HETEROCYCLES, Vol. 57, No. 7, 2002, pp. 1293 - 1297, Received, 8th April, 2002

SYNTHESES OF 3-ACYLINDOLES *VIA* THE ALKYLATION OF THE DIANION OF 3-ACETYLINDOLE

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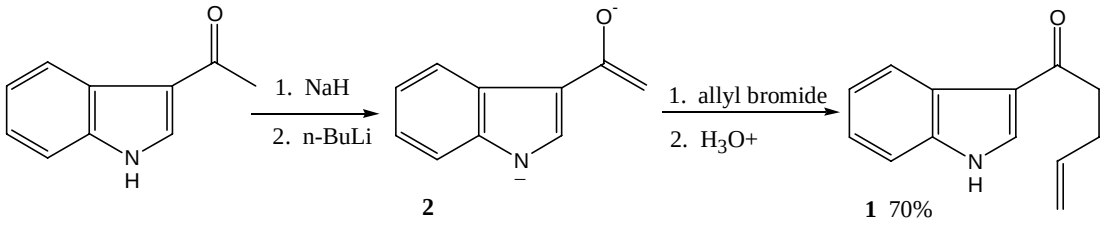
Abstract - The dianion of 3-acetylindole can be generated upon sequential treatment with NaH and n-BuLi. This dianion can be C-alkylated at the acetyl methyl group with high regioselectivity, leading to efficient syntheses of 3-acylindoles. Addition of excess electrophile leads to a dialkylated product.

In a recent study[1] involving tandem radical addition reactions to substituted indoles, we required acylindole (**1**) as a substrate. Acylindoles may be prepared by Friedel-Crafts acylation of indole, although this direct approach can be poorly regioselective or lead to diacylation.[2] Friedel-Crafts acylation of *N*-benzenesulfonylindole with acetic anhydride and $AlCl_3$ with subsequent *N*-deprotection is known to provide an efficient route to 3-acetylindole.[3] When the analogous reaction was attempted employing 4-pentenoic anhydride, none of the desired acylation product was obtained, apparently due to oligomerization of the olefinic anhydride under the Lewis acid conditions. The only previously cited synthesis[4] of acylindole (**1**) was accomplished through a more circuitous route than we had hoped to employ. We reasoned that a route involving alkylation of the dianion (**2**) of readily available 3-acetylindole might provide convenient access to acylindole (**1)** (Eq. 1). The NaOH-promoted aldol condensation of 3-acetyl indole with benzaldehyde, which we suspect may proceed through **2**, has been reported to generate a poor yield of addition product (**6)**.[5] More recently, products arising from alkylation of the dianion of 3-acetylindole with benzophenone have also been observed, again in poor yield.[6] Alkylation of the dianion of structurally related 2-acetylindole with pyridinium salts also been observed in synthetic studies leading to the syntheses of ervitsine alkaloids.[7] Nonetheless, systematic studies of the nucleophilicity of dianion (**2)** have not been reported.

We wish to report a new protocol for the syntheses of 3-acylindoles. In our procedure, the acidic indole N-H is deprotonated at 0 ^{o}C upon treatment with NaH. Resonance donation from the formally anionic nitrogen should diminish the electrophilicity of the acetylindole carbonyl functionality, allowing the convenient, but normally nucleophilic base n-BuLi to be employed for the second deprotonation, leading to generation of the dianion (**2**) at -78 ^{o}C. A similar approach is well documented for the generation and alkylation of acetoacetate ester dianions.[8] Subsequent addition of a variety of electrophiles, followed by gradual warming and aqueous

workup, typically led to selective C-alkylation. Recrystallization was sufficient in most cases to obtain suitably pure products.

Eq. 1



2 **1** 70%

Table I.

