Tetrahedron Letters,Vol.26,No.16,pp 2017-2020,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

ACTION OF *tert*-BUTYL AZIDOFORMATE ON THE CONJUGATE BASES OF 1,2,3,4-TETRAHYDRO-9*H*-CARBAZOLE AND OTHER INDOLE DERIVATIVES

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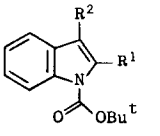
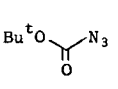
Summary. *tert*-Butyl azidoformate (2) reacts with the conjugate bases of 3a, 7a, 9 ($R^1 = R^2 = CH_3$), and 9 ($R^1 = CH_3$, $R^2 = H$) to give products [4, 8, 12, and 14, respectively] in addition to the expected *N*-(*tert*-butoxycarbonyl)indole derivatives.

1-*N*-(*tert*-butoxycarbonyl)indole (1a) is readily prepared[1] in high yield by treating indole first with sodium hydride and then with *tert*-butyl azidoformate[2] (2) in tetrahydrofuran. In an attempt to convert 1,2,3,4-tetrahydro-9*H*-carbazole (3a) into its 9-*N*-(*tert*-butoxycarbonyl) derivative by a related procedure[3], we obtained the latter compound (3b) in only 46% yield, together with another product (m.p. 116.5°C, 22%) to which structure 4 has been assigned on the basis of microanalytical[4] and n.m.r. spectroscopic data[5]. This assignment is supported by degradative evidence and has been confirmed by an independent synthesis (see below).



1 a; $R^1 = R^2 = H$



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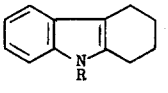
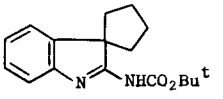


3 a; R = H
b; R = CO_2Bu^t



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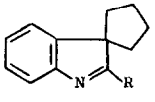
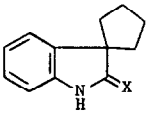
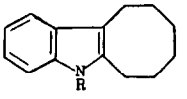


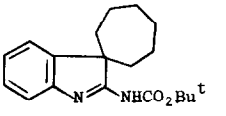
5 a; R = NH_2
b; R = SMe



6 a; X = O
b; X = S



7 a; R = H
b; R = CO_2Bu^t



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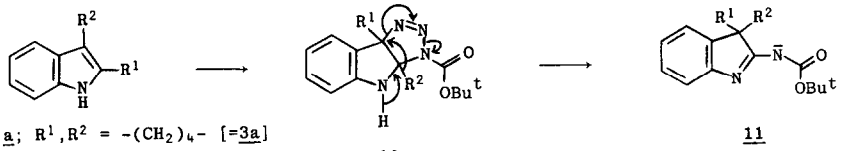
When 4 was treated with an excess of trifluoroacetic acid in dichloromethane solution at room temperature, 5a was obtained and was isolated as a colourless hygroscopic crystalline solid, m.p. 205°C, in 52% yield. Treatment of 5a with sodium nitrite in aqueous acetic acid gave the known[6,7,8] oxindole derivative (6a) in 65% yield. The latter compound, which was identical [i.r., ^1H and ^{13}C n.m.r. spectra] with authentic material[8], was heated, under reflux, with Lawesson's reagent[9] in toluene solution and the resulting product (6b) was treated first

with sodium hydride and then with methyl iodide in tetrahydrofuran at room temperature to give 5b as a colourless oil in 55% overall yield, based on 6a. Ammonolysis of 5b [6*M*-methanolic ammonia, 140°C, 21 hr] gave 5a (72% yield) which, on treatment with sodium hydride followed by *tert*-butyl phenyl carbonate in tetrahydrofuran, gave the original rearrangement product (4) in 82% yield. When 7a, a higher homologue of 3a, was treated with n-butyllithium and *tert*-butyl azidoformate (2) under the conditions used for 3a, 7b and 8 [m.p. 130°C] were obtained and isolated in yields of 19 and 27.5%, respectively. A possible mechanism for the rearrangement reactions is indicated in Scheme 1.

