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Vinylogous Annulation Cascade Toward Stereoselective Synthesis of Highly Functionalized Indanone Derivatives

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Abstract: A base promoted vinylogous annulation cascade of alkylidene malononitriles with cyclopentene-1,3-diones with a subsequent reduction sequence has been devised to furnish densely functionalized 3-hydroxyindanone scaffolds in high yields with excellent diastereoselectivity. Unlike preceding approaches that account for the formation of the pentanoid ring, this strategy features construction of the aromatic ring. The protocol is scalable, displays very broad substrates scope including late-stage functionalization of bioactive estrone, applicable to activated coumarin system, and is suitable to access an indenoquinoline derivative.

Keywords: Vinylogous annulation; Cascade reaction; Diastereoselectivity; 3-Hydroxy indanones; Late-stage functionalization

Indanones and derivatives thereof, particularly 3-hydroxy indanones, represent a class of valuable benzofused carbocyclic compounds that are ubiquitous in various natural products and biologically active molecules including clinical drug candidates (Figure 1).[1] They also serve as important building blocks to construct different heterocyclic frameworks with increased molecular complexity.[2] Consequently, synthetic endeavors toward these high-value scaffolds remain in the limelight of contemporary organic synthesis. Strategically, 3-hydroxy indanones can be accessed either through the formation of the pentanoid ring or *via* construction of the aromatic ring (Scheme 1). However, majorities of the existing synthetic protocols are grounded on strategic construction of pentanoid ring.[3] On the contrary, fabrication of aromatic ring *en route* to production of 3-hydroxy indanone derivatives is increasingly challenging and currently, such practical synthetic routes are scarce.[4] Typically metal catalyzed cyclotrimerization[4a] and dehydro Diels-Alder reactions[4b] of well-organized substrates at elevated temperature were considered for this purpose.

The principle of vinylogy, as defined by Fuson, features the transmission of electronic effects of a specific functional group through a conjugated π-system.[5] This concept allows functionalization at a distant position from the parent functional group and became a putative strategic manoeuver in the synthetic chemist's repertoire.[6] We envisioned that exploitation of vinylogous nucleophilic reactivity of alkylidene malononitriles (**1**) and subsequent annulation cascade with cyclopentene-1,3-diones (**2**) would be a convenient route to access 3-hydroxy indanone frameworks (Scheme 1).[7] The enolate **A** thus formed from alkylidene malononitrile **1** in the presence of a suitable base will undergo regioselective vinylogous Michael addition followed by cyclization to give intermediate **B**. It will then isomerize to intermediate **C**, which upon oxidation would produce the annulated stable aromatic product **3**. A successful chemoselective reduction on **3** could furnish densely substituted 3-hydroxy indanone.

We commenced our investigations following the model reaction of acyclic alkylidene malononitrile **1a**

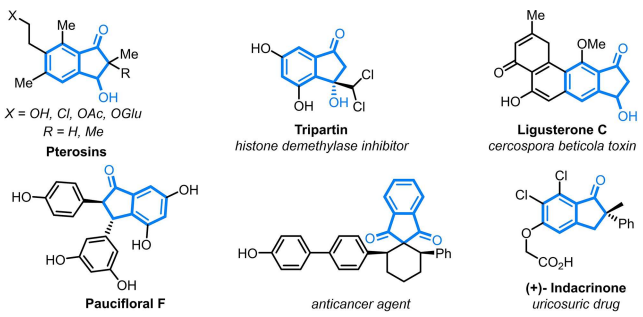
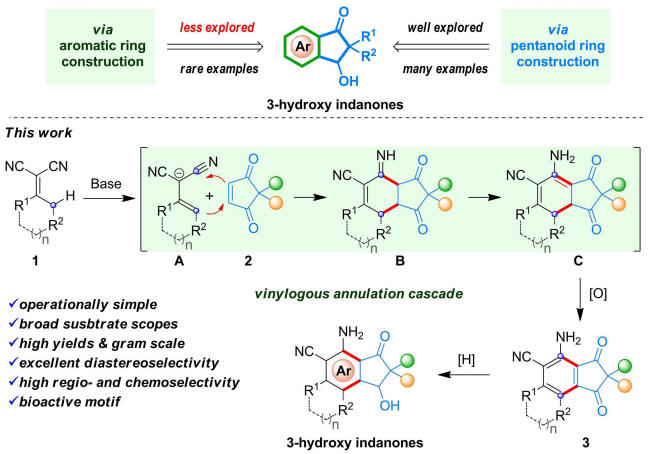
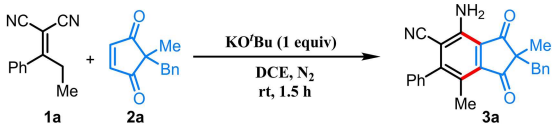


Figure 1. Bioactive indanone derivatives.

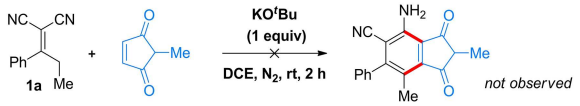


Scheme 1. Synthetic planning towards 3-hydroxy indanones.

