

Solid Acid-Catalysed Michael-Type Conjugate Addition of Indoles to Electron-Poor C=C Bonds: Towards High Atom Economical Semicontinuous Processes

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Abstract: In this paper a novel application of solid acid catalysts in the chemoselective Friedel–Crafts (FC) alkylation of indoles is reported. The optimal protocol allows highly functionalised indolyl compounds to be synthesised in excellent yields through conjugate addition of indoles with α,β -unsaturated ketones and nitro compounds. Finally, the use of commercial Amberlyst-15 as the heterogeneous catalyst for highly atom efficient continuous and semi-continuous Friedel–Crafts processes is described.

Keywords: Amberlyst 15; continuous process; Friedel–Crafts alkylation; heterogeneous catalysis; indoles; Michael addition

Solid acid catalysis is a growing field of research as the demand for clean and eco-friendly chemical processes is increasing.^[1] Many organic reactions are known to be catalysed by clays, ion-exchange resins and zeolites both in natural and modified form.^[2] Among them, heterogeneously catalysed Friedel–Crafts alkylation reactions are receiving a great deal of attention even for large scale processes.^[3]

Catalytic and stereoselective alkylation of indoles *via* 1,4-addition to electron-deficient double bonds is an important organic reaction that affords products that may be transformed into valuable building blocks.^[4] As a continuation of our ongoing investigations in this area,^[5] we now describe our preliminary results in the optimisation of a novel heterogeneously catalysed FC

Michael-type addition of indoles to α,β -unsaturated carbonyls and nitro compounds.

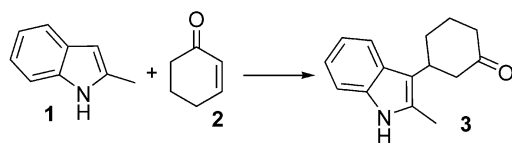
Firstly, by selecting the batch 1,4-addition of 2-methylindole (**1**) to 2-cyclohexen-1-one (**2**) as the model reaction, a range of solid acids were screened as catalysts (Scheme 1).^[6]

From the data collected in Table 1 it emerges that, although in the absence of promoting agent the reaction did not occur in significant extents over 24 h reaction time, commercial ion-exchange sulfonic resins such as Amberlyst-15, 35, 36 and 40, employed at 20% wt, allowed **3** to be isolated in high yields (61–76%). On the contrary, montmorillonite-based catalyst (F-13 and F-20X, entries 3, 4) provided **3** in unacceptable yields (23–35%). This finding can be rationalised by considering the capacity (equiv./kg) of the solid acids utilised. In fact, when the Amberlyst-15 dry (4.70 equiv./kg) was replaced by the less acid clays F-13 and F-20X (capacity: 0.4 and 0.2 equiv./kg respectively) a remarkable drop in chemical yield was observed. Moreover, the perfluorinated resin-sulfonic acid Nafion-H[®] was also examined as the catalyst, but in this case the desired indole compound **3** was isolated only in 46% yield (entry 11). It is worthy of note that conventional Brønsted acid catalysis (*p*TSA 10 mol%) was poorly effective for this transformation, in fact, undesired polymerisation of the indole occurred yielding **3** only in traces (entry 2).

Chemical outcomes can be further improved by increasing the loading of Amberlyst-15 and 35 to 50% wt, in these cases **3** was isolated in 98% and 85% yield respectively.^[7]

Both scope and generality of the procedure were evaluated by reacting several α,β -unsaturated carbonyls and nitro compounds with **1** in the presence of Amberlyst-15 and 39 (20% wt). All the reactions provided the desired 1,4-adducts in good yields (up to 96%) by a proper choice of the solvent (generally reagent grade Et₂O and CH₂Cl₂ afforded the highest yields) depending on the substrates solubility (Table 2).

The reusability of the solid acid was also effectively proved by recycling the catalyst (Amberlyst-15 20% wt) for 5 runs in the addition of 2-methylindole to **4**. No margin of activity loss was observed even if a moder-



Scheme 1. Model reaction for the catalyst screening. Reaction conditions: cat (20% wt), **1** (1.5 equivs.), **2**, (1 equiv.).

