Regioselective Fischer Indole Synthesis Mediated by Organoaluminum Amides

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Summary: Amphiphilic reagents such as organoaluminum amides are found to be highly effective for the Fischer indole synthesis. In particular, diethylaluminum 2,2,6,6-tetramethylpiperidide (DATMP) is the reagent of choice for regioselective Fischer indole synthesis. For example, treatment of the (*E*)-*N*-methyl-*N*-phenylhydrazone of 5-methyl-3-heptanone with DATMP affords 3-*sec*-butyl-2-ethyl-1-methylindole as the sole isolable product; its *Z*-isomer affords 1,3-dimethyl-2-(2-methylbutyl)indole with high regioselectivity under similar reaction conditions.

Since the discovery of the synthesis of indoles from arylhydrazones by Emil Fischer *et al.*,[1] the Fischer indole synthesis has undoubtedly been the best known and most thoroughly investigated of all indole syntheses because of the continuing interest in its mechanism and its numerous synthetic applications to pharmacologically active indole alkaloids.[2,3] However, the usefulness of this indole synthesis for selective organic synthesis has never been developed because of the lack of appropriate reagents. Development of *a regioselective Fischer indole synthesis*, in which the carbon–carbon bond-forming reaction proceeds with high regioselectivity, would provide a new and efficient route to various indoles of synthetic and pharmacological significance.[4] Here we wish to disclose the first example of regioselective Fischer indole synthesis mediated by organoaluminum amides as illustrated in Scheme I.

The mechanism postulated for the Fischer indole synthesis comprises the initial isomerization of arylhydrazones to the corresponding enehydrazines, subsequent intramolecular [3,3] sigmatropic rearrangement of the resulting enehydrazines, and final loss of ammonia to furnish the indole nuclei.[5] The first step could be achieved regioselectively with certain amide bases. The subsequent rearrangement could be accelerated by certain Lewis acids. The combination of amide bases and Lewis acids brings to mind amphiphilic reagents such as aluminum amides, which seem to be most suitable for the regioselective indole synthesis from arylhydrazones under mild conditions. To this end, we screened a series of organoaluminum amides to effect the formation of indoles from 3-pentanone *N*-methyl-*N*-phenylhydrazone (1) (R^1 = Et, R^2 = R^3 = Me), and the yields of 1,3-dimethyl–2–ethylindole (2) (R^1 = Et, R^2 = R^3 = Me) under the given reaction conditions are indicated in Table I.[6] As revealed in Table I, diethylaluminum 2,2,6,6-tetramethylpiperidide (DATMP) is the most efficacious reagent.[7] Magnesium amides lowered the yields of the indoles, and aluminum amides derived from hexamethyldisilazane and aromatic amines gave only trace amounts of the desired indole.

Scheme I

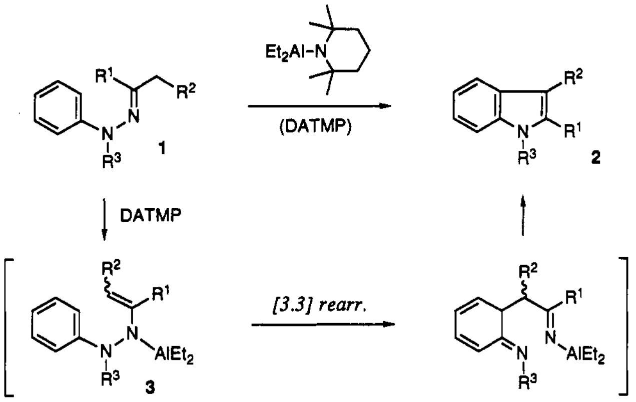

Table I. Metal Amide-Promoted Fischer Indole Syntheses[a]

reagent[b]	condns (°C, h)	% yield[c]
$Et_2Al(TMP)$[d]	−40, 2; −20, 3	78
$Et_2Al(TMP)$	0, 0.5	75
$Et_2AlN(c\text{-}Hex)_2$[d]	0, 1.5; 25, 24	78
$i\text{-}Bu_2Al(TMP)$[d]	0, 1; 25, 36	76
$Et_2AlNPr^i_2$[d]	0, 0.3; 25, 20	58
PCl_3	25, 17	53
BrMg(TMP)	25, 21	47
$BrMgNPr^i_2$[e]	25, 2	36
EtMgBr[f]	25, 20	17
Et_2AlNPh_2	25, 21	3
$Et_2AlN(SiMe_3)_2$	25, 24	
Et_2AlNEt_2	25, 24	
$Et_2AlN(Me)Ph$	25, 17	

[a] Unless otherwise noted, the conversion of hydrazone 1 (R^1 = Et, R^2 = R^3 = Me) to indole 2 (R^1 = Et, R^2 = R^3 = Me) was carried out in benzene/hexane. [b] TMP = 2,2,6,6-tetramethylpiperidide. [c] Isolated yield. [d] In toluene/hexane. [e] In ether/hexane. [f] In benzene/ether.

