Pergamon

Tetrahedron Letters 39 (1998) 3095–3098

TETRAHEDRON LETTERS

Synthesis of Indole-3-carboxamides via a Haloform Cleavage Reaction of 3-Trifluoroacetylindole with Lithium Dialkylamides

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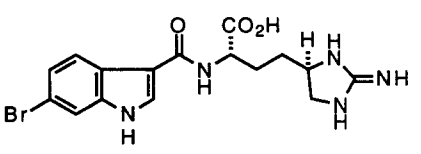
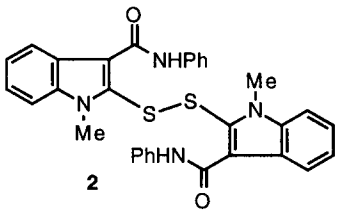
Received 17 December 1997; revised 17 February 1998; accepted 18 February 1998

Abstract: Reaction of 3-trifluoroacetylindole (**4**) with lithium dialkylamides affords the corresponding indole-3-carboxamides (**5**) in good to excellent yields.

Recent years have seen the discovery of several biologically active natural and synthetic indole-3-carboxamides.[1-3] For example, cytotoxic extracts of the marine ascidian *Leptoclinides dubius* contain four novel indole-3-carboxamides including **1**, which contains the rare amino acid L-enduracididine,[1] and a large group of synthetic 2,2'-dithiobis(1*H*-indole-3-carboxamides) of type **2** have significant tyrosine kinase inhibitory activity.[2]

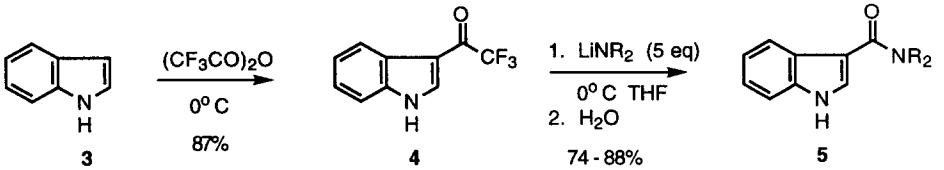


1



2

The availability of 3-trifluoroacetylindole (**4**) from indole (**3**)[4] and the reports that **4** readily undergoes a haloform reaction with sodium hydroxide to afford indole-3-carboxylic acid[4] suggested to us that amide anions might convert 3-trifluoroacetylindole (**4**) into indole-3-carboxamides (**5**). Moreover, zwitterionic adducts between trifluoromethyl ketones and tertiary amines are known,[5] thus illustrating the enhanced electron deficiency of the trifluoromethyl carbonyl group. Indeed, treatment of 3-trifluoroacetylindole (**4**), which is prepared from indole (**3**) in high yield with trifluoroacetic anhydride,[4] with excess lithium dialkylamides results in the smooth conversion to the corresponding indole-3-carboxamide (**5**). The secondary lithium *t*-butylamide also reacts in this fashion to yield **5e**. Our results are summarized in the Table. Amide **5d** is a new compound and **5e** is characterized for the first time.[8,9]

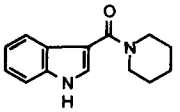
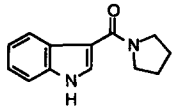
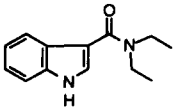
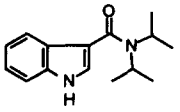
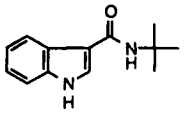


3 **4** **5**

Reactions with the corresponding amines gave hemiaminals and reactions with the lithium amides of aromatic amines gave mixtures and were generally less satisfactory. Sodium amide gave no reaction with **4.**

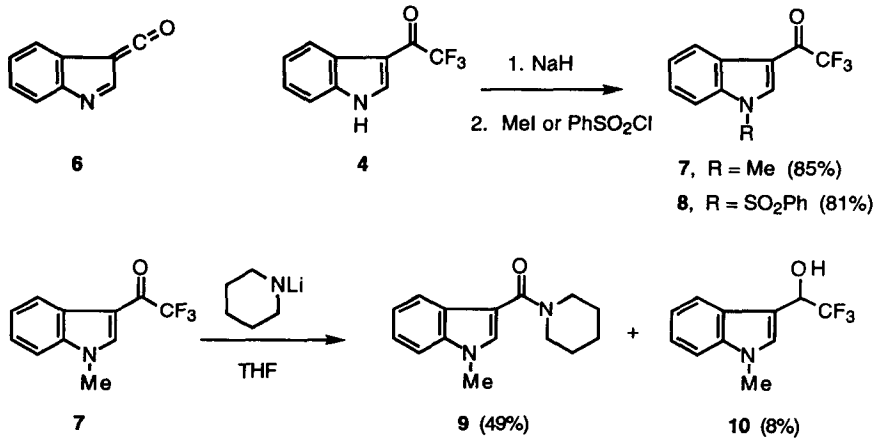
00040-4039/98/$19.00
PII: S0040-4039(98)00505-X

Table. Reactions of Trifluoroacetylindole (4) with Lithium Dialkylamides

Amine	Product		Yield[a]	Melting Point (°C)	Literature Mp (°C)
		**5a**	88%	161-163	160[6]
		**5b**	87%	234-236	230[6]
		**5c**	74%	150-151	151-151.5[7]
		**5d**	85%	185-188	—
		**5e**	78%	188-190	—

[a]Isolated yields of chromatographed product.

