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Alkylation of indoles with α,β-unsaturated ketones using alumina in hexanes.

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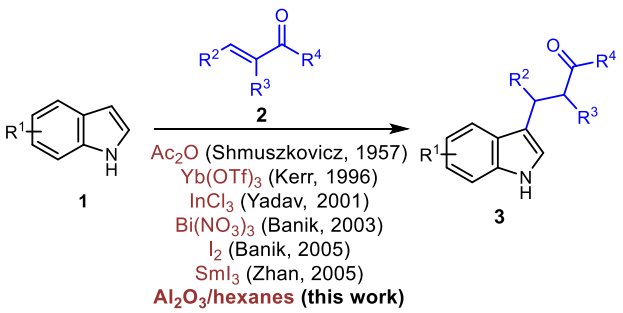
Abstract. We evaluated the influence of solvent on the alumina-promoted C3-alkylation of indoles with α,β-unsaturated ketones. We found that lipophilic solvents were generally superior to hydrophilic ones with hexanes offering the 3-alkyl indole products in high yields. Thus, we demonstrate an inexpensive and procedurally simple new process that pairs acidic alumina with hexanes to achieve this important Michael alkylation. The substrate scope includes twenty-four examples with reaction yields ranging from 61 to 96 %.

Keywords: indoles; α,β-unsaturated ketones; alumina; hexanes; Michael addition

Activated γ-aluminum oxides or "aluminas", sold ubiquitously for use in chromatography, have amorphous surfaces with exposed acidic and basic sites that also make them useful to synthetic chemists as heterogeneous reagents, catalysts, or catalyst supports, with the procedural convenience of easy removal from reaction products via filtration.[1] When a solvent is employed in an alumina-promoted chemical transformation, dissolved substrates must interact with the alumina surface at the alumina-solvent interface. We have observed that only minimal solvent screening is typically reported in most of the published synthetic methods literature in this field and this led us to consider whether solvent may be an underappreciated variable in the context of reactivity at alumina surfaces. With the pragmatic aim of advantageous new synthetic methods that benefit from inexpensive heterogeneous alternatives to traditional homogeneous reagents[2] we decided to investigate the effect of solvent on alumina activity.

As a suitable system for this study, we chose the acid-promoted Michael addition of indoles (**1**) to α,β-unsaturated ketones (**2**) (Scheme 1). The indole scaffold is common in natural products and medicinal chemistry and has accordingly received much attention from our synthetic community,[3] and C3-substituted indoles are particularly significant as highlighted by Njardarson and co-workers who observed that fifteen of seventeen Food and Drug Administration (FDA)-approved indole-containing drugs have substitution at the C3 position.[4]



Scheme 1. Lewis Acids used for alkylation of indoles with α,β-unsaturated ketones.

The C3-alkylation of indoles with enones was first shown to be induced by Ac_2O in 1957,[5] and has since been revisited and improved using a range of Lewis Acid promoters including $Yb(OTf)_3$,[6] $InCl_3$,[7] $Bi(NO_3)_3$, [8] I_2,[9] SmI_3,[10] and others[11] (Scheme 1). To our knowledge, alumina has not been previously used for this transformation. The analogous reaction between indoles and nitroolefins to make 3-nitroethylindoles has been reported with alumina, but under solvent-free conditions.[12]

In our hands, treatment of indole (**4**) with methyl vinyl ketone (**5**, 1.3 equiv.) and acidic alumina (2 g/mmol of indole) at room temperature for two hours in twelve different solvents revealed a dramatic solvent effect on the yield the corresponding 3-alkyl indole **6** (Table 1, entries 1-12). These ranged from <10 % in acetone and ethanol to >90 % in toluene and hexanes. The highest product yield of 94 % was observed in hexanes, along with complete consumption of indole in two hours. Lipophilic solvents (hexanes, n-hexane, heptanes, toluene, chloroform) were generally superior to hydrophilic solvents (acetone, ethanol, 2-butanol).

