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Grinding assisted, column chromatography free decarboxylative carbon-carbon bond formation: Greener synthesis of 3, 3-disubstituted oxindoles

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ABSTRACT

The decarboxylative carbon-carbon bond formation reaction of β-ketoacid derivatives with isatylidene malononitrile derivatives catalyzed by DBU afford adducts in excellent yield. The desired product can be easily isolated using simple filtration method without performing any column chromatography. The decarboxylative adduct was further subjected to reductive-cyclization to obtain biologically important spirooxindoles in 89% yield.

In recent times the use of mechanochemical techniques has gained interest since it addresses the environmental concerns by eliminating the use of solvent in synthetic procedures.[1] The application of this technique to organocatalytic transformation provides new openings for developing environmentally friendly methodologies. The asymmetric organocatalytic reactions performed using mechanochemical methods have advantages over the conventional solution based reactions such as faster reaction rate, low catalyst loading and elimination of toxic organic solvents.[2] Recently, there have been an upsurge in the use of mechanochemical methods for performing organocatalytic reactions such as aldol reaction,[3] Michael reactions,[4] Baylis-Hillman reaction[5] and Mannich reaction[6] but their use for decarboxylative carbon-carbon bond formation reactions have been less explored.[7]

The decarboxylative carbon-carbon bond formation reaction provides an opportunity to mimic Nature which uses this approach for the synthesis of polyketides and fatty acids involving diverse families of polyketide synthase enzymes.[8,9] Polyketide synthase catalyzes the decarboxylative carbon-carbon bond formation reaction using histidine (**His244**), asparagine (**Asn274**), cysteine (**Cys112**) and glycine (**Gly306**) residues in their active site. According to mechanism proposed by Qiu et al.,[10] the decarboxylation addition reaction is initiated with ionization of malonic ester by His244 followed by decarboxylation promoted by the favourable Vander Waal interactions of ester group of malonylCoA with Phe205 (Fig. 1).

This natural process inspired us also to employ this approach for the decarboxylative addition of β-ketoacids (**2a**) to isatylidene malononitriles (**1a**) using organic bases. We, herein, report the development of an efficient, green, solvent free and clean protocol for the decarboxylative addition of β-ketoacids (**2a**) to isatylidene

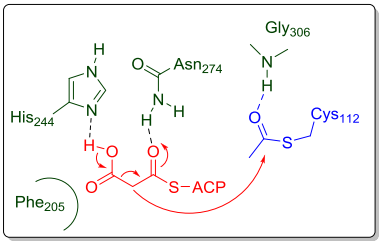

Fig. 1. Proposed reaction mechanism for Claisen condensation using polyketide synthase enzyme.

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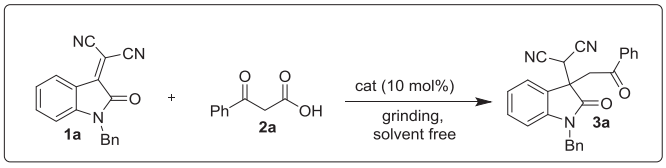
0040-4020/

Table 1
Optimization study.[a]



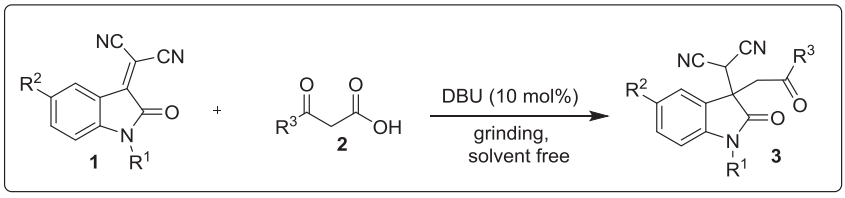
Entry	Catalyst (10 mol %)	Time (min)	Yield (%)
1	DMAP	30	88
2	DABCO	15	93
3	DBU	5	98
4	Triethylamine	15	94
5	Diethylamine	18	87
6	Diisopropylethylamine	15	84
7	Pyridine	15	87
8	Piperidine	15	91
9	Pyrrolidine	25	89
10	–	50	n.r.
[b]11	DBU	10	92

[a] Reaction conditions: 0.1 mmol of isatylidene malononitrile **1a**, 0.12 mmol β-ketoacids **2a** *via* grinding and 10 mol% catalyst.
[b] 5 mol% of DBU was used.

malononitriles (**1a**) for procuring 2-(1-benzyl-2-oxo-3-(2-oxo-2-phenylethyl) indolin-3-yl) malononitrile derivatives catalyzed by DBU. An important feature of this reaction is that the pure product can be easily separated by simple filtration without need of any chromatographic technique. During the preparation of this manuscript, similar reaction catalyzed by molecular sieves, where the purification of products have been performed using column chromatography has been reported.[11] However, the present procedure takes 5–25 min and is column chromatography free.