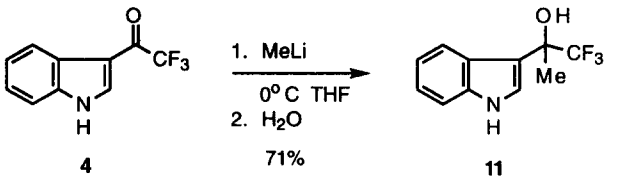
It was of interest to examine the reaction of *N*-substituted 3-trifluoroacetylindoles since it seemed possible that the reaction of **4**→**5** involves the intermediacy of ketene **6**. Therefore, *N*-methyl- (**7**)[10] and *N*-phenylsulfonyl-3-trifluoroacetylindole (**8**)[11] were prepared from **4** (NaH/MeI or $PhSO_2Cl$). However, reaction of **7** with lithium piperidide under the standard conditions afforded carboxamide **9**[12] in 49% yield and alcohol **10** in 8% yield.[13] A similar reaction with **8** gave a complex mixture containing carboxamide **5a** (9%) and smaller amounts of 3-trifluoroacetylindole (**4**). Thus, although ketene **6** may be involved in the chemistry of **4**, clearly it is not a requisite intermediate since *N*-substituted-3-trifluoroacetylindoles can undergo the same reaction, albeit at what appears to be a slower rate.



6 **4** **7**, R = Me (85%); **8**, R = SO_2Ph (81%)

7 **9** (49%) **10** (8%)

Surprisingly, the reaction of 3-trifluoroacetylindole (**4**) with MeLi and *n*-BuLi under the same conditions as those with lithium amides yielded only the corresponding tertiary alcohols, e.g., **11**[14], the products of normal 1,2-addition to the carbonyl group. No evidence of haloform-type cleavage products was seen in these cases.



4 **11**

Previous methods for the synthesis of indole-3-carboxamides involve the reaction between indole Grignard reagents and *N,N*-dialkylchloroformamides,[7] DCC-coupling of indole-3-carboxylic acid and aniline,[15] reaction of indole with phenyl isothiocyanate followed by alkaline H_2O_2,[16] reaction of indole-3-carbonyl chloride with amines,[17] reaction of indole with chlorothioformamidinium salts, and then base hydrolysis,[18] irradiation of 3-diazo-4-oxo-3,4-dihydroquinolines in the presence of amines (Wolff rearrangement),[19] and reductive cyclization of *N,N*-dialkyl-2-(2-nitrophenyl)-2-cyanoacetamides.[6]

We believe that the method described herein is a reasonably general method for the synthesis of indole-3-carboxamides that may be superior both in scope and efficiency to several of the known procedures for this transformation. Moreover, this lithium amide cleavage of the trifluoroacetyl group to yield amides appears to be a new variation of the haloform reaction.[20] Our further studies in this area will be reported in due course.

General Procedure: A solution of freshly distilled amine (1.6 mmol) in dry tetrahydrofuran (THF) (2 mL) under N_2 at 0°C was treated with *n*-BuLi (0.6 mL, 1.6 mmol, 2.5 M in hexanes). After being stirred for 1 h at 0°C, the resulting lithium amide solution was treated at 0°C with stirring with a solution of 3-trifluoroacetylindole (**4**) (130 mg, 0.60 mmol) in THF (5 mL). The reaction mixture was stirred overnight while being allowed to warm to room temperature. The mixture was quenched with H_2O (5 mL), stirred for 30 min, further diluted with ice water (50 mL), and stirred for 1 h. Some of the amides precipitated at this point and were collected by suction filtration and dried in vacuo. The filtrate was extracted with CH_2Cl_2 (4 x 50 mL) and the CH_2Cl_2 extracts were washed with brine, dried (Na_2SO_4), concentrated in vacuo, and chromatographed over silica gel to give additional product. If the product did not precipitate, then the reaction mixture was processed as described above to give the yields shown in the Table.

Acknowledgments: This work was supported in part by the Donors of the Petroleum Research Fund, administered by the American Chemical Society, and Pfizer.

