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A SIMPLE SYNTHESIS OF 2-VINYLINDOLES

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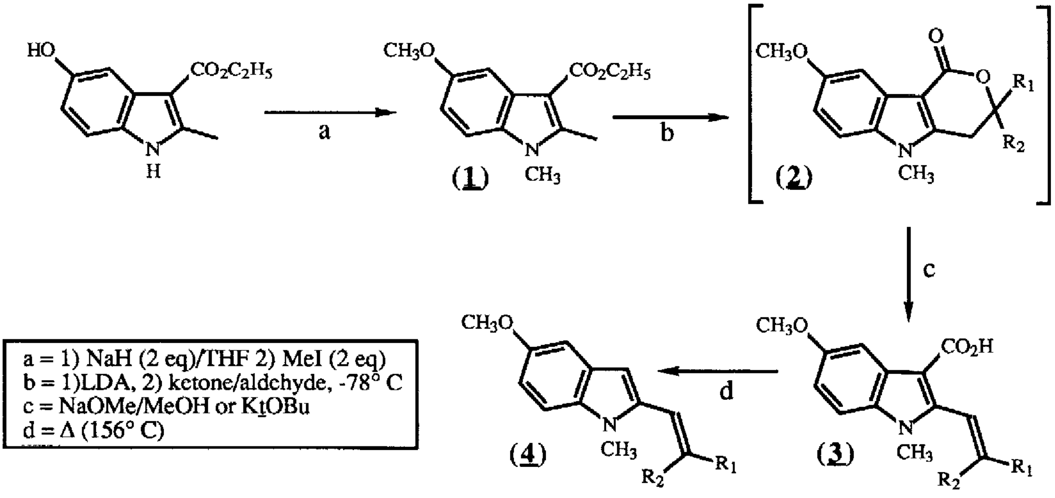
Abstract: A two step synthesis of 2-vinyl indoles is described. Reaction of the anions of 2-methylindole-3-carboxylates (1) and (5) with ketones and aldehydes leads directly to 2-vinylindole-3-carboxylic acids (3) and esters (7), respectively. Decarboxylation of the acids (3) yields the desired 2-vinylindoles (4).

The synthesis and reactivity of 3-vinylindoles are well documented[1]. Most notably, these compounds have been used as both dienes and dienophiles in a number of different Diels-Alder reactions. The analogous 2-vinylindoles, however, have not received an equal amount of attention, which can be attributed to difficulties surrounding their synthesis[2]. Despite this difficulty of synthesis, 2-vinylindoles have been used as intermediates in the formation of *Aspidosperma* alkaloids[3] and have been studied as 2π and 4π components in a limited number of Diels-Alder reactions[1] including cycloadditions with tetrazines[4]. Recently, Pindur[5] and Bergman[6] have reported limited syntheses of 2-vinylindoles, but the need for easier access to these potentially useful indole building blocks still remains.

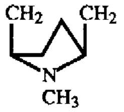
In this communication, we would like to report a facile, general, two-step synthesis of 2-vinylindoles starting from 3-carboethoxy-2-methylindoles, which are readily available from the classic or modified Fischer Indole synthesis[7] and the Nenitzescu Indole synthesis (which produces 5-hydroxyindole 3-carboxylates). Straightforward methylation or acylation of the indole nitrogen using sodium hydride and an electrophile leads to (1) or (5)[8], respectively, in high yield. Reaction of indole (1) (Scheme I) with an excess of lithium diisopropylamide (LDA) at -78° C easily forms the 2-methyl anion which is subsequently reacted with either an aldehyde or ketone at -78° C. As the reaction is warmed to room temperature, the formed alkoxide slowly lactonizes to form the pyrano[3,4-b]indole (2), which was isolated in only a single case[9]. Once the alkoxide has lactonized, the 2-methyl protons are susceptible to deprotonation in situ by remaining base (either residual LDA or ethoxide from the lactonization), which leads to "elimination" of the 3-carboxylic acid, forming the 2-vinylindole 3-carboxylic acid (3). This "intramolecular elimination" reaction can be facilitated with added base; therefore, a solution of sodium methoxide in absolute methanol was added to the resulting reaction mixture after it had warmed to room temperature, and this mixture was heated at reflux to fully effect the desired transformation. This one pot conversion of a 3-carboethoxy-2-methylindole (1) to the 2-

vinylindole 3-carboxylate (3) occurred in good to excellent overall yield as shown in the table accompanying Scheme I. The NMR spectra of olefins (3b) and (3d) indicated the expected *trans* geometry in these molecules as demonstrated by their olefin proton coupling constants of 17.2 and 16.5 Hz, respectively. Decarboxylation of the carboxylic acids (3) in refluxing bromobenzene (156° C) yielded the 2-vinylindoles (4) in excellent overall yields (for two steps).

Scheme I

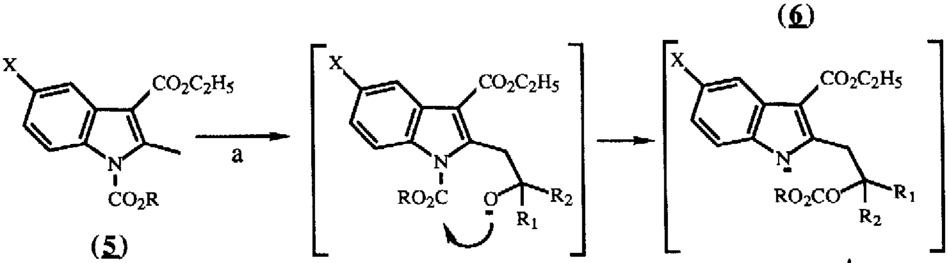


a = 1) NaH (2 eq)/THF 2) MeI (2 eq)
b = 1)LDA, 2) ketone/aldehyde, -78° C
c = NaOMe/MeOH or K*t*OBu
d = Δ (156° C)

