheses via Allene Intramolecular Cycloaddition and Oxidation Procedures[a]

entry	dienamide	reaction condition[b]	adduct (% yield)	indole (% yield)
1	 4	a. R = E 160° 9h (E = COOEt)	 10 a. (100)	 16 a. (69)[c]
2		b. R = COPh 160° 6h	b. (100)	b. (50)[c]
3	 5	160° 9h	 11 (49)[e]	 17 (80)[c]
4		200° 16h	(76)[f]	
5	 6	160° 8h	 12 (100)	 18 (50)[d]
6	 7	160° 12h	 13 (100)	 19 (trace)[c] (67)[d]  20 (27)[c] (trace)[d]
7	 8	a. R = E 100° 2h[g]	 14 a. (>75)[h]	 21 a. (75)[d]
8		b. R = COPh 100° 1h[g]	b. (>80)[h]	b. (64)[d]
9	 9	100° 5h[g]	 15 (>74)[h]	 22 (36)[d]

[a] See ref.7,8. [b] All thermal reactions were carried out in a sealed tube(toluene). [c] Oxidation method A: DDQ, PhH,25°C. [d] Oxidation method B: activated MnO_2,PhH,25°C. [e] (Z)-enriched 5 was recovered in 46%. [f] (Z)-5 was recovered in 13%. [g] Cyclization occurred spontaneously under the conditions of allene synthesis. [h] Over-all yields from the propargyl amides.

The method described above provided a new route to indoles, and application of this versatile strategy to the construction of the more complicated heterocyclic ring systems as seen in natural products is now under investigation.

References and Notes

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3) For recent indole syntheses, see: a) A.B. Smith, III and M. Visnick, Tetrahedron Lett., 26, 3757 (1985); b) A.P. Kozikowski and X.-M. Cheng, ibid., 26, 4047 (1985); c) E.C. Taylor, A. H. Katz, H. Salgado-Zamora, ibid. 26, 5963 (1985); d) A.T. Hewson, L.A. March, I.W. Nowell, S.K. Richardson, Chem. Commun., 1985, 618; e) P. Martin, Helv. Chim. Acta, 67, 1647 (1984); c) S. Blechert, Tetrahedron Lett., 25, 1547 (1984); f) M. Vedachalam, M. Mohan, P.C. Srinivasan, ibid., 24, 3531 (1983); g) Y. Ito, K. Kobayashi, N. Seko, T. Saegusa, Bull. Chem. Soc. Jpn., 57, 73 (1984); h) P.A. Wender and A.W. White. Tetrahedron, 22, 3767 (1983).

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5) W. Oppolzer, L. Bieber, E. Francotte, Tetrahedron Lett., 981 (1979).

6) P. Crabbe, H. Fillion, D. Andre, J. L. Luche, Chem. Commun., 1979, 859.

7) Satisfactory spectroscopic data were obtained for all new compounds.

8) ^{1}H NMR spectra (δ, $CDCl_3$) except for the common COOEt signals: 10a; 6.10 (1H, ddm, J = 15.0, 10.5 Hz), 5.64 (1H, dm, J = 10.5, 1.7 Hz), 5.36 (1H, bs), 4.84 (1H, bs), 4.4-4.0 (2H,m), 2.64-2.16 (4H, m). 11; 6.10 (1H, ddm, J = 15.0, 11.0 Hz), 5.67 (1H, dm, J = 10.0 Hz), 5.36 (1H, bs), 4.80 (1H, bs), 4.36-4.0 (2H, m), 2.64-2.0 (3H, m), 1.52-1.16 (2H, m), 0.91 (3H, t, J = 7.0 Hz). 12; 5.84 (1H, dm, J = 9.0 Hz), 5.35 (1H, bs), 4.81 (1H, bs), 4.3-4.04 (2H,m), 2.71-1.96 (4H,m), 1.66 (3H,s). 13; 5.75 (1H, dm, J = 8.4 Hz), 5.31 (1H, bs), 4.81 (1H, bs), 4.32-4.04 (2H, m), 2.91-1.28 (11H, m). 14a; 5.31 (2H, bs), 5.01 (1H, bs), 4.42-3.95 (2H, m), 2.68-1.93 (6H, m), 1.01 (3H, t, J = 7.2 Hz). 15; 7.16 (5H,s), 5.88-5.52 (1H,m), 5.38 (1H, dm, J = 12.0 Hz), 5.24 (1H, bs), 4.76 (2H, bs), 3.4-2.58 (2H,m), 2.58-1.88 (4H,m). 24; 6.14-5.79 (1H, m), 5.86 (1H, dm, J = 11.4 Hz), 5.79-5.46 (1H,m), 5.34 (1H, bs), 5.22-4.77 (2H,m), 2.74-1.97 (6H, m).

9) 19; IR (neat) 1730 and 1620 cm^{-1}, ^{1}H NMR δ 7.89 (1H,s), 7.49 (1H,d,J = 3.6 Hz), 7.23 (1H,s), 6.46 (1H,d,J = 3.6 Hz), 4.45 (2H,q,J = 7.2 Hz), 3.08-2.68 (4H,m), 2.03-1.65 (4H,m), 1.43 (3H,t,J = 7.2 Hz); MS m/z 243 (M^+). 20; mp 64.5-66 °C; IR 1730 cm^{-1}, ^{1}H NMR δ 8.63 (1H,s), 8.11-7.79 (3H,m), 7.71 (1H,d,J = 3.9 Hz), 7.58-7.30 (2H,m), 6.65 (1H,d, J= 3.9 Hz), 4.49 (2H,q,J=7.2 Hz), 1.45 (3H,t,J=7.2 Hz); MS m/z 239 (M^+).

10) It was reported that the analogous reaction of N-acyl-N-(3-buten-1-yl)-1-amino-1,3-butadiene proceeds much slowly (160 °C, 16 h) to give a hexahydroindole in a low yield (38%): see, W. Oppolzer, W. Frostl, Helv. Chim. Acta, 58, 590 (1975).

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