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A Revision of the Biginelli Reaction Under Solid Acid Catalysis. Solvent-free Synthesis of Dihydropyrimidines Over Montmorillonite KSF

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Abstract: The reaction of aldehydes, β-dicarbonyl compounds and urea (Biginelli reaction) has been performed over solid acid catalysis, under solventless conditions or in water affording dihydropyrimidines in good yield and selectivity.

Recently Wender defined the "*ideal synthesis*" as one in which the target compound is produced in one step, in quantitative yield from readily available and inexpensive starting materials in a resource-effective and environmentally acceptable process.[1] The one-pot multicomponent condensations (MCCs) represent a possible instrument to perform a near ideal synthesis because they possess one of the aforementioned qualities, namely the possibility of building-up complex molecules with maximum simplicity and brevity.[2]

In these reactions more than two reagents are assembled in a one-pot process giving a product which contains the essential parts of all of the starting materials. Moreover, the possibility of performing multicomponent reactions under solventless conditions with heterogeneous catalysts could enhance their efficiency from an economic as well as an ecological point of view.

Since the revision of fundamental synthetic reactions under heterogeneous catalysis represents the subject of continuous investigation in our research group,[3] we have recently examined the Biginelli reaction with clay catalysis.

The Biginelli reaction, first described more than a century ago and recently reviewed,[4] consists of the one-pot condensation of β-dicarbonyl compounds with aldehydes and ureas or thioureas which affords dihydropyrimidine derivatives which exhibit important pharmacological properties (i.e. calcium channel blockers, anti-hypertensive agents, alpha$_1$-a-antagonists).[5]

The reaction is commonly performed in ethanol or THF under strong protic acid catalysis.[4b] Combinations of Lewis acids with transition metal salts were also utilised and a polyphosphate ester was recently claimed to greatly improve the yield of the process.[6]

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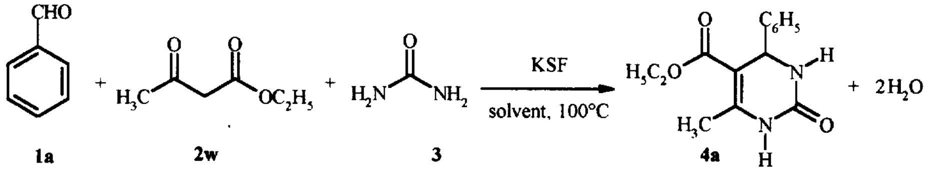
In the presence of the acidic clay montmorillonite KSF[7] (0.5 g) the model reaction of benzaldehyde **1a** (1.1 g, 10 mmol), ethyl acetoacetate **2w** (1.3 g, 10 mmol) and urea **3** (0.9 g, 15 mmol) with or without water or toluene (5 ml) as solvent, at 100°C was analysed after 10 and 48 hours.

Table 1. Reaction of benzaldehyde **1a**, ethyl acetoacetate **2w** and urea **3** under different reaction conditions.



Entry	Solvent	t (h)	**4a** Yield (%)	**4a** Selectivity* (%)
a	Water	10	38	88
b	Water	48	78	96
c	Toluene	10	35	90
d	Toluene	48	72	98
e	None	10	36	89
f	None	48	77	98

* Selectivity = (**4a** yield/**1a** conversion)x100

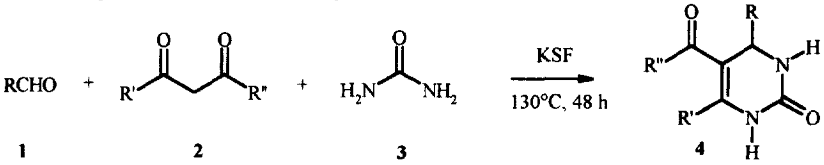
Results reported in Table 1 are quite surprising since similar yields were observed by carrying out the reaction in two solvents such as toluene and water with highly different properties, *e.g.* dielectric constants. Particularly impressive is the good yield observed in water despite the reaction requiring the elimination of two water molecules.

These results allow the conclusion that the interaction of the polar surface of the catalyst with the polar reagents and their subsequent activation is independent of the dielectric constant of the diluent.[8]

Concerning the reaction in water, we initially suspected that the activation of reagents could be promoted by the protic acidity developed from the clay. On the other hand by carrying out the same reaction for 48 hours in the acidic water (5 ml) obtained after filtration of a stirred suspension of KSF (0.5 g) [pH = 2.1], compound **4a** was obtained in only 38% yield confirming the important role of the catalyst surface in the activation of the reagents.

