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INTRAMOLECULAR RING CLOSURE OF α,β-UNSATURATED 3-ACYLINDOLES

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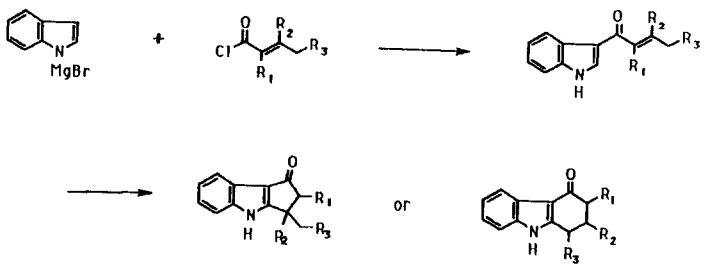
Abstract: A number of unsaturated 3-acylindoles were prepared and annulated (with HCl or NaCl-$AlCl_3$) to 3,4-dihydrocyclopent[*b*]indol-1(2*H*)-ones or 1,2,3,9-tetrahydro-4*H*-carbazol-4-ones depending on the structure of the substrate and/or the reaction conditions.

The growing number of natural products containing a cyclopent[*b*]indole structural element, *e.g.*, tremorgenic mycotoxins such as the penitrems[1] and the potential antifertility agent yuehchukene[2,3], motivated us to explore new approaches to cyclopent[*b*]indoles. We here present new methodology for the synthesis of 3,4-dihydrocyclopent[*b*]indol-1-ones and 1,2,3,9-tetrahydrocarbazol-4-ones starting from the indole Grignard reagent[4] and substituted acryloyl chlorides as outlined in scheme 1. The reactants, products, conditions and yields are given in Table 1.

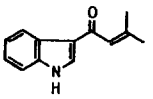
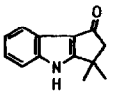
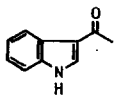
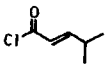
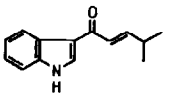
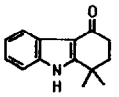
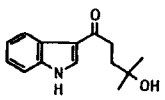
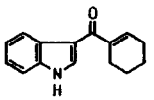
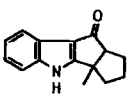
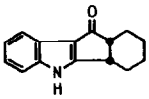
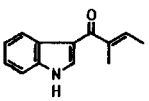
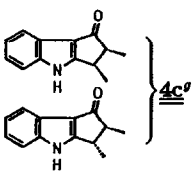
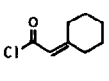
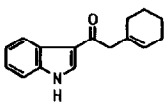
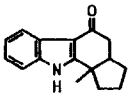
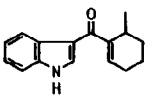
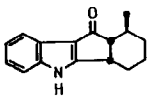


Scheme 1

Joule[5] has recently cyclized[6] **7** to **8** in refluxing 6M HCl. This method was adopted using conc. aqueous HCl in dioxane and the results were satisfactory (Table 1) in some cases. However, sometimes (entries 1 and 5) *retro* aldol condensations were encountered yielding 3-acetylindole and secondary products of acetone and cyclohexanone[7], respectively. Furthermore, in one case (entry 2) the tertiary alcohol **2d** was formed *via* double bond migration and hydration. HCl(g) in dry dioxane or acetonitrile at reflux gave no ring closure. Cyclizations induced by heating (130°C, 2-5 min.) in an $AlCl_3$-NaCl melt[8] was found to be complementary to the HCl/dioxane-method (Table 1). In some cases ring contractions were encountered (entries 3 and 5). Alkyl groups are known to migrate under the given conditions[9] and the structure of the products seems to be derived from nucleophilic attack on the most stable cation *e.g.* **3c**$^+$ and **5c**$^+$. The high stability of the 1-methyl-1-cyclopentyl cation is well documented[10].

Mechanistically, the products could be derived from either direct electrophilic alkylation at the indolic 2-position or *via* alkylation at the 3-position followed by migration of the alkyl substituent. The latter alternative seems unlikely since it would involve a strained 4-membered spiroindolenine intermediate. Since acetylation

Table 1[a]

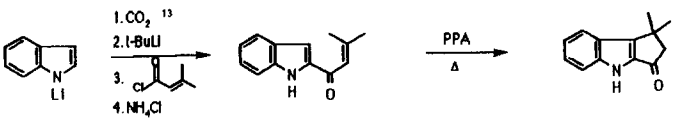
Entry	Acid chlorides[b]	3-Acylindole	Yield[c,d] (%)	Cyclization products: from NaCl/$AlCl_3$	Yield[c] (%)	from HCl/Dioxane	Yield[c] (%)
1	 **1a**	 **1b**[e]	60	 **1c**	50	 **1d**	50
2	 **2a**	 **2b**	26	 **2c**	44	 **2d**	41
3	 **3a**	 **3b**	47	 **3c**	52	 **3d**	80
4	 **4a**	 **4b**	43	 **4c**[g]	15	**4c**[i]	68
5	 **5a**	 **5b**[f]	35	 **5c**	40	**1d**	81
6	 **6a**	 **6b**	24	——[h]	–	 **6d**	50

a) All products were characterized by MS, IR and 200MHz ^{1}H-NMR. **3c**, **5c** and **3d** also by ^{13}C-NMR. The stereochemical assignments in the case of **3d** and **6d** were verified by NOE. b) Prepared by mixing the corresponding acid with 1.5 eq. $SOCl_2$ and one drop of DMF and refluxing for 2 hours. The crude product was distilled to give pure acid chloride. c) Isolated yields, not optimized. d) Yields of 3-acyl indoles are sometimes low due to side reactions, *e.g.* 1,3-diacylation, see ref. 4. e) See ref. 3. f) The double bond migrated during the reaction. g) 55% *trans*, 45% *cis*. h) Unidentified products. i) 80% *trans*, 20% *cis*.