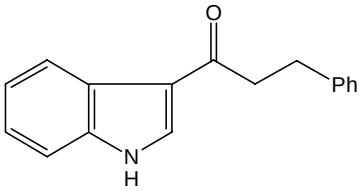
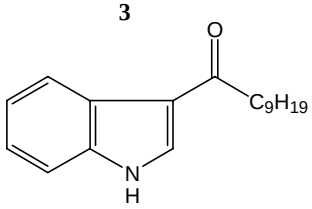
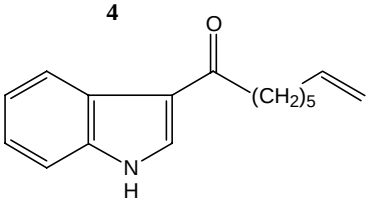
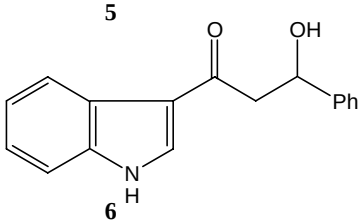
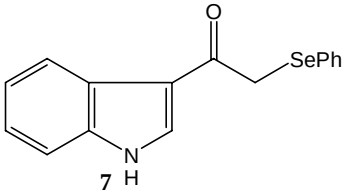
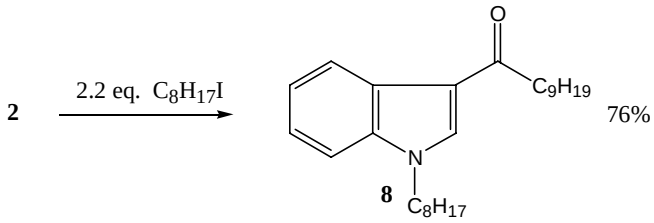
Electrophile	Product	Yield (%)
benzyl bromide	 **3**	68
1-octyl iodide	 **4**	76
6-bromo-1-hexene	 **5**	57
benzaldehyde	 **6**	72
PhSeCl	 **7**	26

Table I includes successful examples of reactions of this type. Complete characterizations of all previously unreported compounds were carried out. In cases where the acylindole product was previously reported, satisfactory comparisons to literature characterization values were obtained. All compounds which were volatile enough to allow for characterization by GC/MS exhibited suitable molecular ions, as well as a peak at m/z 144, corresponding to an indolylacyl fragment. Reactive alkyl halides such as allyl bromide, benzyl bromide, and 1-octyl iodide, as well as a less reactive halide, 6-bromo-1-hexene, proved effective electrophiles for regioselective C-alkylation. Benzaldehyde also proved useful in this regard, but the attempted reaction with benzoyl chloride was not regioselective, yielding mixtures of N- and C-alkylated

products. The heteroatom electrophile, PhSeCl, while successful, provided relatively poor yields of the phenylseleno- substituted product.

One of the more potentially useful aspects of this approach is that it allows for syntheses of indole derivatives without the necessity of N-protection. Nonetheless, we were also interested in examining the potential for dialkylation, both to provide evidence for the existence of a dianion, as well as to expand the uses of this methodology. Heating dianion (**2)** to reflux with 2.2 equivalents of 1-octyl iodide did lead to generation of the dialkylated product (**8**), indicating the feasibility of this process (Eq. 2).

Eq. 2



In conclusion, we have demonstrated a straightforward method for the generation of 3-acylindoles from 3-acetylindole. This process will probably prove most useful in situations where the desired acyl substituent is not readily available as its acid chloride or acid anhydride, or is incompatible with the strong Lewis acid conditions typically required for Friedel-Crafts acylations.

ACKNOWLEDGEMENTS

We thank the National Science Foundation (Grant CHE-9732600) and the Petroleum Research Fund of the ACS (Grant 33156-B1) for their support of this project. Purchase of the NMR spectrometer used in this work was supported through the Kresge Foundation.

EXPERIMENTAL SECTION

General: THF was freshly distilled from K/benzophenone prior to use. Reagent grade hexane and ethyl acetate were distilled prior to use. All other solvents and reagents were used as received from readily available sources. Combustion analyses were performed by Atlantic Microlab of Norcross, GA. TLC was performed using Aldrich 0.25-mm plastic silica gel plates with fluorescent indicator. Spotted TLC plates were viewed under short wave UV light and iodine vapor. Flash chromatography was conducted on Acros 0.035-0.07 mm Silica Gel. Gas chromatography and MS were performed using a Hewlett-Packard 5890 gas chromatograph with a 25-m x 0.22-mm HP-5 crosslinked methyl silicone capillary column coupled to a Hewlett-Packard 5970 mass selective detector (EI, 70 eV). NMR spectral analyses were obtained on a Bruker Avance 400 nuclear magnetic resonance spectrometer. IR spectra were obtained on a Perkin-Elmer 1600 FT-IR as KBr Pellets, except where noted. Mps were obtained on a Hoover-Thomas melting point apparatus, and are uncorrected. All yields are reported for materials that were homogeneous by TLC and pure by NMR spectroscopy.

