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A New Indole Synthesis *via* [3+3] Annulation of 2-(Benzotriazol-1-ylmethyl)-pyrroles with α, β-Unsaturated Aldehydes and Ketones

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Abstract: Poly-substituted indoles are readily accessible from substituted 2-(benzotriazol-1-yl methyl)pyrroles by lithiation, reaction with α,β-unsaturated aldehydes and ketones, and subsequent facile dehydrobenzotriazolylation-cyclodehydration. The substituted 2-(benzotriazol-1-ylmethyl)-pyrrole precursors are obtained by reacting α-bromoketones with terminally lithiated propargylbenzotriazole, and treating the resulting epoxide with a primary amine.

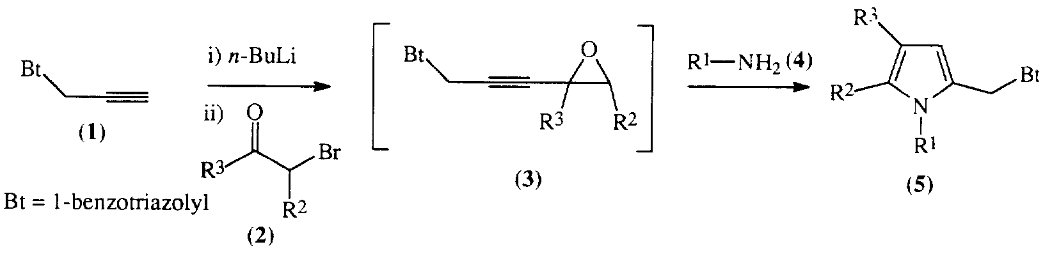
INTRODUCTION

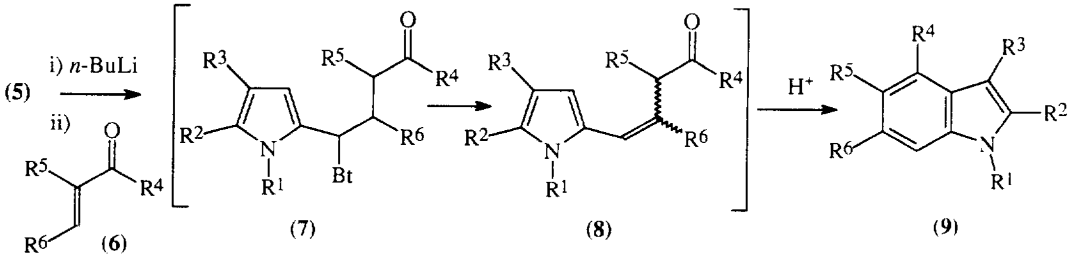
Poly-substituted indoles are of importance as precursors for biologically active compounds[1,2]. The synthesis of such moieties usually proceeds *via* building up of the pyrrole portion onto the benzene ring[2,3]. A number of methods have been developed which access the indole by synthesising the benzene portion onto the pyrrole nucleus[2,4-6] (and analogously a carbazole from an indole[5,7]), however, there are no simple examples of the direct reactions of pyrrole derivatives with readily available α,β-unsaturated aldehydes and ketones, to give poly-substituted indoles by cyclisation.

We recently described a benzotriazole-mediated synthesis of alkyl substituted pyrroles[8]. This methodology has now been extended to the synthesis of poly-substituted alkyl and aryl indoles, by a route which incorporates the reaction of substituted 2-(benzotriazol-1-ylmethyl)pyrroles with α,β-unsaturated aldehydes and ketones.

DISCUSSION

Muratake and Natsume showed that pyrrole derivatives of type **8** undergo facile cyclodehydration to indoles[6]. We proposed to generate such moieties **8** from 2-(benzotriazol-1-ylmethyl)pyrrole derivatives **5** by lithiation α to the benzotriazole group[9], reaction of this stabilised anion[10] with α,β-unsaturated aldehydes and ketones **6**, and subsequent acid catalysed elimination of 1-benzotriazole from **7**. The previous cyclodehydrations occured by mild acid catalysis[6], and so pyrroles **5** should be converted into the required indoles **9** in one pot. We herein report the realisation of this route, which incorporates the synthetic utility of 1-benzotriazole as a good nucleofuge, and also as an α-lithiation directing and anion stabilising group[9,10].





Propargylbenzotriazole (**1**) was prepared by modification of the literature procedure[11]. The reaction of **1** with one equivalent of *n*-butyllithium at -78°C gave the terminally lithiated alkyne[12], which underwent nucleophilic addition to α-bromoketones **2** to give epoxides **3**. These were reacted without isolation, with primary amines **4** to give the pyrroles **5**. Lithiation α to benzotriazole, and subsequent 1,4-addition to α,β-unsaturated aldehydes or ketones **6** gave intermediates **7**, which could be isolated, but were usually reacted directly. Acid catalysed dehydrobenzotriazolylation-cyclodehydration, column chromatography and recrystallisation, or Kugelrohr distillation, gave the desired indoles **9**, in good yield, Table 1. In many cases the reaction intermediates **8** were isolated and characterised.

