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REACTIONS ON SOLID SUPPORTS PART IV[1] : REACTIONS OF αβ-UNSATURATED CARBONYL COMPOUNDS WITH INDOLES USING CLAY AS CATALYST

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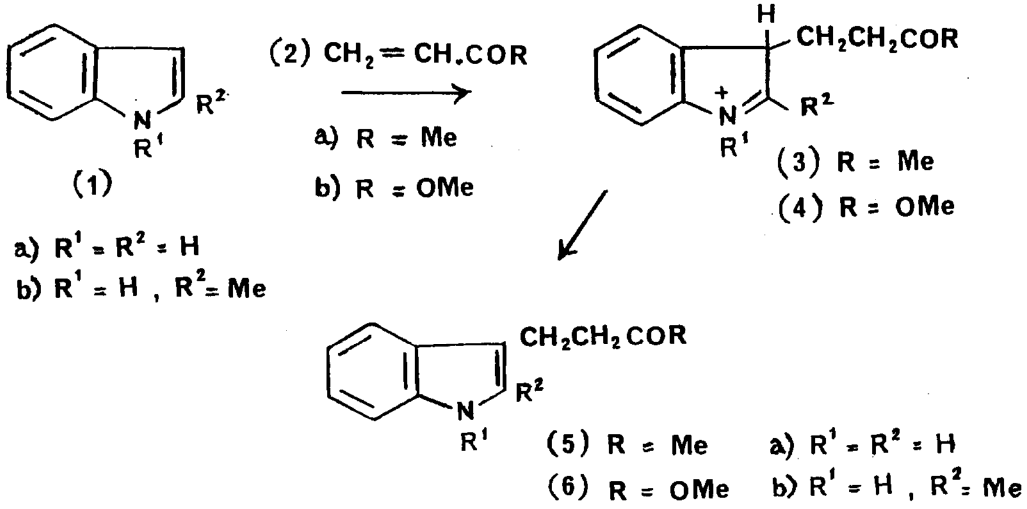
Summary : Indoles react with αβ-unsaturated carbonyl compounds in the presence of clay catalysts to give substituted indoles in good yields; in one case a 3-benzyl substituent already present migrated to the 2-position, being displaced by the incoming electrophile, thus confirming that electrophilic substitution in indole occurs primarily at the 3-position.

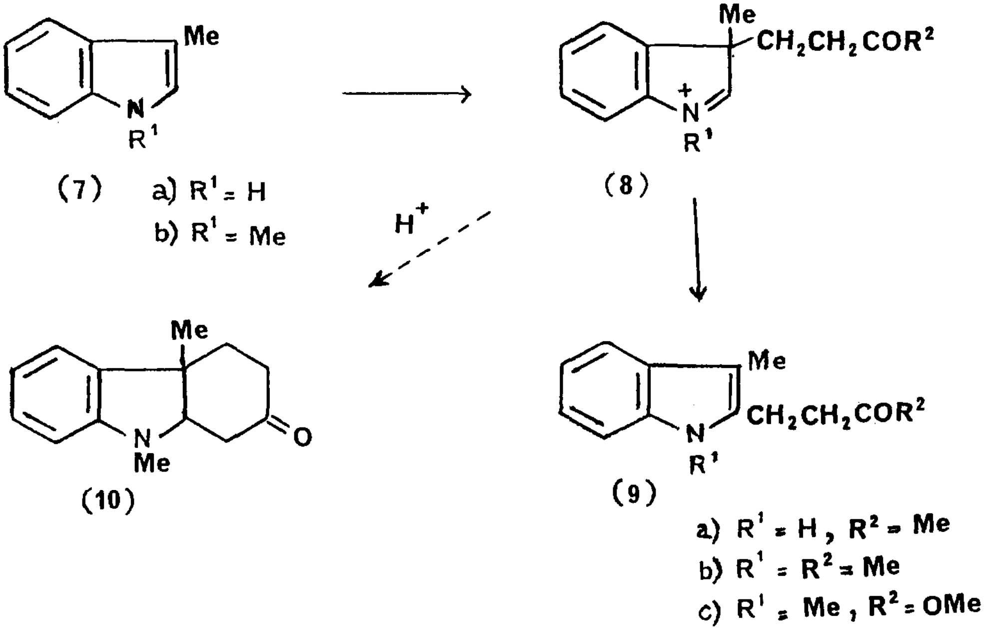
Over the last decade, the acidic nature of Montmorillonite and Bentonite clays has been advantageously utilised to catalyse many types of organic reactions[2,3]. In many instances, the reactions occur much more readily and specifically than when Lewis or Bronsted acids are used. Acid catalysed electrophilic substitution of indoles and pyrroles requires careful control of acidity to prevent side reactions such as dimerisation and polymerisation[4], and we have already reported the applications of clay catalysts in the preparation of dipyrromethanes required for porphyrin synthesis[2]. Indoles will also undergo similar reactions to form di-indolylmethanes, or mixed aryl indolylmethanes[5]. In the present paper, we describe the use of clay catalysts in the alkylation of indoles by Michael-type reactions with αβ-unsaturated ketones and αβ-unsaturated esters.



Scheme 1

3-Unsubstituted indoles afford the corresponding 3-substituted indoles (5) in good yield with simple αβ-unsaturated ketones such as methylvinyl ketone (2a) via the intermediate 3H-indolenine (3a) (Scheme 1). In a typical procedure, a solution of indole (1a) (1.0g, 8.6mmol) and methylvinyl ketone (0.6g, 8.6mmol) in dichloromethane (50cm^3) was gently refluxed with Montmorillonite clay (0.5g) for 2h. The colour of the clay turned light brown and the reaction was followed to completion by t.l.c. H.p.l.c. analysis showed that the product (5a) was formed in essentially quantitative yield. Filtration and evaporation of the filtrate gave 1-(3'-indolyl)-butan-3-one (5a) in 75% yield after crystallisation from light petroleum (b.p. 40 - 60°):toluene (3:1).