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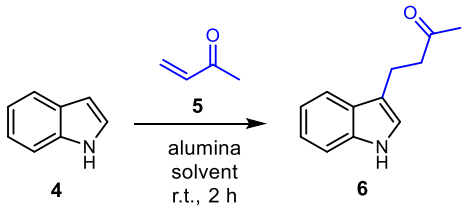
The interface between a lipophilic solvent and the hydroxyl-rich alumina surface may be considered somewhat analogous to an oil-water interface. Accordingly, we hypothesize that the rationale for the reactivity observed upon pairing of lipophilic solvents with alumina may be analogous to that offered for rate enhancement seen for reactions "on water".[13] These are reactions run in oil-water emulsions that demonstrate rate acceleration explained by a combination of 1) increased concentration of reactants at the oil-water interface, and 2) the enhanced hydrogen bonding capacity of unbound, or "dangling", –OH groups that protrude from the aqueous phase into the organic phase.[14]

Table 1. Optimization of reaction conditions.



Entry	Solvent	Alumina type	Yield of **6** (%)[b]
1	ethanol	acidic	1
2	acetone	acidic	8
3	THF	acidic	13
4	2-butanol	acidic	44
5	acetonitrile	acidic	66
6	diethyl ether	acidic	77
7	DCM	acidic	80
8	ethyl acetate	acidic	81
9	MTBE	acidic	81
10	chloroform	acidic	84
11	toluene	acidic	90
12	hexanes	acidic	94
13	n-hexane	acidic	95
14	heptane	acidic	95
15	hexanes	none	0
16	hexanes	neutral	41
17	hexanes	basic	66
18	hexanes	acidic 2[c]	96
19	hexanes	acidic 3[c]	92
20	hexanes	acidic	94[d]
21	hexanes	acidic	96[e]

[a] Procedure: indole (0.5 mmol), alumina (1 g; acidic; *see Supporting Information*), solvent (5 mL) and methyl vinyl ketone (0.65 mmol, 1.3 equiv.), stirred at r.t. for 2 hours; mixture was filtered and washed with EtOAc (3 x 5 mL); solvent was removed and crude residue was analyzed by NMR. [b] Determined by ^{1}H NMR with dibromomethane as the internal standard. [c] Alumina purchased from a different supplier was used (see *Supporting Information*). [d] Amount of methyl vinyl ketone was reduced to 0.55 mmol (1.1 equiv.). [e] Amount of alumina was reduced to 0.5 g (1 g/mmol).

We chose hexanes as our preferred solvent for small scale reactions because of its ubiquity and low cost. For preparative scale reactions, heptanes or *n*-heptane would be a better option because of lower volatility and toxicity relative to hexanes and *n*-hexane (*see Scheme 3 below*). We observed no background reaction in hexanes in the absence of alumina (Table 1, entry 15), reduced yields with neutral and basic aluminas (entries 16 & 17), and comparable yields with acidic aluminas from two other manufacturers (entries 18 & 19, see Supporting Information for details). Lowering the relative amount of methyl vinyl ketone from 1.3 to 1.1 equiv. slightly diminished yield (entry 20) while reducing the alumina loading from 2 to 1 g/mmol of indole, increased the yield to 96 % (entry 21).

Our subsequent expansion of the substrate scope to other α,β-unsaturated ketones showed that methyl vinyl ketone was the most reactive electrophile while most others benefited from heating of the reaction mixture to reflux temperature (68 °C) as well as employment of 2 g of alumina per 1 mmol of indole. Thus our preferred general set of conditions for this reaction ultimately became: indole (1.0 equiv.), enone (1.3 equiv.), alumina (2 g/mmol), and hexanes (5 mL/mmol), stirred at reflux temperature, and monitored by thin layer chromatography (TLC) for disappearance of indole (2 - 24 hours).

