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ACYLATION OF THE ZINC SALT OF INDOLE

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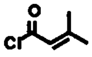
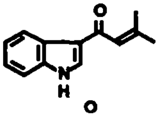
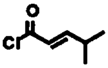
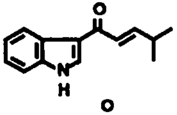
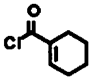
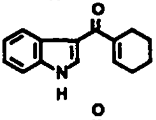
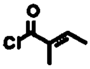
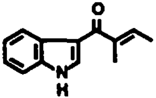
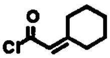
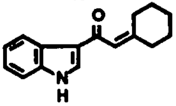
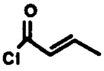
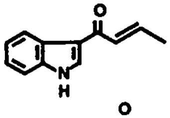
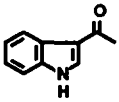
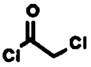
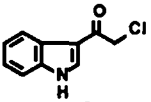
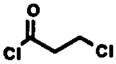
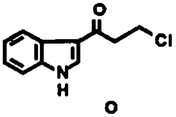
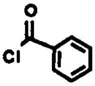
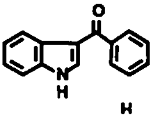
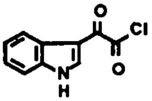
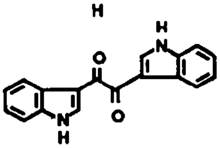
Abstract: The indole Grignard reagent was transmetallated with $ZnCl_2$ and the resulting zinc salt of indole was acylated with a number of acid chlorides and gave 3-acylindoles in yields superior to those obtained with the indole Grignard reagent.

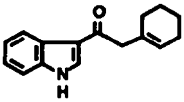
During synthetic work on cyclopent[b]indolones,[1] α,β-unsaturated 3-acylindoles were needed. Among the great number of synthetic routes to 3-acylindoles[2] Vilsmeier acylation,[3] Friedel-Crafts acylation of *N*-phenylsulphonylindole,[4] and the reaction of the indole Grignard reagent[5] with acid chlorides are the most general and useful. Acylations of indoles using *N,N'*-diacyl-4,5-dihydroimidazolium ions or similar reagents are still in a preliminary stage.[6] In our hands, Vilsmeier acylation of indole with *N,N*,3,3-tetramethylacrylamide under different conditions, was unsuccessful. Although Friedel-Crafts acylations of *N*-phenylsulphonylindole generally give good yields, this method was considered to be too lengthy; as it involves *N*-protection, acylation, and *N*-deprotection. For the present purpose, reaction of the indole Grignard reagent with an acid chloride seemed to be the method of choice. According to the literature[7] (and likewise confirmed by our experiments), acylation of an indole Grignard reagent with an acid chloride is optimally performed in the non-polar solvent benzene (together with a small amount of diethyl ether needed for making the initial alkyl Grignard reagent). However, in some cases the yields were still low (partly due to 1,3-diacylation); *e. g.* **4** was obtained in only 26% yield[1a] and recently Wenkert[8] *et al.* reported **12** in modest yield (21%). In the alkylation of indolyl anions, replacing a metal with a less electropositive one (*e. g.* replacing potassium with lithium) as well as changing to a more unpolar solvent has been demonstrated to raise the ratio of 3- to 1-alkylation, which is rationalized with a lowering of the degree of dissociation of the nitrogen-metal bond.[9-11] By analogy, we believed that replacement of magnesium with zinc also should result in a similar effect and thus facilitate 3-substitution. The literature revealed only one report[12] on the preparation of the zinc salt[13] of indole: Thus, Powers[12] *et al.* transmetallated the indole Grignard reagent with anhydrous zinc chloride, followed by deuteration in one experiment and reaction with iodomethane in another.

Table: Acylation of the Zinc Salt of Indole Using Acid Chlorides.

Entry	Acid Chloride	Product	Isolated yields (%)	Lit. yields* (%)
1	 1	 2	70	60[1a,20]
2	 3	 4	60	26[1a]
3	 5	 6	65	47[1a]
4	 7	 8	52	43[1a]
5	 9	 10	70	35[1a]
6	 11	 12	37	21[8]
7	 13	 14	55	"very unsatisfactory"[21]
8	 15	 16	36	"small quantity"[15]
9	 17	 18	42	36.6[23]
10	 19	 20	47	30-32[24]
11	 21	 22	65	93[26a] 30-35[26b]

*) Lit. yields refer to acylations using the indole Grignard reagent.