The best result was achieved by carrying out the reaction without any solvent at 130°C for 48 hours, compound **4a** being obtained in 82% yield (98% selectivity). Table 2 shows results of the dihydropyrimidine synthesis *via* the solventless Biginelli reaction between aromatic and aliphatic aldehydes, β-dicarbonyl compounds and urea over montmorillonite KSF catalysis.

Table 2. KSF-promoted synthesis of different dihydropyrimidines **4** under solventless conditions.



Entry	R	R'	R''	Product	Yield (%)	Selectivity* (%)
a	C_6H_5	CH_3	OC_2H_5	**4a**	82	98
b	4-ClC_6H_4	CH_3	OC_2H_5	**4b**	76	96
c	4-$OCH_3C_6H_4$	CH_3	OC_2H_5	**4c**	79	94
d	4-OHC_6H_4	CH_3	OC_2H_5	**4d**	88	98
e	$C_6H_5CH=CH$	CH_3	OC_2H_5	**4e**	70	96
f	C_6H_5	C_6H_5	OC_2H_5	**4g**	75	98
g	C_6H_5	CH_3	CH_3	**4h**	74	97
h	C_6H_5	CH_3	C_6H_5	**4i**	74	98
i	C_4H_9	CH_3	OC_2H_5	**4f**	86	95

* Selectivity = (4 yield/1 conversion)x100

Products **4**[9] were obtained in good yield and excellent selectivity through a quite simple procedure.[10] The catalyst could be recovered by filtration and reused two times in the model reaction giving product **4a** in 80% and 81% yield after washing with hot methanol and heating at 120°C for 5 hours.

In conclusion the Biginelli reaction was efficiently performed with clay catalysis under solventless conditions or in water. In addition the possibility of building up complex molecules from simple starting reagents in a mixture of clay and water could be in agreement with the fascinating theory that clays could have served as templates for elaboration of the first biomolecules in prebiotic times.[11]

Acknowledgements

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7. KSF is a commercial (Fluka) montmorillonite with surface area 15±10 m^2/g, acidity 0.85 meq. H^+/g [determined in our laboratory by temperature programmed desorption of ammonia gas (NH_3-TPD)] and with the following chemical composition (average value): SiO_2 (54.0%), Al_2O_3 (17.0%), Fe_2O_3 (5.2%), CaO (1.5%), MgO (2.5%), Na_2O (0.4%), K_2O (1.5%).

8. Vastly increased rates of the xonotlite-promoted Knoevenagel reaction in hydrocarbon and in water solution have been previously observed: Laszlo, P. *Acc. Chem. Res.*, **1986**, *19*, 121.

9. All products **4a-h** were characterised (IR, ^1H NMR and MS) and their mps compared with literature reported mps. Product **4i**: white solid, mp 161-162°C; ^1H NMR (300 MHz, DMSO-d_6): δ 0.85 (3H, t, $\underline{CH_3}CH_2CH_2CH_2$, J = 6.4 Hz), 1.18 (3H, t, $\underline{CH_3}CH_2O$, J = 7.1 Hz), 1.1-1.3 (4H, m, $CH_3\underline{CH_2CH_2}CH_2$), 1.3-1.5 (2H, m, $CH_3CH_2CH_2\underline{CH_2}$), 2.16 (3H, s, CH_3), 4.05 (2H, q, $CH_3\underline{CH_2}O$, J = 7.1 Hz), 4.0-4.2 (1H, m, CH), 7.28 (1H, s, NH[3]), 8.89 (1H, s, NH[1]); IR (KBr) 3244 (NH), 3117 (NH), 1727 (C=O), 1707 (C=O), 1653 (C=C) cm^{-1}; MS *m/z* (M^++1) 241 (20%), 183 (100%); anal. calcd for $C_{12}H_{20}N_2O_3$: C, 60.0; H, 8.4; N, 11.7; found: C, 60.1; H, 8.5; N, 11.9.

10. Aldehyde **1** (10 mmol), β-dicarbonyl compound **2** (10 mmol), urea **3** (0.9 g, 15 mmol) and montmorillonite KSF (0.5 g) were heated at 130°C under stirring for 48 hours. Hot methanol (100 ml) was added and the mixture was filtered to remove the catalyst. Products **4** crystallized after several hours and were recovered by filtration.

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