As summarized in Scheme 2, we demonstrated the substrate scope of this reaction by applying it to a range of indole and α,β-unsaturated ketone substrates to generate a library of twenty-four 3-alkyl indoles (compounds **10** – **33**). First methyl vinyl ketone was paired with six substituted indoles to yield 3-alkyl indoles containing a second alkyl (**11, 12, 16**), alkoxy (**13, 15**), or halogen (**14**) substituent in good yields. Next, indole was paired with nine phenyl vinyl ketones to yield compounds **17 - 25** with a range of substituents including a hydroxyl moiety, which was well tolerated with phenol **25** obtained in 82 % yield. Indole was also alkylated with six chalcone derivatives to yield compounds **26** – **33** in high yields ranging from 86 % – 96 %. Finally, indole was reacted with 2-chloro-1-phenylpropenone resulting in the α-chloro ketone **32** in 61% yield and with 1,2-diphenylprop-2-en-1-one to offer **33** in 62 % yield.

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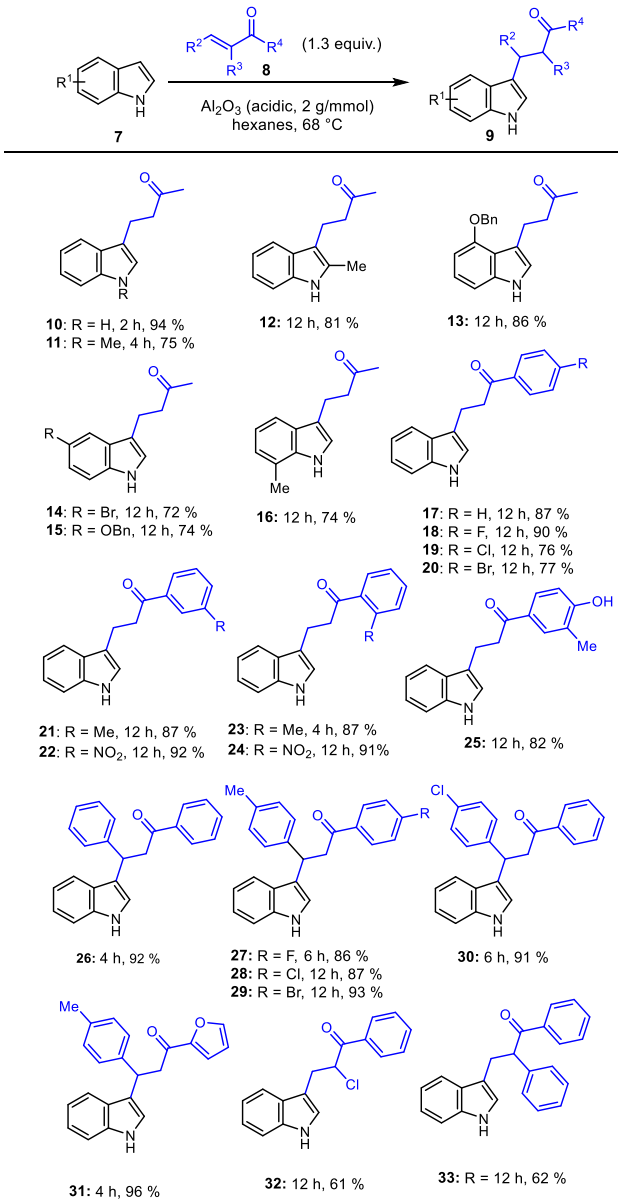
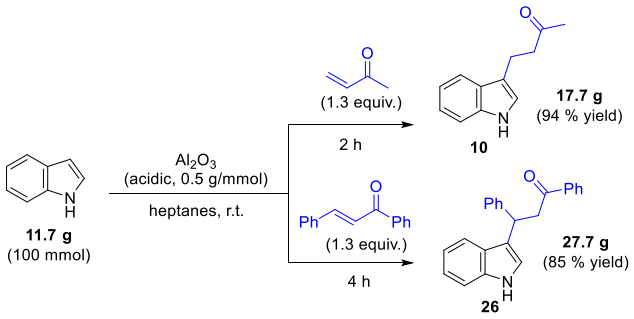


Scheme 2. Substrate Scope [a]

[a)] Reaction conditions: indole substrate (1 equiv.), α,β-unsaturated ketone (1.3 equiv.) Al_2O_3 (acidic, 2 g/mmol of indole), and hexanes (10 mL/mmol of indole) was heated to reflux for 4-16 h.; Reported yields are for isolated products after chromatography.