References and Notes:

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8. **5d**: Mp 185-188 °C; IR (KBr) 3222 (NH), 2967 (CH), 1594 (C=O), 1533 (C=O) 1444, 1350, 1216, 1122, 744 cm^{-1}; H^1 NMR ($CDCl_3$) δ 10.65 (s, 1 H), 7.76 (d, 1 H, J = 9 Hz), 7.41 (m, 2 H), 7.12 (m, 2 H), 4.03, (bs, 2 H), 1.40 (d, 12 H, J = 6.6 Hz); C^{13} NMR ($CDCl_3$) δ 167.9, 135.9, 126.4, 124.08, 122.5, 120.5, 120.2, 113.3, 111.9, 24.0, 21.5; MS *m/z* 244 (M^+), 201, 144, 116, 86. Anal. Calcd for $C_{15}H_{20}N_2O$: C, 73.74; H, 8.25; N, 11.47. Found: C, 73.73; H, 8.33; N, 11.46.
9. Although **5e** was reported by Ito (Ito, Y.; Kobayashi, K.; Saegusa, T. *Tetrahedron Lett.* **1979**, 1039-1042), no data were given. **5e:** Mp 188-190 °C; IR (film) 3399, 3231, 2964, 1627 (C=O), 1538, 1449, 1231, 737 cm^{-1}; H^1 NMR ($CDCl_3$) δ 10.92 (s, 1H), 8.24 (d, 1 H, J = 6 Hz), 8.01 (d, 1 H, J = 3 Hz), 7.47 (d, 1 H, J = 9 Hz), 7.20-7.12 (m, 2 H), 6.82 (s, 1 H), 1.52 (s, 9 H); C^{13} NMR ($CDCl_3$) δ 136.8, 128.6, 124.6, 122.9, 121.7, 119.5, 112.6, 51.8, 29.6; MS *m/z* 216 (M^+), 161, 144, 116, 89. Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.14; H, 7.41; N, 12.87.
10. **7**: Mp 104-105 °C; lit.[4a] mp 105 °C; H^1 NMR ($CDCl_3$) δ 8.38 (d, 1 H, J = 1.8), 8.31 (d, 1 H, J = 9 Hz), 7.65 (d, 1 H, J = 8.4 Hz), 7.47-7.37 (m, 2 H), 4.08 (s, 3 H); C^{13} NMR ($CDCl_3$) δ 124.9, 124.3, 122.9, 110.4, 24.0; F^{19} NMR ($CDCl_3$ referenced to $CFCl_3$) δ −193.5; MS *m/z* 227 (M^+), 158, 130, 103, 77.
11. **8**: Mp 149-150 °C; IR (KBr) 3133, 1696, 1534, 1446, 1383, 1271, 1189, 1133, 970, 870, 745, 682, 582 cm^{-1}; H^1 NMR ($CDCl_3$) δ 8.48 (s, 1 H), 8.31 (d, 1 H, J = 6 Hz), 8.00 (m, 3 H), 7.68-7.34 (m, 5 H); C^{13} NMR ($CDCl_3$) δ 137.2, 135.4, 130.2, 127.6, 127.6, 127.0, 126.0, 123.1, 113.5, 24.0; F^{19} NMR ($CDCl_3$ referenced to $CFCl_3$) δ −73.4; MS *m/z* 353 (M^+), 284, 184, 141, 115, 77. Anal. Calcd for $C_{16}H_{10}NF_3O_3S$: C, 54.39; H, 2.85; N, 3.96. Found: C, 54.36; H, 2.82; N, 3.98.
12. **9**: Mp 104 °C; IR (KBr) 2934, 2850, 1611, 1534, 1433, 1233, 748 cm^{-1}; H^1 NMR ($CDCl_3$) δ 7.70 (d, 2 H, J = 6 Hz), 7.38-7.18 (m, 4 H), 3.83 (s, 3 H), 3.67 (t, 4 H, J = 5.7), 1.69 (m, 6 H); C^{13} NMR ($CDCl_3$) δ 131.5, 122.5, 120.9, 109.9, 26.6, 25.0; MS *m/z* 242 (M^+), 158, 131, 103, 77. Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.23; H, 7.51; N, 11.50.
13. The reduction of ketones to alcohols by lithium dialkylamides has ample precedent: (a) Wittig, G.; Schmidt, H.-J.; Renner, H. *Chem. Ber.* **1962**, *95*, 2377-2383. (b) Majewski, M. *Tetrahedron Lett.* **1988**, *29*, 4057-4060, and references cited therein.
14. **11**: Mp 99 °C; IR (film) 3396 (O-H), 2975, 1619, 1459, 1421, 1376, 1338, 1287, 1242, 1172, 1102, 1012, 910, 821 cm^{-1}; H^1 NMR ($CDCl_3$) δ 8.22 (s, 1 H), 7.92 (d, 1 H, J = 8.1 Hz), 7.42 (d, 1 H, J = 7.8 Hz) 7.28-7.16 (m, 4 H), 2.54 (s, 1 H), 1.91 (s, 3 H); F^{19} NMR ($CDCl_3$ referenced to $CFCl_3$) δ -81.4; MS *m/z* 229 (M^+), 160, 118, 43. Anal. Calcd for $C_{11}H_{10}NOF_3$: C, 57.64; H, 4.40; N, 6.11. Found: C, 57.76; H, 4.41; N, 6.12.
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