7 8

3c* 5c*

of certain 3-alkylindoles does involve[11] migration of the acetyl group in preference to alkyl groups an intermediate 3-attack could possibly involve migration of the acyl group giving the isomeric cyclopent[*b*]indol-3-ones. We confirmed the position of the keto group in 1c by preparation of its isomer 9c, (Scheme 2), which showed different physical properties (mp, NMR, IR). Hence a direct electrophilic alkylation at the 2-position seems more likely[12].



Scheme 2

9c

In summary new methodology for the synthesis of 3,4-dihydrocyclopent[*b*]indol-1(2*H*)-ones and 1,2,3,9-tetrahydro-4*H*-carbazol-4-ones with the carbonyl group as a handle for further synthetic elaboration has been developed. The mechanism is likely to involve a direct electrophilic alkylation at the indolic 2-position. Furthermore, the synthesis of 9c may provide a general route to 1,4-dihydrocyclopent[*b*]indol-3(2*H*)-ones.

General experimental procedures are given, exemplified with the synthesis of 3b, 3c and 3d.

3-(1-Cyclohexenoyl)-indole (3b)

Indole (2.34 g, 20 mmol) was added to an ethereal solution of EtMgBr (10 ml, 2M) in dry benzene (40 ml). The solution was then allowed to stand for 20 min. whereupon 1-cyclohexenecarboxylic acid chloride (3.18 g, 22 mmol) in dry benzene (10 ml) was added dropwise while stirring, which was continued for 15 min. when the solution was rapidly quenched with NH_4Cl (aq. sat. 15 ml). The mixture was stirred for 15 min. more when the organic phase was separated, washed with water, evaporated and the residue dissolved in CH_2Cl_2 (50 ml). This solution was then washed with $NaHCO_3$ (aq. sat. 15 ml), brine (15 ml) and dried ($MgSO_4$). The filtered solution was added to benzene (20 ml) and the methylene chloride was evaporated which caused crystallization of the product. The crystals were collected, washed with cold benzene and dried, yield 2.1 g (47%) of colourless crystals : mp. 183-4°C; IR(KBr): 3210, 1645 cm^{-1}; ^1HNMR ($CDCl_3$): δ 8.5(br,1H), 8.3(m,1H), 7.65(d,1H,J=3.5 Hz), 7.4(m,1H), 7.25(m,2H), 6.6(m,1H), 2.45(m,2H), 2.25(m,2H), 1.75(m,4H); MS *m/z* 225(M +), 167, 149(100), 144.

Ketone 3c

To a melt (135°C) from $AlCl_3$ (6.0 g) and NaCl (1.5 g), 3b (400 mg) was rapidly added and the reaction mixture was stirred for 5 min. and then poured into ice (100 g). After extraction with CH_2Cl_2 (50 ml), the organic layer was washed with $NaHCO_3$ (aq. sat. 20 ml) and brine (20 ml), followed by drying over $MgSO_4$. Evaporation gave a brown solid which was purified by flash chromatography (CH_2Cl_2/MeOH, 99:1) to give 200 mg (50%) of off-white crystals. Crystallization from CH_2Cl_2/MeOH or sublimation (250°C in bath, 10 mmHg) gave the analytical sample : mp. 259-61°C; IR(KBr): 3200, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.5 (br,1H), 8.15(m,1H), 7.37(m,1H), 7.25(m,1H), 3.09(dd,1H,J=5Hz,J=7.5Hz), 2.4-2.2(m,2H), 2.2-1.7(m,4H), 1.67(s,3H); ^{13}C NMR ($DMSO_{d6}$): δ 195.6(s), 159.25(s), 135.5(s), 124.2(s), 121.6(d), 120.9(d), 119.35(d), 111.5(d), 108.1(s), 50.8(d), 48.4(t), 42.6(s), 37.8(t), 27.3(t), 20.1(q); MS *m/z* 225(100)(M^+), 210, 197, 184, 182, 168

Ketone 3d

Compound 3b (200 mg) was dissolved in dioxane (10 ml) whereupon conc. HCl (10 ml) was added and the mixture refluxed for 2 hours. Following neutralization of the cold mixture with aqueous Na_2CO_3 and extraction with CH_2Cl_2 (20 ml), the organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave 160 mg (80%) of light brown crystals. Sublimation (230°C in bath, 10 mmHg) gave the analytical sample: mp. 218-20°C; IR(KBr): 3200, 1655 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 10.7(br,1H), 7.8(m,1H), 7.4(m,1H), 7.2(m,2H), 3.5(m,1H), 3.0(m,1H), 2.2-2.0(m,1H), 2.0-1.7(m,2H), 1.7-1.3(m,5H); ^{13}C NMR ($DMSO-_{d6}$) δ 196.6(s), 170.0(s), 141.9(s), 122.8(d), 121.5(d), 121.0(s), 119.6(d), 117.4(s), 112.6(d), 51.1(d), 33.4(d), 26.3(t), 22.4(t), 19.9(t,2C); MS *m/z* 225(100)(M^+), 208, 196, 183, 168, 154

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References and notes

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6 The indol-2-yl isomer of 7 could be similarly cyclized.

7 Treatment of 5b with HCl/dioxane gave 1d and cyclohexanone from *retro*-aldol condensation subsequent to migration of the double bond to the exocyclic position.

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