Table 1. Screening of heterogeneous catalysts for the conjugate addition of 2-methylindole (**1**) to **2**.^[a]

Entry	Catalyst	Capacity [equiv./kg]	Yield [%] ^[b]
1	none	–	traces
2	<i>p</i> TSA	–	traces ^[c]
3	Grade F-13 (dry)	0.4	23
4	Grade F-20X (dry)	0.2	35
5	Amberlyst-15 dry	4.7	62
6	Amberlyst-15 dry	"	98 ^[d]
7	Amberlyst-35 wet	5.2	76
8	Amberlyst-35 wet	"	85 ^[d]
9	Amberlyst-36 wet	5.4	72
10	Amberlyst-40 wet	–	61
11	Nafion-H [®]	5.0	46

^[a] All the reactions were carried out with 0.2 mmol of **2** in Et₂O (1 mL, reagent grade Et₂O was used without inert atmosphere technique) using 20% wt of catalyst (about 10 mol % based on the acid sites). Reaction time 24 h.

^[b] Isolated yields of **3** after flash chromatography.

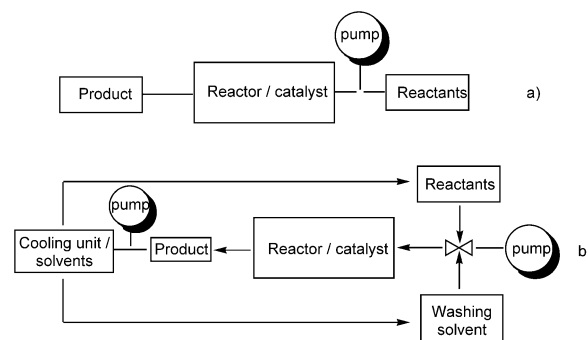
^[c] The reaction was carried out in the presence of 10 mol % of *p*TSA. Polymerisation of **3** occurred.

^[d] 50% wt of catalyst was used (about 25 mol % based on the acid sites).

ate increase of the reaction time was needed for completion.^[8]

It is well known that easily recoverable and reusable solid acid catalysts are valuable candidates for the design of highly performing semicontinuous and continuous processes. In this context, Poliakoff et al. recently reported on the combined use of solid acids and supercritical fluids for selective FC alkylations, hydrogenation reactions and dehydration of alcohols.^[9]

Due to the numerous potential benefits of flow processes namely: environmental concerns, safety and easy

**Figure 1.** Schematic representation of the reactor for a) continuous and b) semicontinuous alkylation of **1** with **2**. The reactor consists in a glass column (15 mm) charged with the desired amount of commercially available Amberlyst-15 dry.

scale-up, the development of practical C–C bond forming reactions in a continuous and semicontinuous manner is still a crucial task.^[10]

The remarkable effectiveness of ion-exchange resins in catalysing this class of Michael additions prompted us to investigate the possibility to optimise a flow reaction protocol involving common laboratory equipment. To this aim a glass column (15 mm diameter) filled with Amberlyst-15 was connected to a flask containing a pre-formed solution of reactants *via* an HPLC pump responsible for controlling the flow rate (Figure 1a). The dependence of the reaction outcome on the feeding rate was first evaluated by studying the addition of **1** (0.1 M) to **2** (0.1 M) in a CH₂Cl₂:EtOH solution (9:1) as the solvent at room temperature with various amounts of Amberlyst-15 dry (1 g, 3.5 g and 7 g).

The data obtained for 2 mmol of reactants are summarised in Figure 2 and from the graphics two main aspects clearly emerged. First, at comparable feeding rates the lower the loading, the higher is the conversion in **3**;

Table 2. Conjugate addition of **1** to electron-poor C–C double bonds promoted by ion-exchange resins.^[a]

Entry	Substrate	Catalyst/solvent	Product	Yield [%] ^[b]
1		Amberlyst-15 dry/CH ₂ Cl ₂	9	95
2		Amberlyst-15 dry/Et ₂ O	10	90
3		Amberlyst-15 dry/Et ₂ O	11	81
4		Amberlyst-39 wet/CH ₂ Cl ₂	12	96
5		Amberlyst-39 wet/CH ₂ Cl ₂	13	81

^[a] All the reactions were carried by using 20% wt of catalyst.

^[b] Isolated yields after flash chromatography.