Although unprotected 3-pentanone *N*-phenylhydrazone (1) (R^1 = Et, R^2 = Me, R^3 = H) did not afford indole 2 (R^1 = Et, R^2 = Me, R^3 = H), its *N*-allyl and *N*-benzyl derivatives 1 (R^1 = Et, R^2 = Me, R^3 = allyl or benzyl) were transformed cleanly to indoles 2 (R^1 = Et, R^2 = Me, R^3 = allyl or benzyl) in 82 and 74% yields, respectively, with DATMP.

With the effective DATMP reagent in hand, we set out to study the regiochemistry of the DATMP-mediated formation of indoles from arylhydrazones of unsymmetrical ketones. 5-Methyl-3-heptanone *N*-methyl-N-phenylhydrazones (4) (*E*/*Z* ratio = ~1:1) were prepared in

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(1) (a) Fischer, E.; Jourdan, F. *Ber.* **1883**, *16*, 2241. (b) Fischer, E.; Hess, O. *Ibid.* **1884**, *17*, 559.

(2) Reviews of Fischer indole synthesis: (a) Robinson, B. *Chem. Rev.* **1963**, *63*, 373; **1969**, *69*, 227. (b) Remers, W. A.; Brown, R. K. In *Indole*; Houlihan, W. J., Ed.; Wiley-Interscience: New York, 1972; 232–317. (c) Ishii, H. *Acc. Chem. Res.* **1981**, *14*, 275.

(3) Reviews of indole synthesis: (a) Katritzky, A. R.; Rees, C. W. *Comprehensive Heterocyclic Chemistry*; Pergamon: Oxford, 1984; Vol. 4. (b) Hegedus, L. S. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1113.

(4) Manske, R. H. F. *The Alkaloids*; Wiley: New York, 1950–1979; Vols. 1–17. (b) Hesse, M. *Indolalkaloide in Tabellen*; Springer: Berlin, 1964. (c) Glasby, J. S. *Encyclopedia of the Alkaloids*; Plenum Press: New York, 1975.

(5) (a) Robinson, G. M.; Robinson, R. *J. Chem. Soc.* **1918**, *113*, 639; **1924**, *125*, 827. (b) Allen, C. F. H.; Wilson, C. V. *J. Am. Chem. Soc.* **1943**, *65*, 611. (c) Carlin, R. B.; Fischer, E. E. *Ibid.* **1948**, *70*, 3421. (d) Hughes, D. L.; Zhao, D. *J. Org. Chem.* **1993**, *58*, 228.

(6) Organoaluminum amides can be easily prepared from the corresponding lithium amides and a dialkylaluminum halide. See: Mole, T.; Jeffrey, E. A. *Organoaluminum Compounds*; Elsevier: Amsterdam, 1972.

(7) Yasuda, A.; Tanaka, S.; Oshima, K.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1974**, *96*, 6513.

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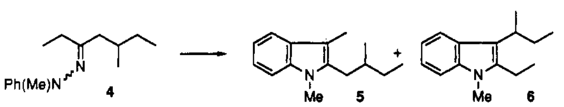
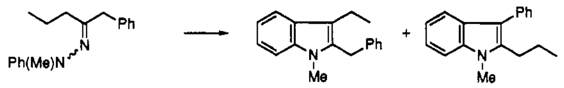
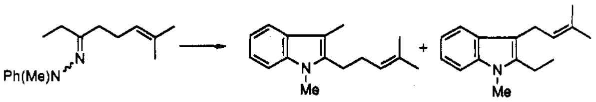
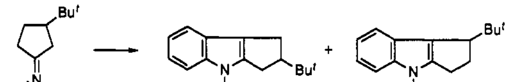
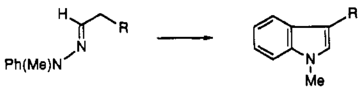
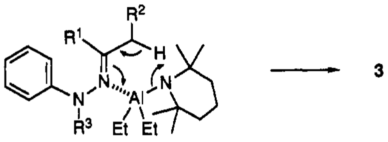
Table II. Regioselective Fischer Indole Syntheses Promoted by DATMP[a]

entry	arylhydrazone	condition (°C, h)	indoles	% yield[b] (ratio)[c]
				