Using optimized[14] conditions (see Experimental Section) the yields of α,β–unsaturated 3-acylindoles were improved substantially (see Table, entry 1-6). The lower base strength of the zinc indole reagent was demonstrated in the synthesis of **10** (Entry 5), which gave the expected product in good yield. In contrast, acylation of indole magnesium bromide using the same acid chloride (**9**) gave the isomerized product **10a** in only 35% yield.[1a]



10a

The improved yields are not restricted to unsaturated acylindoles. For example, reaction of the indole Grignard reagent with chloroacetyl chloride is known to give mainly 1,3-di(chloroacetyl)indole and only a small amount of the desired 3-chloroacetylindole (**16**),[15] however the same reaction run with the zinc indole reagent gave **16** as the main product. The simple purification procedure (no need of chromatography, except in entry 6) makes the method suitable also for large-scale preparations. We believe this acylation-method of indole to be suitable also for substituted indoles as well as some other heterocycles, *e. g.* pyrrole, and it should provide an attractive alternative to other methods available today.

Experimental Section

Glassware used in the reactions were dried in an oven (160°) over night. Reaction set ups were assembled hot and kept dry using a drying tube (silica gel). Diethyl ether was pre-dried over $CaCl_2$ and then stored over sodium wire. $ZnCl_2$ (1,0 M solution in diethyl ether) was purchased from Aldrich. Commercial acid chlorides were used as purchased except in the cases of **3**, **5**, **7**, and **9** which were made from the corresponding acids using standard methods. The acid chloride **21** was made from indole and oxalyl chloride according to the method of Speeter and Anthony.[16] Melting points were determined on a calibrated Reichert WME Kofler hot stage. NMR spectra were recorded on a Bruker WP-200. Chemical shifts are reported relative to tetramethylsilane. IR spectra were obtained using a Perkin Elmer 1710 IR FT instrument. Mass spectra were obtained with a LKB-9000 or a Finnigan 4500 spectrometer.

All reactions were run on the same scale (15 mmol) and the following general procedure was used:

3-(3,3-Dimethylacryloyl)indole (2). General procedure.

Indole (1.755 g, 15 mmol) in ether (20 mL) was added to a solution of EtMgI (10 mL, 1.575 M in ether) under stirring. The resulting two-phase system was allowed to stand for 15 min whereafter $ZnCl_2$ (15 mL, 1.0 M in ether) was added with stirring. The two-phase[17] system was allowed to stand under stirring for 30 min when

3,3-dimethylacryloyl chloride (1) (1.87 g, 15.75 mmol) in ether (10 mL) was added *rapidly* under vigourous stirring. The reaction mixture was allowed to stand for 2 h whereupon NH_4Cl (aq. sat. 25 mL) was added. The organic layer[18] was separated, washed with $NaHCO_3$ (aq. sat. 15 mL) followed by brine (15 mL), dried ($MgSO_4$) and evaporated to give a crystalline residue. The crude product was triturated with cold ether and the crystals were collected. Yield: 2.1 g (70%).

Mp 137-138° C (lit. 136.5°-138° C[19], 136-137° C[20]); ^{1}H NMR ($CDCl_3$) δ 1.99 (br s, 3H), 2.26 (br s, 3H), 6.63 (br s, 1H), 7.2-7.4 (m, 3H), 7.85 (d, J=3.0 Hz, 1H), 8.5 (m, 1H) ppm; IR (KBr) 3274, 1645 cm^{-1}; mass spectrum, m/z 199 (M$^+$, base peak).

3-(4-Methylpent-2-enoyl)indole (4).

Yield: 1.9 g (60%).

Mp 162-163° C; ^{1}H NMR ($CDCl_3$) δ 1.13 (d, J=6.7 Hz, 6H), 2.56 (m, J=6.7 Hz, 6.7 Hz, 1H), 6.72 (br d, J=15.4 Hz, 1H), 7.04 (dd, J=15.4 Hz, 6.7 Hz, 1H), 7.2-7.5 (m, 3H), 7.90 (d, J=3.0 Hz, 1H), 8.45 (m, 1H) ppm; IR (KBr) 3149, 1650 cm^{-1}; mass spectrum, m/z 213 (M$^+$), 144 (base peak).

(Cyclohex-1-en-1-yl)-3-indolylmethanone (6).

Yield: 2.2 g (65%).

Mp 183-184° C; ^{1}H NMR ($CDCl_3$) δ 1.75 (m, 4H), 2.25 (m, 2H), 2.45 (m, 2H), 6.6 (m, 1H), 7.2-7.5 (m, 3H), 7.65 (d, J=3.0 Hz, 1H), 8.3 (m, 1H) ppm; IR (KBr) 3207, 1593 cm^{-1}; mass spectrum, m/z 225 (M$^+$), 144 (base peak).

3-(*E*-2-methylbut-2-enoyl)indole (8).

Yield: 1.55 g (52%).

Mp 170-171° C; ^{1}H NMR ($CDCl_3$) δ 1.87 (br d, J=6.8 Hz, 3H), 2.00 (br s, 3H), 6.41 (br q, J=6.8 Hz, 1H), 7.2-7.4 (m, 3H), 7.62 (d, J=3.0 Hz, 1H) ppm; IR (KBr) 3210, 1596 cm^{-1}; mass spectrum, m/z 199 (M$^+$), 144 (base peak).