Scheme 1

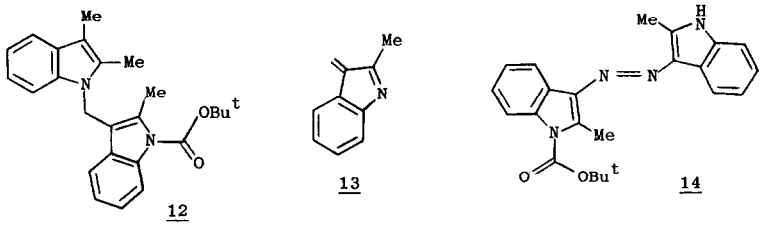


9 a; $R^1,R^2 = -(CH_2)_4-$ [=3a]
b; $R^1,R^2 = -(CH_2)_6-$ [=7a]

10

11

The above rearrangement reaction (Scheme 1) did not occur in the case of 2,3-dimethylindole (9; $R^1 = R^2 = CH_3$). Treatment of the latter compound (9; $R^1 = R^2 = CH_3$) with sodium hydride (*ca.* 3 mol. equiv.) followed by *tert*-butyl azidoformate (2; *ca.* 1.2 mol. equiv.) in tetrahydrofuran at room temperature for 14 hr gave unchanged starting material (9; $R^1 = R^2 = CH_3$, 39%), its 1-*N*-(*tert*-butoxycarbonyl) derivative (1; $R^1 = R^2 = CH_3$, 20%), and a dimeric compound (12%), m.p. 137°C, with molecular formula $C_{25}H_{28}N_2O_2$. The latter compound has been assigned structure 12 on the basis of an X-ray crystal structure determination (Figure 1). This assignment is in accordance with ^1H and ^{13}C n.m.r. spectroscopic data. The mechanism for the dimerization reaction is at present unclear. However, a process involving the conjugate addition of the anion of 2,3-dimethylindole to its dehydro-derivative (13), followed by *N*-*tert*-butoxycarbonylation would lead to 12.



12

13

14

It is clear from the above discussion that *tert*-butyl azidoformate (2) is an unsuitable reagent for the introduction of 1-*N*-(*tert*-butoxycarbonyl) protecting groups in both 2,3-cycloalkenyl (such as 3a and 7a) and 2,3-dialkyl indole derivatives (such as 9; $R^1 = R^2 = CH_3$). The latter acylating agent (2) should be used with caution in the 1-*N*-protection of any indole (and presumably also pyrrole) derivative. Thus while 2 reacts with the sodium salt of 3-methylindole (9; $R^1 = H$, $R^2 = CH_3$) to give the expected 1-*N*-(*tert*-butoxycarbonyl) derivative (1; $R^1 = H$, $R^2 = CH_3$) as the sole product in 75% isolated yield, it reacts with the sodium

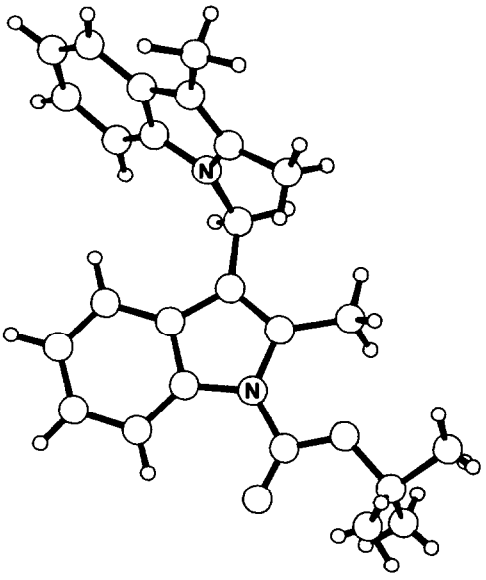
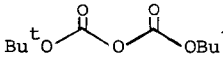


Figure 1. Computer-drawn plot of molecular structure of 12

salt of 2-methylindole (9; $R^1 = CH_3$, $R^2 = H$) to give its 1-*N*-(*tert*-butoxycarbonyl) derivative (1; $R^1 = CH_3$, $R^2 = H$) in only 11% yield together with a crystalline product, m.p. 165 - 167°C, to which structure 14 has been assigned[10]. The latter product was isolated in 60% yield.