1	*Z*-isomer (*E*/*Z* = 4:96)	0, 0.5; 25, 3.5		93 (>99:<1)
2	[PCl_3	25, 24		50 (97:3)][d]
3	*E*-isomer (*E*/*Z* = 96:4)	0, 0.5; 25, 17		42 (7:93)
4	[PCl_3	25, 30		59 (97:3)][d]
5	[ZnI_3	25, 20		24 (91:9)][d]
				
6	*Z*-isomer (*E*/*Z* = 6:94)	0, 0.5; 25, 3		67 (98:2)
7	*E*-isomer (*E*/*Z* = 92:8)	0, 0.5; 25, 16		32 (14:86)
				
8	*Z*-isomer (*E*/*Z* = 10:90)	0, 0.5; 25, 1		62 (84:16)
9	*E*-isomer (*E*/*Z* = 94:6)	0, 0.5; 25, 18		74 (8:92)
				
10	*Z*-isomer (*E*/*Z* = 9:91)	0, 0.5; 25, 14		95 (91:9)
11	*E*-isomer (*E*/*Z* = 95:5)	0, 0.5; 25, 18		70 (23:77)
				
12	R = H	25, 24		32
13	R = $SiMe_2Bu^t$	25, 24		57
14	R = Et	0, 0.5; 25, 12		54

[a] Unless otherwise noted, the arylhydrazone was treated with DATMP (5 equiv) in toluene/hexane under the given reaction conditions. [b] Isolated yield. [c] The regioisomeric ratio of indoles was determined by 200-MHz ^{1}H NMR and/or GLC analysis. [d] Reference 8.

the usual manner, and the *E*/*Z* isomers were easily separated by column chromatography on silica gel.[8] Treatment of (*Z*)-4 (*Z*/*E* ratio = 96:4) with DATMP (5 equiv) at 0 °C for 30 min and at 25 °C for 3.5 h yielded 1,3-dimethyl-2-(2-methylbutyl)indole (5) as the sole isolable product in 93% yield (entry 1 in Table I). None of the isomeric indoles were detected by ^{1}H NMR analysis. Similarly, (*E*)-4 (*E*/*Z* = 96:4) was transformed to 3-*sec*-butyl-2-ethyl-1-methylindole (6) almost exclusively in 42% combined yield with the ratio of 5/6 = 7:93 (entry 3). It should be noted that reaction of an *E*/*Z* mixture of 4 with conventional Lewis acids gave rise to indole 5 exclusively, as has been reported previously.[8] Indeed, attempted indole formation from (*E*)-4 with PCl_3 or ZnI_2 resulted in predominant formation of 5 (entries 4 and 5), indicating the facile *E*/*Z* equilibration caused by Lewis acids before the enehydrazine formation. Hence, the superiority of DATMP as a regioselective agent over previously known catalysts is apparent. Other selected examples are listed in Table II, which also includes the results of classical Fischer indole synthesis for comparison.[8] These results clearly support regioselective enehydrazine formation by preferential abstraction of the α-methylene hydrogen *anti* to the hydrazone by DATMP, as shown for 7. The slightly low reactivity of hydrazone *E*-isomers is partially ascribed to slow enehydrazine formation *via* conformationally less favorable hydrogen abstraction by DATMP in the sterically congested *E*-hydrazone–DATMP complex. Indole synthesis with acetaldehyde phenylhydrazones, which is reportedly unsuccessful in the presence of various Lewis acidic catalysts,[9] was achieved with the DATMP reagent (entry 12). The yield was improved when (*tert*-butyldimethylsilyl)acetaldehyde phenylhydrazone was used (entry 13).



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Supplementary Material Available: Typical experimental procedures and spectral data of products (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for order information.

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(8) The regiochemical assignments of *E*- and *Z*-isomers were made by ^{13}C NMR analysis. See: Prochazka, M. P.; Carlson, R. *Acta Chem. Scand.* **1989**, *43*, 651.

(9) Snyder, H. R.; Smith, C. W. *J. Am. Chem. Soc.* **1943**, *65*, 2452.