3-(Cyclohexylideneacetyl)indole (10).

Yield: 2.50 g (70%).

Mp 130-131° C; ^{1}H NMR ($CDCl_3$) δ 1.6-1.8 (m, 6H), 2.3 (m, 2H), 2.9 (m, 2H), 6.51 (br s, 1H), 7.2-7.4 (m, 3H), 7.86 (d, J=3.2 Hz, 1H), 8.5 (m, 1H) ppm; IR (KBr) 3274, 1647 cm^{-1}; mass spectrum, m/z 239 (M$^+$), 144 (base peak).

3-(*Trans*-but-2-enoyl)indole (12).

A dark-red, resinous residue was obtained. Flash chromatography (hexane/ethyl acetate, 60/40) gave 1.03 g (37%) crystals.

Mp 171-173° C (lit.[8] 173-174° C); ^{1}H NMR ($CDCl_3$) δ 1.97 (dd, J=6.8 Hz, 1.5 Hz, 3H), 6.8 (dd, J=15.1 Hz, 1.5 Hz, 1H), 7.0-7.3 (dq, J=15.1 Hz, 6.8 Hz, 1H), 7.3-7.5 (m, 3H), 7.88 (d, J=3.0 Hz, 1H) ppm; IR (KBr) 3128,1657 cm^{-1}; mass spectrum, m/z 185 (M$^+$), 144 (base peak).

3-Acetylindole (14).

Yield: 1.3 g (55%).

Mp 187-189° C (lit. 191-193° C[3], 191° C[21]); ^{1}H NMR ($CDCl_3$) δ 2.53 (s, 3H), 7.2-7.5 (m, 3H), 7.86 (d, J=3.1 Hz, 1H), 8.3 (m, 1H) ppm; IR (KBr) 3157, 1613 cm^{-1}; mass spectrum, m/z 159 (M^+), 144 (base peak).

3-(Chloroacetyl)indole (16).

Yield: 1.05 g (36%).

Mp 231-233° C dec. (lit. 230-232° C dec[15], 233-234° C[3], 230-232° C[22]); ^{1}H NMR ($CDCl_3$) δ 4.58 (s, 2H), 7.2-7.6 (m, 3H), 8.98 (d, J=3.2 Hz, 1H), 8.3 (m, 1H) ppm; IR (KBr) 3186, 1646 cm^{-1}; mass spectrum, m/z 193 (M^+), 144 (base peak).

3-(3-Chloropropionyl)indole (18).

Yield: 1.3 g (42%).

Mp 151-152° C (lit.[23] 152-153° C); ^{1}H NMR ($CDCl_3$) 3.34 (t, J=6.9 Hz, 2H), 3.97 (t, J=6.9 Hz, 2H), 7.2-7.5 (m, 3H), 7.90 (d, J=3.2 Hz, 1H), 8.35 (m, 1H) ppm; IR (KBr) 3217, 1635 cm^{-1}; mass spectrum, m/z 207 (M^+), 144 (base peak).

3-Benzoylindole (20).

Yield: 1.55 g (47%).

Mp 242-244° C (lit. 241-243.5° C[3], 245-47° C[24]); ^{1}H NMR ($CDCl_3$) 7.2-7.6 (m, 6H), 7.69 (d, J=3.1 Hz, 1H), 7.8 (m, 2H), 8.4 (m, 1H) ppm; IR (KBr) 3140, 1597 cm^{-1}; mass spectrum, m/z 221 (M^+), 144 (base peak).

3,3′-Diindolylethanedione (22).

Yield: 2.80 g (65%).

Mp 278-280° C (lit. 267-269° C[25], 279-280° C[26a]); ^{1}H NMR (DMSO-d_6) 7.2-7.6 (m, 6H), 8.21 (d, J=3.2 Hz, 2H), 8.25 (m, 2H) ppm; IR (KBr) 3306, 1603 cm^{-1}; mass spectrum, m/z 288 (M^+), 144 (base peak).

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(13) We generally use the term "the zinc salt of indole" (as Powers *et al.* in ref. 12) just for the case of simplicity and without implying anything about the structure of the reagent.

(14) Performing the reactions under dry nitrogen did not improve the yields.

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(17) Powers *et al.* (ref. 12) reported a 0.17 M ethereal solution of the indole zinc salt to be "a clear solution". We made dilute solutions (0.1 and 0.05 M) without getting a homogenous system. In addition we found yields to be lower using more dilute solutions.

(18) In some reactions we found the product to be only partly soluble in the ethereal phase. It was possible to obtain a clear organic layer by adding methylene chloride and/or a small amount of methanol.

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