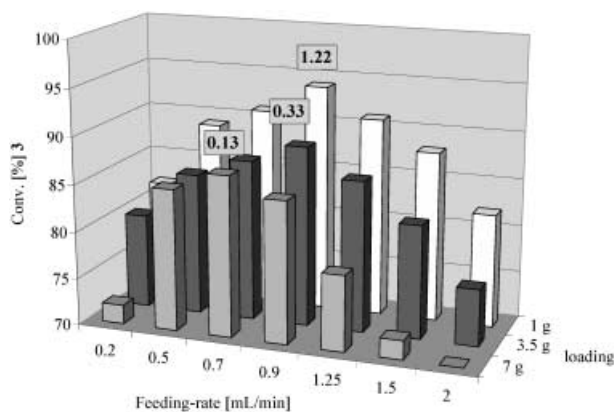


Figure 2. Monitoring the dependence of the conversion of the reaction in **3** on the feeding rate of the reactants as well as the catalyst loading. The WHSV values at the highest conversions for 7 g, 3.5 g and 1 g loading were 0.13 h^{-1} , 0.33 h^{-1} and 1.22 h^{-1} , respectively.

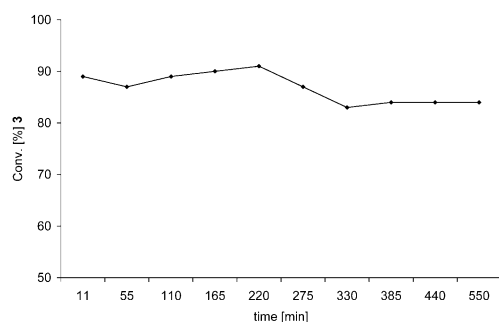


Figure 3. In the probe continuous Michael-type addition of 2-methylindole to **2** the conversion in **3** was found nearly constant (84–91%) over 10 h reaction time.

this finding can be easily rationalised taking into account the competitive polymerisation of the reagents promoted by the acidic sites of the resin. Second, the lower the loading of catalyst employed, the higher is the optimal feeding rate of the process. In particular, 0.90 mL/min, 0.85 mL/min and 0.67 mL/min provided the highest conversions in **3** (94%, 89% and 87%) for 1 g, 3.5 g and 7 g of Amb-15 respectively.

The aforementioned study can be also described in terms of WHSV (weight hourly space velocity).^[11] In this context, the respective WHSV values at the highest conversions were 0.13 h^{-1} (7 g), 0.33 h^{-1} (3.5 g) and 1.22 h^{-1} (1 g).

Then, the synthesis of **3** was conducted at room temperature in the continuous mode (PFR type: plug flow reactor) by maintaining a flow rate of 0.90 mL/min (WHSV 1.22 h^{-1}) of a 1:1 mixture of **1** and **2** (0.1 M) in $\text{CH}_2\text{Cl}_2:\text{EtOH}$ through the reactor (Amberlyst-15, 1 g, reaction time 10 h). Periodical checks by ^1H NMR showed nearly constant conversions in **3** (84–91%) along the en-

tire reaction course without appreciable loss in catalytic activity (Figure 3).

The high impact of organic solvents in environmental and economical assessments of organic transformations is widely recognised/estimated^[12] and the recycle of the reaction media could contribute to develop environmentally more benign processes. The present catalytic system can address this issue, in fact, by modifying the apparatus employed for the continuous reaction with a cold trap connected to the collecting product flask (Figure 1b), 5 cycles of semicontinuous addition of 2-methylindole to 2-cyclohexen-1-one (0.1 M, 0.90 mL/min flow rate) were carried out with high conversions (90–94%), always recovering and recycling the reaction solvent ($\text{CH}_2\text{Cl}_2:\text{EtOH}$, 9:1) as well as the washing solvent ($\text{CH}_2\text{Cl}_2:\text{EtOH}$, 9:1).

In conclusion, a novel procedure for ion-exchange resin catalysed Michael-type addition of indoles to electron-deficient C=C double bonds is described. Examples of practical continuous and highly atom economic semicontinuous versions are presented by using common laboratory equipments and mild experimental conditions. These preliminary results, in principle, afford an attractive alternative to scale-up batch Michael-type alkylation of indoles and studies addressed towards the extension of this protocol to other C–C bond forming flow reactions are actually under investigation.

Experimental Section

Typical FC-Type Michael Addition

A sample vial containing 1 mL of reagent grade Et_2O was charged with 0.2 mmol of α,β -unsaturated compound, 0.3 mmol of indole and 4 mg of Amberlyst-15 (20% wt, corresponding to $\approx 10 \text{ mol } \%$ acid sites content). The mixture was stirred for 24 h with a basic orbital mixer then the catalyst was recovered by filtration. Evaporation of the solvent and subsequent purification by flash chromatography furnished the desired indolyl compound.

The β -indolyl compounds **3**,^[5b] **9**,^[5b] **12**^[5a] and **13**^[5a] have been previously characterised.

