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# Non-catalytic alkylation of the 2-positioned methyl group in 3-acyl-2-methylindoles

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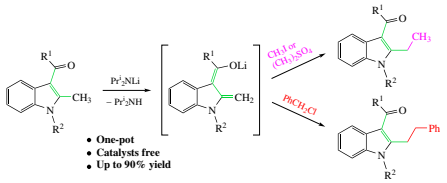
**Non-catalytic alkylation of 3-acyl-2-methylindoles upon the deprotonation with lithium diisopropylamide occurs at the 2-positioned methyl group. With the use of methyl iodide (dimethyl sulfate) or benzyl chloride, the reaction affords 3-acyl-2-ethylindoles or 3-acyl-2-(2-phenylethyl)indoles, respectively, with isolated yields up to 90%.**

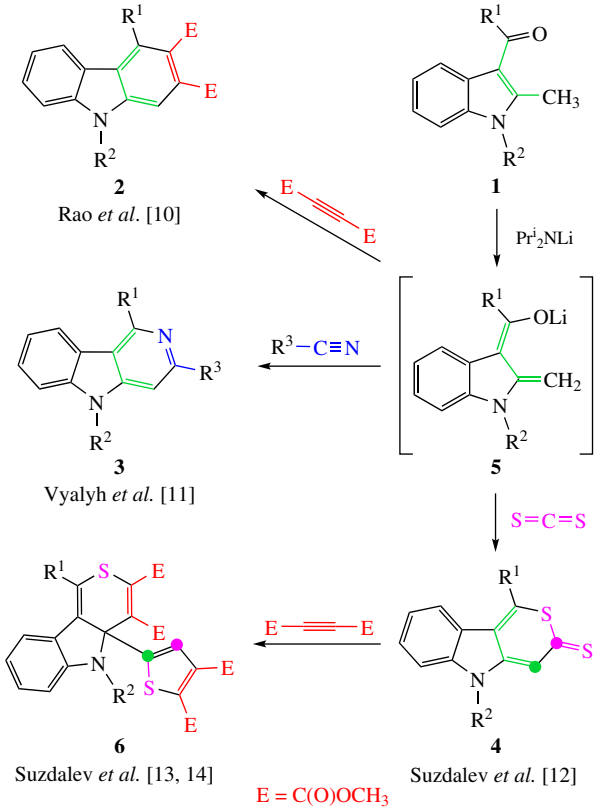



*Keywords*: indole, 3-acyl-2-methylindoles, CH-acids, alkylation, lithium diisopropylamide, lithium butadienolate.

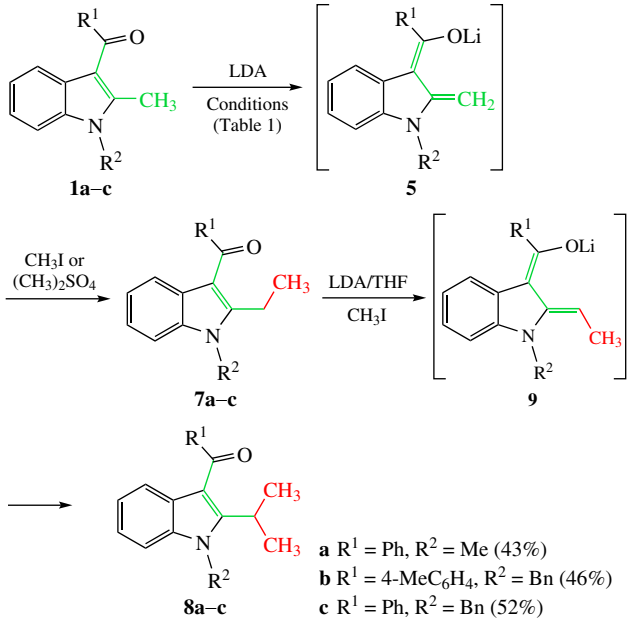
The indole core is an important pharmacophore responsible for the emergence of various types of biological activities.[1–3] 3-Acylindole derivatives (such as clometacin, pravadoline or JWH-015) are of particular interest since they are agonists of cannabinoid receptors and can act on the CP-55,940 cannabinoid binding site.[4,5] For example, the anti-inflammatory and analgesic drug pravadoline is used as a cyclooxygenase inhibitor with non-ulcerogenic properties.[6] Pravadoline and its analogues are able to inhibit prostaglandin synthesis in the mouse brain,[7] show antinociceptive activity and interact with G-coupled proteins in the brain.[8] The antifungal activity of 3-acylindoles has also been described.[9] In addition to biological activity, 3-acyl-2-methylindoles **1** are of special interest for organic synthesis, since they can be converted into carbazoles[10] **2**, γ-carbolines[11] **3**, and thiopyrano[4,3-*b*]indole-3(5*H*)thiones[12] **4** through lithium intermediates **5** (Scheme 1).