General Procedure for C-alkylation: A 0.80 g (5 mmol) portion of 3-acetylindole was dissolved in 25 mL of THF and the resulting solution was cooled to 0 ^{o}C. A 0.22 g (5.5 mmol) portion of NaH (60% in mineral oil) was added, and the solution was allowed to stir for 20 min, at which point H_2 evolution had ceased. The solution was then cooled to -78 ^{o}C and 3.4 mL of *n*-BuLi (1.6 M in hexanes, 5.5 mmol) were added *via*

syringe. Stirring was continued for and additional 30 min, and 5.5 mmol of the electrophile was added *via* syringe. The resulting mixture was allowed to warm gradually to 0 ^{o}C over 2 h. The reaction was quenched with 25 mL of saturated aqueous NH_4Cl, and the resulting mixture was extracted with three 25 mL portions of EtOAc. The combined organic phases were washed with 25 mL of water, 25 mL of brine, dried over anhydrous $MgSO_4$ and filtered. Removal of solvents by rotary evaporation yielded solid product which was recrystallized from hexane/EtOAc.

1-(1*H*-Indol-3-yl)pent-4-en-1-one (1). Allyl bromide was used as electrophile, generating 700 mg (70%) of **1** as white crystals, mp 162-163 ^{o}C (lit.,[3] 160-161 ^{o}C): ^{1}H NMR ($CDCl_3$) δ 2.58 (m, 2H), 3.02 (t, J = 7.5 Hz, 2H), 5.03 (ddd, J = 1.3, 3.2, 10.3 Hz, 1H), 5.13 (ddd, J = 1.7, 3.2, 17.1 Hz, 1H), 5.96 (ddt, J = 10.2, 17.1, 6.6 Hz, 1H), 7.34 (m, 2H), 7.45 (m, 1H), 7.92 (d, J = 3.1 Hz, 1H), 8.42, (m, 1H), 8.86 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 35.5, 39.4, 111.8, 115.5, 118.5, 122.8, 123.1, 124.1, 125.9, 131.5, 136.8, 138.1, 195.9; IR 3178, 1620 cm^{-1}; MS m/z 199 (M^+), 144 (indolyl-CO^+).

1-(1*H*-Indol-3-yl)-3-phenylpropan-1-one (3). Benzyl bromide was used as electrophile, generating 860 mg (68%) of **3** as white crystals, mp 159-160 ^{o}C (lit.,[4] 163 ^{o}C): ^{1}H NMR ($CDCl_3$) δ 3.15 (m, 2H), 3.23(m, 2H), 7.22 (m, 1H), 7.30 (m, 6H), 7.43 (m, 1H), 7.82 (d, J=3.0 Hz, 1H), 8.44 (m, 1H), 8.74 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 31.2, 42.1, 111.8, 118.5, 122.9, 123.1, 124.2, 125.9. 126.5, 128.9 (2 peaks), 131.4, 136.7, 142.1, 195.6; IR 3215, 1626, 1611 cm^{-1} (lit.,[4] 3200, 1635, 1615 cm^{-1}); MS m/z 249 (M^+), 144 (indolyl-CO^+).

1-(1*H*-Indol-3-yl)decan-1-one (4). 1-Octyl iodide was used as electrophile, generating 1.03 g (76%) of **4** as white crystals, mp 147-147.5 ^{o}C: ^{1}H NMR spectrum was identical to reported literature;[9] ^{13}C NMR ($CDCl_3$) δ 14.5, 23.1, 25.6, 29.7, 29.9, 30.0 (2 peaks), 32.3, 40.5, 111.7, 118.7, 122.9, 123.0, 124.1, 126.0, 131.2, 136.7, 197.1; IR 3171, 1619 cm^{-1}; MS m/z 271 (M^+), 144 (indolyl-CO^+).

1-(1*H*-Indol-3-yl)oct-7-en-1-one (5). 6-Bromo-1-hexene was used as electrophile, generating 690 mg (57%) of **5** as white crystals, mp 153-154 ^{o}C: ^{1}H NMR ($CDCl_3$) δ 1.45 (m, 4H), 1.82 (m, 2H), 2.09 (m, 2H), 2.90 (t, J = 7.5 Hz, 2H), 4.96 (m, 1H), 5.02 (ddd, J = 1.6, 3.5, 17.1 Hz, 1H), 5.83 (ddt, J = 10.2, 17.1, 6.7 Hz, 1H), 7.30 (m, 2H), 7.45 (m, 1H), 7.90 (d, J = 3.0 Hz), 8.45 (m, 1H), 8.70 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.3, 29.2, 29.4, 34.1, 40.3, 111.6, 114.7, 118.8, 123.0, 123.1, 124.1, 125.9, 131.1, 136.7, 139.4, 196.8; IR 3170, 1618 cm^{-1}. Anal Calcd for for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.84; H, 7.97; N, 5.77.