1-[4-(*i*-Propyl)phenyl]-3-(1*H*-2-methylindol-3-yl)-butan-1-one (**10**)

Brown viscous oil. Yield: 90%; $R_f = 0.35$ (*c*-Hex/ Et_2O , 85:15); ^1H NMR (CDCl_3 , TMS, 200 MHz): $\delta = 1.25$ (3H, d, $J = 7.0 \text{ Hz}$), 1.50 (3H, d, $J = 7.0 \text{ Hz}$), 1.55 (3H, d, $J = 7.0 \text{ Hz}$), 2.42 (3H, s), 2.87–3.01 (1H, m), 3.39 (2H, dd, $J = 7.4, 16.2 \text{ Hz}$), 3.72–3.82 (1H, m), 7.07–7.14 (3H, m), 7.23–7.27 (2H, m), 7.68–7.72 (2H, m), 7.82–7.86 (2H, m); ^{13}C NMR (CDCl_3 , TMS, 50 MHz): $\delta = 12.1, 21.0, 23.7, 27.4, 34.2, 45.6, 110.4, 115.6, 118.9, 119.0, 120.6, 126.4, 127.1, 128.2, 130.2, 135.2, 135.4, 154.1, 199.5$; GC-MS: $m/z = 51$ (1), 77 (4), 91 (6), 115 (5), 130 (5), 143 (11), 147 (11), 158 (100), 319 (13); IR (nujol): $\nu = 738$ (m), 824 (w), 1056 (w), 1182 (w), 1209 (w), 1282 (w),

1368 (w), 1600 (w), 1680 (m), 3039 (w), 3357 (m) cm^{-1} ; anal. calcd. for $\text{C}_{22}\text{H}_{25}\text{NO}$: C 82.72, H 7.89, N 4.38; found: C 82.74, H 7.83, N 4.38.

1-(4-Chlorophenyl)-3-(1*H*-2-methylindol-3-yl)-butan-1-one (11)

Brown viscous oil. Yield: 81%; R_f = 0.35 (*c*-Hex/Et₂O, 85:15); ¹H NMR (CDCl_3 , TMS, 200 MHz): δ = 1.51 (3H, d, J = 7.0 Hz), 2.38 (3H, s), 3.30 (1H, dd, J = 7.4, 16.0 Hz), 3.54 (1H, dd, J = 6.6, 16.2 Hz), 3.73 (1H, pq, J = 7.0 Hz), 7.06–7.14 (2H, m), 7.23–7.28 (2H, m), 7.33 (2H, dd, J = 1.8, 8.4 Hz), 7.65–7.69 (1H, m), 7.79 (2H, dd, J = 1.8, 8.4 Hz); ¹³C NMR (CDCl_3 , TMS, 75 MHz): δ = 11.9, 21.0, 27.4, 45.5, 110.5, 115.1, 118.9, 118.9, 120.6, 127.0, 128.6, 129.4, 130.4, 135.5, 139.1, 160.2, 198.9; GC-MS: m/z = 51 (3), 75 (6), 91 (5), 111 (10), 130 (13), 139 (16), 158 (100), 191 (10), 207 (71), 253 (5), 281 (9), 311 (10); IR (nujol): ν = 742 (m), 825 (m), 1012 (m), 1091 (s), 1283 (m), 1399 (m), 1437 (m), 1457 (s), 1588 (s), 1696 (s), 2853 (m), 2963 (m), 3055 (w), 3398 (br) cm^{-1} ; anal. calcd. for $\text{C}_{19}\text{H}_{18}\text{ClNO}$: C 73.19, H 5.82, N 4.49; found: C 73.16, H 5.78, N, 4.48.

Typical Experimental Semicontinuous Procedure

A preformed 0.1 M solution of **1** (2 mmol) and **2** (2 mmol) was continuously introduced in a glass column (15 mm diameter) charged with 1 g of commercially available Amberlyst-15 dry. When all the reactants solution was passed through the reactor (0.9 mL/min), the reaction mixture was collected in a separate flask and the solvent was recovered by evaporation and recycled in the reactant-containing unit. Then, to guarantee a complete recovering of the products, the reactor was washed with 20 mL of CH_2Cl_2 :EtOH (9:1) followed by recycling the washing solvent as well. ¹H NMR analysis of the crude residues afforded the conversions in **3**: I cycle: 94%, II cycle: 90%, III cycle: 89%, IV cycle: 90%, V cycle: 93%.

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