Previously, we discovered a new cascade reaction of thiopyrano[4,3-*b*]indole-3(5*H*)thiones **4** with dimethyl acetylenedicarboxylate leading to thiopyrano[4,3-*b*]indoles of type **6**.[13,14] For a detailed study of the structural and electronic effects on this unusual transformation, we needed to expand the range of initial compounds **1**, namely, to obtain 3-acyl-2-alkylindoles with a 2-positioned alkyl group having two or more carbon atoms. The simplest method for the synthesis of such compounds seemed to be the acylation of 2-alkylindoles unsubstituted at position 3. However, this approach is not reliable since the preparation of '2-Alk-3-H' indoles by the Fischer reaction is problematic due to the poor regioselectivity in the course of the cyclization.[15–19] Although other methods for the preparation of 3-acyl-2-alkylindoles proceeding through the formation of the pyrrole cycle of the indole core are described,[20–23] almost all of them are multistage, non-selectivite, or require the use of expensive palladium or platinum catalysts.

The aim of this work was to develop the synthetic procedure towards 3-acyl-2-alkylindoles **7** with an alkyl group higher than the methyl one from simple synthetic precursors, namely from 3-acyl-2-methylindoles **1**, by alkylation of its 2-methyl group. Previously,[24] deprotonation of the 2-positioned methyl group of the indole was carried out using butyllithium, which is unacceptable in our case due to the presence of a reactive acyl group at position 3. Therefore, we tested a non-nucleophilic base such as lithium diisopropylamide (LDA). There is a single example in the literature of using LDA for alkylation of the methyl group of 1,2-dimethyl-3-(ethoxycarbonyl)indole,[25] but these results were not systematized, the method was not optimized, and it had not been used for alkylation of 3-acyl-2-methylindoles.




**Scheme 1**




**1a–c** **5** **7a–c** **9** **8a–c**

**a** $R^1$ = Ph, $R^2$ = Me (43%)
**b** $R^1$ = 4-Me$C_6H_4$, $R^2$ = Bn (46%)
**c** $R^1$ = Ph, $R^2$ = Bn (52%)

**Scheme 2**

The non-catalytic alkylation of 3-acyl-2-methylindole derivatives **1** should proceed through initial formation of intermediate lithium butadienolates **5** (*cf.* refs. 11, 12) and their subsequent reactions with alkyl halides or dimethyl sulfate (Scheme 2). Compounds **1** are the vinylogues of alkyl ketones and should possess sufficient acidity of the methyl protons, and their deprotonation under the action of LDA should afford enolates **5**.

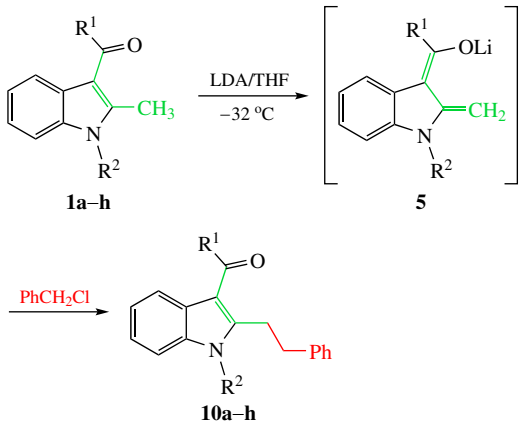
We first examined the methylation reaction. It turned out that it was non-selective and gave a mixture of starting compounds **1**, monomethylation (**7**) and dimethylation (**8**) products (Scheme 2). It is obvious that dialkylation occurs through formation of a new enolate **9** from product **8** by deprotonation with an excess of lithium diisopropylamide and its subsequent alkylation. The possibility of the second alkylation of 2-ethylindoles was noted earlier.[24]

In order to optimize the reaction conditions for achieving the highest yields of compounds **7** (Table 1), methylation of indole **1c** as the model was carried out in various solvents (THF, diethyl ether, benzene) at different temperatures (storage with an