Initially 0.1 mmol of isatylidene malononitrile (**1a**) and 0.12 mmol of β-ketoacid (**2a**) and 10 mol% of DMAP was ground with in a pestle and mortar for 5 min under aerobic conditions (Table 1, **entry 1**). The reaction mixture converts to a paste. It was allowed to stand for 10 min and then again ground for 5 min. The resulting mixture was allowed to stand for another 10 min until the starting materials gets completely consumed as indicated by TLC. The work up of reaction involves the addition of 2 mL of saturated solution of ammonium chloride resulting in the solid product which was filtered and washed with water and dried under vacuum. The pure product could be isolated in 88% yield. Furthermore, the other organocatalysts were also screened, such as DABCO and DBU, the reaction in the case of DABCO takes longer time and yields product in 93% yield but the reaction with DBU completes in 5 min providing product in 98% yield. (Table 1, **entry 2–3**). When other

Table 2
Substrate Scope for the decarboxylative addition reaction of isatylidene malononitrile with β-ketoacid derivatives.[a]



Entry	2 (R^3)	1 (R^1, R^2)	3	Time (min)	Yield[b] (%)
1	**2a** (R^3=Ph)	**1a** (R^1=Bn, R^2=H)	**3a**	5	98
2	**2a** (R^3=Ph)	**1b** (R^1=Bn, R^2=F)	**3b**	5	95
3	**2a** (R^3=Ph)	**1c** (R^1=Bn, R^2=Cl)	**3c**	10	94
4	**2a** (R^3=Ph)	**1d** (R^1=Bn, R^2=Br)	**3d**	10	93
5	**2a** (R^3=Ph)	**1e** (R^1=Bn, R^2=I)	**3e**	8	90
6	**2a** (R^3=Ph)	**1f**(R^1=Bn, R^2=Me)	**3f**	8	91
7	**2a** (R^3=Ph)	**1g** (R^1=Bn, R^2=OMe)	**3g**	10	92
8	**2a** (R^3=Ph)	**1h** (R^1=allyl, R^2=H)	**3h**	10	89
9	**2a** (R^3=Ph)	**1i** (R^1=allyl, R^2=F)	**3i**	5	94
10	**2a** (R^3=Ph)	**1j** (R^1=allyl, R^2=Cl)	**3j**	10	92
11	**2a** (R^3=Ph)	**1k** (R^1=allyl, R^2=Br)	**3k**	15	91
12	**2a** (R^3=Ph)	**1l**(R^1=allyl, R^2=I)	**3l**	12	90
13	**2a** (R^3=Ph)	**1m** (R^1=allyl, R^2=Me)	**3m**	8	90
14	**2a** (R^3=Ph)	**1n** (R^1=allyl, R^2=OMe)	**3n**	10	91
15	**2a** (R^3=Ph)	**1o** (R^1=Me, R^2=H)	**3o**	15	92
16	**2a** (R^3=Ph)	**1p** (R^1=Me, R^2=Cl)	**3p**	5	94
17	**2a** (R^3=Ph)	**1q** (R^1=Me, R^2=Br)	**3q**	5	90
18	**2a** (R^3=Ph)	**1r** (R^1=naphthyl, R^2=H)	**3r**	12	90
19	**2b** (R^3=Me)	**1a**(R^1=Bn, R^2=H)	**3s**	25	89
20	**2b** (R^3=Me)	**1h**(R^1=allyl, R^2=H)	**3t**	20	91
21	**2b** (R^3=Me)	**1o**(R^1=methyl, R^2=H)	**3u**	20	89
22	**2c** (R^3=Et)	**1a** (R^1=Bn, R^2=H)	**3v**	12	92
23	**2d** (R^3=4-FPh)	**1a** (R^1=Bn, R^2=H)	**3w**	15	93
24	**2e**(R^3=4-ClPh)	**1a** (R^1=Bn, R^2=H)	**3x**	15	95
25	**2f** (R^3=4-BrPh)	**1a** (R^1=Bn, R^2=H)	**3y**	15	93
26	**2g** (R^3=4-OMePh)	**1a** (R^1=Bn, R^2=H)	**3z**	10	95
27	**2h** (R^3=4-MePh)	**1a** (R^1=Bn, R^2=H)	**3za**	8	96
28	**2i** (R^3=naphthyl)	**1a** (R^1=Bn, R^2=H)	**3zb**	10	89
29	**2j** (R^3=2-thiophene)	**1a** (R^1=Bn, R^2=H)	**3zc**	6	94
30	**2k** (R^3=Ph)	**1s** (R^1=H, R^2=H)	**3zd**	10	92

[a] Reaction conditions: 0.1 mmol of isatylidene malononitrile **1**, 0.12 mmol β-ketoacid derivatives *via* grinding.
[b] Yield of isolated product.