	R_1	R_2	Yield of (3) [%]	Yield of (4) [%]
a)	$-(CH_2)_4-$		50	90
b)	Ph	H	85	95
c)	CH_3	CH_3	86	94
d)	$(CH_2)_2CH_3$	H	51	93
e)			58	99

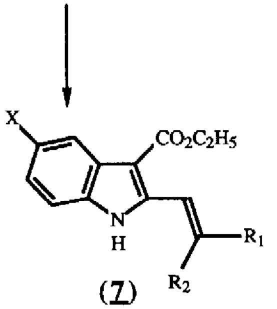
The indole nitrogen requires protection in this reaction sequence. This protection can employ N-methylation, but there is little opportunity to return to the unsubstituted indole NH. Therefore, the use of N-carboethoxy carbamate protection was explored using (5a) (R=Me, X=OMe) and (5b) (R=*t*-Bu, X=H) (Scheme II). Formation of the 2-methyl anion with LDA proceeded smoothly as before, as did the attack of this anion on aldehydes and ketones. However, at this point in the reaction sequence, a difference was seen. The formed alkoxide deprotected the indole nitrogen forming the carbonate (6)[10], which was easily eliminated in refluxing methoxide/methanol/THF solution to yield the 2-vinylindole-3-carboxylate (7). The olefin proton coupling constant (J=16.5 Hz) measured in the ^{1}H NMR spectrum of (7a) indicated the presence of the expected trans gemoetry of the olefin in this molecule. However, the NMR spectra of (7b) and (7c) demonstrated a mixture of olefins, assumed by analogy to be trans:cis in ratios of 2:1 and 3:2, respectively. These results indicate a preference for the expected trans olefin geometry in these elimination reactions, except when R_1 and R_2 are very similar in size. The conversion of (7) to the corresponding 3-unsubstituted indole by basic hydrolysis, followed by thermally induced decarboxylation, is under study[11]. Also, studies involving the chemistry of these 2-vinylindoles and optimization of the synthesis of the pyrano[3,4-b]indoles are presently under way in our laboratories and will be disclosed at a later date.

Scheme II



(5)

(6)



(7)

	X	R	R_1	R_2	% Yield (7)
a)	OCH_3	Et	$(CH_2)_4CH_3$	H	33 [Note 1]
b)	OCH_3	Et	$(CH_2)_3CH_3$	CH_3	87 [Note 2]
c)	H	t-Bu	Ph	CH_3	75 [Note 3]
d)	H	t-Bu	CH_3	CH_3	61

a = 1) LDA, 2) $R_1R_2C=O$, 3) Δ, MeOH or EtOH, NaH

Note 1: obtained as methyl ester from refluxing NaOMe, MeOH
Note 2: obtained as a 2:1 mixture of trans:cis
Note 3: obtained as a 3:2 mixture of trans:cis

A typical experimental procedure is as follows: To a stirred solution of lithium diisopropyl amide (7.5 mmol from 1.05 mL diisopropylamine and 3.0 mL of 2.5 M n-butyllithium, 1.5 eq) in anhydrous tetrahydrofuran (15 mL) at -78° C was added a solution of the appropriate 2-methylindole (1) or (5) (5.0 mmol, 1.0 eq) in anhydrous tetrahydrofuran (10 mL) rapidly such that the temperature remained below -50° C. The resulting orange solution was cooled to -78° C, stirred at that temperature for 10 min, and then the aldehyde or ketone was added dropwise either in solution (solids) or directly (liquids). The resultant solution was then allowed to warm to room temperature, and a solution of sodium hydride (60%, 0.40 g, 10.0

mmol, 2 eq) in methanol (10 mL) was added. This mixture was then heated at reflux under nitrogen for 2-8 h, depending on the substrate. The resulting reaction solution was evaporated under reduced pressure, and the residual solid was partitioned between water (15 mL) and methylene chloride (15 mL). The organic layer was removed, and the aqueous layer was extracted with methylene chloride (2 x 20 mL). All extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure. The residual solid was purified either by simple ether trituration or flash column chromatography using silica gel to yield the desired 2-vinylindole-3-carboxylic acid (**3**) [from (**1**)] or 2-vinylindole carboxylate (**7**) [from (**5**)]. A mixture of (**3**) (3.00 mmol) and bromobenzene (10 mL) was heated at reflux under nitrogen for 2-8 h, depending on the substrate. The resulting reaction solution was poured through a silica gel filter (approx 25 g) followed by hexanes (500 mL) and then methylene chloride/hexanes (1:1, 500-1000 mL). The latter filtrate was evaporated under reduced pressure to yield the desired 2-vinylindole (**4**).

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[8] All new compounds isolated and disclosed in this paper have been characterized by melting point, IR, ^{1}H and ^{13}C NMR, LRMS, and elemental analysis and/or HRMS.

[9] The specific synthesis of pyrano[4,3-b]indoles, a relatively unknown ring system, will be detailed in a later publication.

[10] In one case, the reaction was immediately quenched after the addition of acetone at -78° C, and (**6d**) was isolated (74% yield) and fully characterized.

[11] Ample literature precedent exists for this transformation; see: Brown, R.K., "The Synthesis of the Indole Nucleus," Volume 25, Part 1 in the series: The Chemistry of Heterocyclic Compounds (W. J. Houlihan, ed.), A. W. Weissberger and E.C. Taylor, eds., **1972**, John Wiley and Sons, New York, New York, p.414.

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