**Table 1** Optimization of methylation of substrate **1c**.

| Entry | Base | Solvent | *T*/°C | Reagent ratio **1c**/base/$CH_3I$ | Reaction mixture composition[a] **1c**/**7c**/**8c** |
|---|---|---|---|---|---|
| 1 | LDA | THF | ~20 | 1 : 2 : 5 | 0.55 : 1 : 0.71 |
| 2 | LDA | THF | –32 | 1 : 2 : 5 | 0.16 : 1 : 0.07 |
| 3 | LDA | THF | –32 | 1 : 3 : 5 | 0.17 : 1 : 0.10 |
| 4 | Bu$^t$OK | THF | –32 | 1 : 2 : 5 | 1 : 0 : 0 |
| 5 | LDA | THF/TMEDA[b] | –32 | 1 : 2 : 5 | 0.86 : 1 : 0 |
| 6 | LDA | $Et_2O$ | ~20 | 1 : 2 : 5 | 0.47 : 1 : 0.67 |
| 7 | LDA | $Et_2O$ | ~20 | 1 : 3 : 5 | 0.10 : 1 : 0.42 |
| 8 | LDA | $Et_2O$ | –32 | 1 : 1 : 5 | 0.13 : 1 : 0 |
| 9 | LDA | $Et_2O$ | –32 | 1 : 2 : 5 | 0.19 : 1 : 0.25 |
| 10 | LDA | $Et_2O$ | –32 | 1 : 3 : 5 | 0.95 : 1 : 0.13 |
| 11 | LDA | PhH | ~20 | 1 : 2 : 5 | 0.36 : 1 : 0.35 |
| 12 | LDA | PhH | –32 | 1 : 2 : 5 | 0.39 : 1 : 0.20 |
| 13 | LDA | THF | ~20 | 1 : 2 : 2[c] | 0.73 : 1 : 0.45 |
| 14 | LDA | THF | –32 | 1 : 2 : 2[c] | 0.58 : 1 : 0.38 |

[a] From NMR. [b] TMEDA is tetramethylethylenediamine. [c] $Me_2SO_4$ as alkylating agent.




**1a–h** **5** **10a–h**

**a** $R^1$ = Ph, $R^2$ = Me (69%)
**b** $R^1$ = 4-Me$C_6H_4$, $R^2$ = Bn (63%)
**c** $R^1$ = Ph, $R^2$ = Bn (90%)
**d** $R^1$ = 4-Me$C_6H_4$, $R^2$ = Me (70%)
**e** $R^1$ = Bu$^t$, $R^2$ = Me (42%)
**f** $R^1$ = Ph, $R^2$ = Et (67%)
**g** $R^1$ = 4-Cl$C_6H_4$, $R^2$ = Et (33%)
**h** $R^1$ = 4-Cl$C_6H_4$, $R^2$ = Me (56%)

**Scheme 3**

alkylating agent at –32 °C or at room temperature). The ratio of the reagents and base nature were also varied. With potassium *tert*-butoxide, the alkylation did not occur (see Table 1, entry 4). In most cases, three-component mixtures of products **7c**, **8c** and unreacted **1c** were obtained ($^1$H NMR spectra of the crude materials). The largest fraction of compound **7c** in the mixture was achieved under conditions of entries 2 and 8. However, it is preferable to carry out the reaction in THF due to better solubility of compound **1c** in it (entry 2). With the use of active dimethyl sulfate in place of MeI, the **1c**/**7c**/**8c** ratios were not good in favour of the desired **7c** (entries 13, 14). Unfortunately, it was not easy to fully separate the resulting mixtures. Meantime, multiple (3–5 times) recrystallizations led to the desired product **7c** containing 97% of the main substance and 3 mol% of the original indole **1c**, which was sufficient for further research.

Carrying out the further methylation of the resulting mixture (**1c** + **7c** + **8c**) gave a mixture with higher content of compound **7c**, however the content of the by-product **8c** also grew. Attempts to perform exhaustive methylation of this mixture in order to prepare product **8c** were not successful due to strong tarring of the reaction mixture.

Methylation of other indoles **1a**,**b** was carried out using an optimized procedure (see Scheme 2). The structures of 2-ethyl derivatives **7a–c** were confirmed by $^1$H and $^{13}$C NMR spectroscopy (see Online Supplementary Materials). Attempts to apply higher alkylating agents (bromoethane, diethyl sulfate or 1-iodopentane) to obtain higher homologues were unsuccessful. Instead of the desired compounds, the mixtures of starting materials together with the products of the reaction of excess LDA with the alkylating agents were formed.

Reactions with active benzyl chloride were successful and produced [1-alkyl-2-(2-phenylethyl)-1*H*-indol-3-yl](aryl)-methanones **10a–h** (Scheme 3). It should be noted that in this case the products were readily isolated in pure form; the starting substances and dialkylation products were not observed in the NMR spectra. To optimize the reaction conditions, we varied the ratio of compound **1c** and benzyl chloride, and the best result was found with a molar ratio **1c**/LDA/BnCl of 1 : 2 : 1.5. A larger excess of benzyl chloride hindered the crystallization of products **10a–h**. The method we developed herein made it possible to significantly simplify the synthesis of 3-acylindole derivatives containing a 2-positioned 2-phenylethyl group. Previously, their preparation was carried out by reactions involving transition metals or by multi-stage syntheses including the Wittig–Horner reaction.[26–29]

To conclude, the methylation of 3-acyl-2-methylindoles in the presence of LDA usually leads to a mixture containing the starting compounds and the products of mono- and dimethylation of the 2-methyl group. No side processes were observed in reactions with benzyl chloride. Optimal conditions were found for the preparation of 3-acyl-2-ethylindoles **7** with a content of the main products up to 97% and 3-acyl-2-(2-phenylethyl)-indoles **10** without admixture of the starting compounds.

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*Online Supplementary Materials*

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7551.

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