Typical Experimental Procedure : 1-Propargylbenzotriazole (**1**) (50 mmol) was dissolved in dry THF (200 mL), under argon, and cooled at -78°C during the dropwise addition of *n*-butyllithium in hexanes (50 mmol)[14]. The reaction mixture was left stirring for 30 minutes at this temperature before adding the α-bromoketone **2** (50 mmol) dropwise, as a solution in dry THF (40 mL). The reaction mixture was stirred at -78°C for 12-16 hours, warmed to -10°C, and quenched with water. Extraction into ethyl acetate, drying over magnesium sulphate, and concentrating [the temperature was kept below 60°C for the duration of the work-up in order to minimise decomposition and by-products] gave the crude epoxides **3**, which were checked by ^{1}H-NMR, before dissolving in propan-2-ol (200 mL), adding the primary amine **4** (50 mmol), and refluxing gently for 1-3 days. The reaction mixture was evaporated to dryness. Column chromatography (on silica with ether:hexane=1:10), gave, after recrystallisation from ether:hexanes=1:5, the pure pyrroles **5**, as colourless crystals in each case.

Pyrrole **5** (3 mmol) was dissolved in dry THF (100 mL), under argon, and cooled to -78°C during the dropwise addition of *n*-butyllithium in hexanes (3 mmol). The reaction mixture was left stirring for 40 minutes at this temperature before adding the α,β-unsaturated aldehyde or ketone **6** (3 mmol), dropwise as a solution in dry THF (15 mL). The reaction mixture was left at -78°C for 12-16 hours, warmed to -10°C, quenched with water, extracted into ethyl acetate, dried over magnesium sulphate, and concentrated. The crude product **7** was dissolved in dry THF (50 mL), Amberlyst 15® catalyst (10 g) added, and the solution refluxed gently for 1-5 days. The catalyst was filtered off and the solvent removed. The crude product was purified by column chromatography on silica with ether:hexanes=1:100. The relevant fractions (fluorescent under UV on TLC plate) were combined, concentrated, and indoles **9a-e, g** were recrystallised from ether:pentane=1:50. Indoles **9f** and **9h** were isolated as oils and further purified by Kugelrohr distillation. All isolated intermediates (**5**) and products (**9**) were fully characterised by ^{1}H, ^{13}C-NMR, GC-MS, and combustion analysis (m.p.'s: **5a**, 129-130°C; **5c**, 129-130°C; **5e**, 70-71°C; **5g**, 86-87°C (lit[8] m.p. 86-87°C); **5h**, 110-112°C; **9a**, 146-147°C; **9b**, 161-162°C; **9c**, 106-107°C; **9d**, 128-129°C; **9e**, 108-109°C; **9g**, 125-126°C).

Table 1. Synthesis of Poly-Substituted Pyrroles **5** and Indoles **9**.

	R^1	**R^2**	**R^3**	**R^4**	**R^5**	**R^6**	**5**[b]	**9**[c]
a	$PhCH_2$	Me	Ph	Ph	H	Ph	48%	56% (40)
b	$PhCH_2$	Me	Ph	H	Ph	Et	-----[a]	76% (62)
c	Bu^t	H	Ph	Me	H	H	32%	60% (47)[d]
d	H	H	Ph	Me	H	H	-----[a]	56% (44)[d]
e	$MeO(CH_2)_2$	Me	Me	Ph	H	Ph	58%	52% (43)
f	$MeO(CH_2)_2$	Me	Me	H	Ph	Et	-----[a]	75% (66)
g	$ArCH_2$	Me	Me	Ph	H	Ph	59%	51%
h	Bu^n	Me	Me	Ph	H	Ph	62%	54%

Ar = *p*-methoxyphenyl; a - same intermediate **5** as preceding entry in this column; b - recrystallised yields of **5**, based on propargylbenzotriazole (**1**); c - percentage yields of **9**, based on **5** and recovered intermediate **8**, percentage conversion in parentheses; d - Amberlyst 15® in refluxing THF affected ring closure, but refluxing toluene caused the *tert*-butyl group to be removed.

We believe this general method should allow rapid access to poly-substituted 1*H*-indoles which are difficult to synthesise using other methods. The synthetic route could also be easily extended to allow substituents to be introduced into position 7 of the 1*H*-indole by first lithiating intermediate pyrroles **5**, and subsequently quenching with an electrophile prior to the elaboration of the indole nucleus.

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11. Benzotriazole (0.5 mol) and powdered sodium hydroxide (0.5 mol) were dissolved in absolute ethanol (150 mL) and water (2 mL), and stirred at 0°C during the dropwise addition of propargyl bromide (0.5 mol as 80% solution in toluene) over 4 hours. The reaction mixture was left stirring for 12 hours, the solvent removed, the residue dissolved in ethyl acetate, washed with saturated aqueous sodium bicarbonate, dried over magnesium sulfate, and concentrated. The residue was recrystallised from ether to give pure 1-propargylbenzotriazole (0.2 mol, 40%) as colourless needles, m.p. 58-59°C (lit[12] m.p. 57-58°C). The mother liquor was concentrated and columned on silica with 10% ether:hexanes to give initially 2-allenylbenzotriazole (0.11 mol, 22%) as colourless needles, m.p. 52-53°C (1-allenylbenzotriazole has previously been reported[13]); followed by a further portion of 1-propargylbenzotriazole (0.16 mol, 32%). Overall recrystallised yield = 72%.
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14. 90% of the theoretical volume of *n*-butyllithium in hexanes was added, after which the solution was titrated dropwise up to the point at which one more drop of *n*-butyllithium turned the solution a deep indigo-blue colour, and this colour did not dissipate to give a deep brown / yellow solution.

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