3-Hydroxy-1-(1*H*-indol-3-yl)-3-phenylpropan-1-one (6). Benzaldehyde was used as electrophile, generating 920 mg (72%) of **4** as white crystals, mp 159-160 ^{o}C (lit.,[4] 159 ^{o}C): ^{1}H NMR (acetone-d_6) δ 3.22 (dd, J = 4.1, 15.7 Hz, 1H), 3.29 (dd, J = 8.6, 15.7 Hz, 1H), 4.66 (d, J = 3.6 Hz, 1H), 5.35 (m, 1H), 7.25 (m, 3H), 7.35 (m, 2H), 7.52 (m, 3H), 8.28 (d, J=3.1 Hz, 1H), 8.40 (m, 1H), 11.08 (br s, 1H); ^{13}C NMR (acetone-d_6) δ 48.8, 70.8, 112.2, 118.0, 122.3, 122.4, 123.5, 126.3, 127.3, 128.5, 134.0, 134.1, 137.4, 145.6, 194.0; IR 3450, 3296, 1620 cm^{-1}.

1-(1H-Indol-3-yl)-2-phenylselanylethanone (7). Benzeneselenenyl chloride was used as electrophile, with the following modifications to the standard procedure: PhSeCl was added to the THF solution of **2** *via* cannula as a solution in 7 mL of THF. Purification was accomplished by flash chromatography with 70%

hexane: 30% EtOAc (v:v) to give 415 mg (26%) of tan crystals, mp 134-135.5 ^{o}C: ^{1}H NMR (acetone-d_6) δ 4.12 (s, 2H), 7.30 (m, 6H), 7.42 (m, 1H), 7.60 (m, 2H), 7.65 (d, J = 3.1 Hz, 1H), 8.40 (m, 1H), 8.90 (br s, 1H); ^{13}C NMR (acetone-d6) δ 33.9, 112.3, 116.2, 122.3, 122.4, 123.6, 126.5, 127.7, 129.5, 131.1, 132.9, 133.9, 137.4, 190.6; IR 3178, 1605 cm^{-1}; MS m/z 314 (M^+), 144 (indolyl-CO^+), 159 (M^+ - SePh). Anal Calcd for $C_{16}H_{13}NOSe$: C, 61.15; H, 4.17; N, 4.46. Found: C, 61.16; H, 4.06; N, 4.43.

1-(1-Octyl-1*H*-indol-3-yl)decan-1-one (8). A 0.80 g (5 mmol) portion of 3-acetylindole was dissolved in 25 mL of THF and the resulting solution was cooled to 0 ^{o}C. A 0.22 g (5.5 mmol) portion of NaH (60% in mineral oil) was added, and the solution was allowed to stir for 20 min, at which point H_2 evolution had ceased. The solution was then cooled to -78 ^{o}C and 3.4 mL of *n*-BuLi (1.6 M in hexanes, 5.5 mmol) were added *via* syringe. Stirring was continued for an additional 30 min, and 2.64 g (11 mmol) of 1-octyl iodide was added *via* syringe. The solution was allowed to warm to rt over 4 h, and heated to reflux for 12 h. The reaction mixture was allowed to cool to rt, and was quenched with 25 mL of saturated aqueous NH_4Cl. The resulting mixture was extracted with three 25 mL portions of EtOAc. The combined organic phases were washed with 25 mL of water, 25 mL of brine, dried over anhydrous $MgSO_4$ and filtered. Removal of solvents by rotary evaporation yielded a solid which was recrystallized from hexane/EtOAc to give 1.45 g of **8** as white crystals, mp 37-38 ^{o}C: ^{1}H NMR ($CDCl_3$) δ 0.95 (m, 6H) 1.30 (m, 22H), 1.80 (m, 2H), 1.90 (m, 2H), 2.83 (t, J = 7.4 Hz, 2H), 4.15 (t, J = 7.7 Hz, 2H), 7.30 (m, 2H), 7.37 (m, 1H), 7.77 (s, 1H), 8.45 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.4, 14.5, 23.0, 23.1, 25.7, 27.3, 29.5 (2 peaks), 29.7, 29.9, 30.0 (2 peaks), 30.2, 32.1, 40.4, 47.5, 110.2, 117.0, 122.7, 123.1, 123.5, 127.0, 134.6, 137.2, 196.3; IR 1650 cm^{-1}. Anal Calcd for $C_{26}H_{41}NO$: C, 81.41; H, 10.77; N, 3.65. Found: C, 81.23; H, 10.88; N, 3.61.

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