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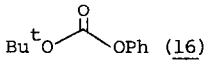

(16)

It was recently reported[11] that the 1-*N*-(*tert*-butoxycarbonyl) derivatives of pyrrole itself and a number of substituted pyrroles are obtained in good yields by treating these substrates with bis-*tert*-butyl dicarbonate in the presence of 4-dimethylaminopyridine in acetonitrile solution. This procedure was also used[11] successfully in the *tert*-butoxycarbonylation of indole and 3-methylindole (9; $R^1 = H$, $R^2 = CH_3$). When we became aware of the shortcomings of *tert*-butyl azidoformate (2) as a reagent for the *tert*-butoxycarbonylation of indole derivatives, we found that if 2 were replaced by *tert*-butyl phenyl carbonate (16) and the acylation procedure described above [i.e. treatment of the indole derivative first with sodium hydride or n-butyllithium in tetrahydrofuran] were otherwise retained, all of the substituted indoles referred to above were converted solely into their 1-*N*-(*tert*-butoxycarbonyl) derivatives. The latter compounds were all isolated in good (74-92%) yields.

Acknowledgement. One of us (D.D.) thanks the S.E.R.C. for the award of a research studentship.

REFERENCES AND FOOTNOTES

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[3] n-Butyllithium (1.9*M* in hexane, 3.1 ml, 5.9 mmol) was added to a stirred solution of 3a (1.0g, 5.9 mmol) in tetrahydrofuran at 0°C, in an atmosphere of nitrogen. The reaction mixture was allowed to warm up to room temperature and *tert*-butyl azidoformate (2; 0.86g, 6.0 mmol) was added. After 12 hr, water was added, and the products were worked up and chromatographed. When sodium hydride was used as base instead of n-butyllithium, 3b and 4 were isolated in 35 and 16% yields, respectively. The conversion of 3a into its conjugate base occurs much more quickly when n-butyllithium (15 min, room temperature) rather than sodium hydride (8 hr, room temperature) is used as base.

[4] Satisfactory microanalytical data were obtained for all new crystalline compounds described.

[5] The ^{1}H and ^{13}C [$\delta(CDCl_3)$: 26.40 (CH_2), 28.31 (CH_3), 39.81 (CH_2), 57.84, 80.06, 110.39, 122.76, 123.60, 127.67, 138.41, 140.49, 164.80, 180.81] n.m.r. spectra were in accordance with structure 4; M^+ = 286.1678 (calc. for $C_{17}H_{22}N_2O_2$: 286.1681). While the reaction between 3a and toluene-*p*-sulphonyl azide is reported not to lead to the 2-*N*-tosyl derivative of 5a [A.S. Bailey, R. Scattergood, and W.A. Warr, *J. Chem. Soc.(C)* 2479 (1971)], the reaction between *p*-chlorobenzenesulphonyl azide and 2-oxo-1,2,3,4-tetrahydro-9*H*-carbazole does lead to a rearrangement product corresponding to 4 [A.S. Bailey and M.H. Vandrevala, *J. Chem. Soc., Perkin Trans. I* 1512 (1980)].

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[10] Treatment of 2-methylindole (9; $R^1 = CH_3$, $R^2 = H$) with picryl azide is reported [A.S. Bailey and J.J. Merer, *J. Chem. Soc.(C)* 1345 (1966)] to lead to a good yield of the charge transfer complex of picramide and 3,3'-azobis-(2-methylindole) [i.e. the compound which would formally be obtained if the *tert*-butoxycarbonyl group were removed from 14].

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(Received in UK 22 February 1985)