Methyl acrylate (2b) was less reactive than methylvinyl ketone and with indole lower yields of the indolyl propionic ester (6a) were obtained (cf. Table). Attempts to improve the yield by using prolonged reaction times, or higher temperatures, were thwarted by the formation of unwanted by-products (dimers, trimers and polymers). However, by changing the ionic characteristics of the clay e.g. use of an aluminium exchanged clay[6], a much higher yield of the indolyl propionic ester (6a) was obtained. The more reactive 2-methyl indole (1b) gave a higher yield of the corresponding ketone (5b) and ester (6b) (cf. Table).



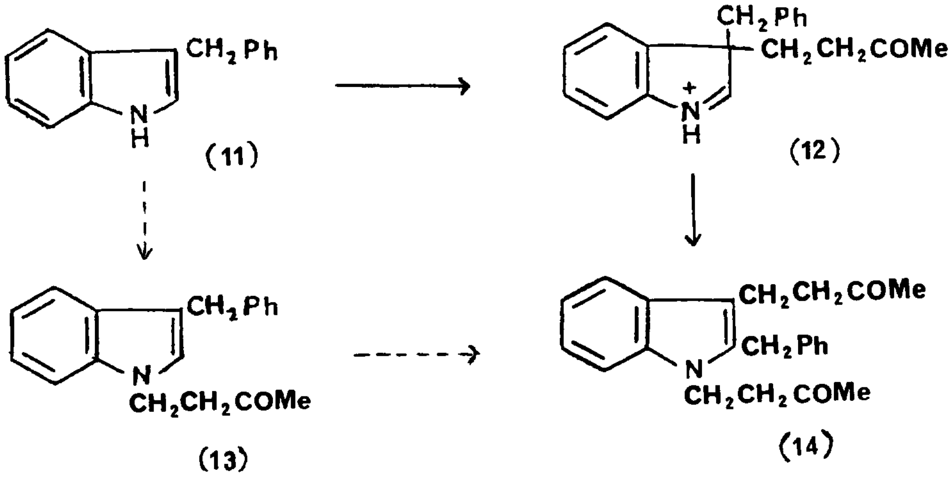
Scheme 2

Reactions were also carried out with 3-substituted indoles and, for example, 3-methyl indole (7a) and methylvinyl ketone (2a) in presence of clay afforded 2(2'-oxobutyl)-3-methylindole (9a) in moderate yield; the slightly more reactive 1,3-dimethylindole (7b) gave rather better yields of the 1,2,3-trisubstituted indoles (9b) and (9c) in clay catalysed reactions with methylvinyl ketone (2a) and methyl acrylate (2b) (cf. Table). The trisubstituted indole (9b) was formed in the reaction of 1,3-dimethyl indole and methylvinyl ketone in glacial acetic acid/acetic anhydride[7], whereas under mineral acid conditions 1,3-dimethylindole and methylvinyl ketone afford the tricyclic indoline (10)[7,8].

Table Clay Catalysed Reactions of Indoles with Methyl Vinyl Ketone and Methyl Acrylate

Indole	αβ-Unsaturated carbonyl compound	Reaction Conditions Temp °C	Time/h	Products	Isolated Yield (%)	m.p. or b.p. °C
1a	2a	40	2	5a	75	93-94
1b	2a	20	0.5	5b	90	78-83/0.01mm
1a	2b	83	24	6a	40	79-80
1a	2b	83	12	6a	70	79-80
1b	2b	83	6	6b	80	88-94/0.01mm
7a	2a	83	12	9a	35	60-70/0.01mm
7b	2a	83	12	9b	70	77-78
7b	2b	83	12	9c	35	82-84/0.01mm
11	2a	20	1	14	25	94-100/0.01mm
				13	15	100-110/0.01mm

In accord with our previous studies of electrophilic substitution in indoles[8-10], we envisage that these reactions of 3-methylindoles involve prior attack at the indole 3-position to form 3,3-disubstituted indolenine (8), and that the incoming alkyl substituent subsequently rearranges into the 2-position (cf. Scheme 2). For this reason, we also investigated the reaction of 3-benzylindole (11) with methylvinyl ketone (2a) in presence of clay as it seemed likely that the benzyl group in the intermediate indolenine (12) formed in this case might undergo preferential migration to the 2-position (rather than the incoming oxoalkyl group) owing to its higher migratory aptitude. In the event, two products were formed, the 1-alkyl-3-benzylindole (13) (25%) and the 1,3-dialkyl-2-benzylindole (14) (15%). The structures of both compounds were determined by spectroscopic methods, including the use of n.O.e.



Scheme 3

difference n.m.r. spectroscopy in the latter case. Thus irradiation of the α-methylene resonance of the 1-(3-oxobutyl) side chain of (14) at δ 3.1 resulted in n.O.e.'s of 4% for the indole 4-H resonance at δ 7.65 and 1% for the benzylic methylene resonance at δ 4.2 as well as 5% for the β-methylene resonance at δ 2.8; irradiation of the β-methylene resonance at δ 2.8 produced n.O.e.'s at the indole 4-H (1%), the α-methylene resonance at δ 2.8 (3%), and the terminal methyl group at δ 2.1 (5%).

These results with 3-benzylindole thus provide further evidence for the primacy of the 3-position in indoles towards electrophilic substitution even when this position is already substituted. Further studies of these and related reactions are in progress, using more complex αβ-unsaturated carbonyl compounds, and modified clays.

Acknowledgements

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