Scheme 3. Preparative Scale Reactions

Finally, we demonstrated larger scale preparations of compounds 10 and 26 by making 17.7 g and 27.7 g of these respectively using our protocol (Scheme 3). For these substrates (indole, methyl vinyl ketone, and chalcone) three modifications to the typical procedure were tolerated well: 1) the use of heptanes instead of hexanes, 2) less alumina, 0.5 g/mmol of indole, and 3) reaction at room temperature rather than reflux. Compounds 10 and 26 were obtained in 94 % and 85 % yields respectively. Experimental details corresponding to these reactions, including photographs, are presented in the Supporting Information document.

In summary, we have reported a procedurally simple new method for C3-alkylation of indoles with α,β-unsaturated ketones that employs acidic alumina in hexanes or heptanes. An evaluation of solvents in this reaction showed that lipophilic solvents are superior to hydrophilic solvents. Based on our informal analysis of reagent costs listed on the websites of common suppliers, we are confident that the cost of alumina (0.5 g/mmol of substrate, or approximately $0.04 USD) is favourable relative to other reagents that are similarly efficacious for this transformation including $InCl_3$ (0.1 mmol, approximately $0.25), SmI_3 (0.1 mmol, approximately $12) and $Bi(NO_3)_3$ (0.15 mmol, approximately $0.13). Due to this cost benefit and the facile removal of alumina by filtration, we believe that our new process is competitive with all previously reported alternatives for this important transformation. Finally, we hope this work might inspire the development of additional synthetic tools that leverage the pairing of alumina surfaces with lipophilic solvents.

Experimental Section

General procedure for the alkylation of indoles with α,β-unsaturated ketones: To a round bottom flask equipped with a stir bar were added: the indole derivative (1.0 equiv.), α, β-unsaturated ketone (1.3 equiv.), Al_2O_3 (acidic, 2 g/mmol of indole), and hexanes (5 mL/mmol of indole). The flask was equipped with a reflux condenser and heated in a sand bath at reflux temperature. The top of the condenser was open to the air. The reaction was monitored periodically by TLC. Upon complete disappearance indole (2-24 hours), the reaction mixture was cooled and filtered through filter paper. The solids were rinsed with EtOAc (x 3), and the combined filtrate was concentrated in vacuo and purified by flash column chromatography using hexanes and EtOAc as eluent to yield the 3-alkyl indole products.

Representative example, Compound 18: The general procedure was used with 1-(4-fluorophenyl)prop-2-en-1-one (97.6 mg, 0.65 mmol), acidic alumina (1g), indole (58.6 mg, 0.5 mmol), and

hexanes (5 mL). TLC analysis at 12 hours indicated complete consumption of indole. Compound 18 was isolated as a white solid (120.4 mg, 0.45 mmol, 90 % yield); Rf = 0.56 (EA/Hex = 30:70 v/v); MP = 121-122 °C; 1H NMR (500 MHz, Chloroform-d) δ 8.00 – 7.96 (m, 2H), 7.95 (s, 1H), 7.65 – 7.62 (m, 1H), 7.37 (dt, J = 8.1, 0.9 Hz, 1H), 7.21 (ddd, J = 8.1, 7.0, 1.2 Hz, 1H), 7.16 – 7.13 (m, 1H), 7.13 – 7.08 (m, 2H), 7.05 (dt, J = 2.0, 0.8 Hz, 1H), 3.38 – 3.33 (m, 2H), 3.25 – 3.20 (m, 2H); 13C NMR (126 MHz, Chloroform-d) δ 198.4, 166.8, 164.8, 136.5, 133.6, 130.8, 130.8, 127.4, 122.3, 121.7, 119.5, 118.8, 115.9, 115.7, 115.6, 111.3, 39.4, 19.9; FTIR (νmax, cm- 1):3308, 3063, 2909, 2852, 1669, 794, 760; HRMS: calculated for C14H14FNO (M+H)+ 286.1137; found 286.1125.

Acknowledgements

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