Table 1. Optimization of reaction conditions.[a]

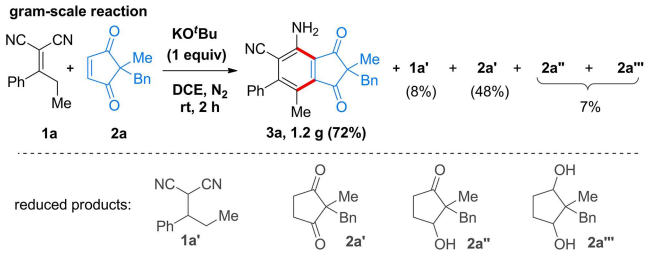


entry	deviation from standard condition	yield (%)[b]
1	**none**	**82**
2	Toluene/mesitylene/PhCl/THF/ CH_3CN instead of DCE	74/70/55/ 0[c]/0[c]
3	LiOtBu/NaH/NaOMe/Cs_2CO_3 instead of KO^{t}Bu	12/25/18/0[d]
4	DBU/^{i}Pr$_2$NEt/Et$_3$N/DABCO instead of KO^{t}Bu	10/16/15/0[d]
5	0.2/0.5/1.5 equiv. of KO^{t}Bu	19/48/53
6	without KO^{t}Bu	0



[a] Reaction conditions: **1a** (0.22 mmol), **2a** (0.36 mmol), N_2, solvent (4 mL), rt, 1.5 h.
[b] Isolated yields.
[c] Decomposition of **1a** was observed.
[d] Unreacted **1a** and **2a** were recovered.

with 2,2-disubstituted cyclopentene-1,3-dione **2a** (Table 1). Gratifyingly, when mixture of **1a** and **2a** was exposed to KO^{t}Bu in anhydrous dichloroethane (DCE) at room temperature, the vinylogous annulation cascade proceeded rapidly with concomitant oxidation and the desired annulated product **3a** was isolated in 82% yield (entry 1). Reaction was also effective in other aromatic nonpolar solvents such as toluene (74%), mesitylene (70%), and chlorobenzene (55%); however, a complex mixture of unidentified products was formed in acetonitrile and THF (entry 2). Screening of other bases, for example LiO^{t}Bu, NaH, NaOMe



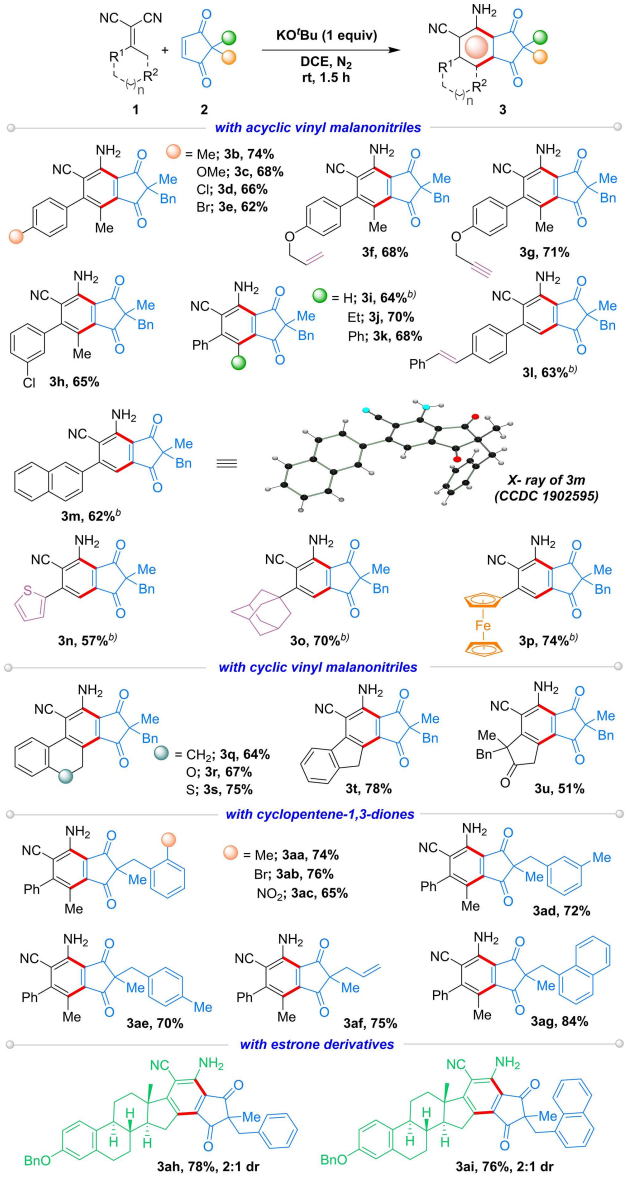
Scheme 2. Gram scale reaction.

and Cs_2CO_3, gave inferior results (entry 3). Organic bases such as DBU, Hünig's base (^{i}Pr$_2$NEt), Et$_3$N, and DABCO were also ineffective for this reaction (entry 4). The reaction was very sensitive to the loading of base; yield decreased drastically with the lowering and increasing amount of KO^{t}Bu and completely shut down in the absence of it (entries 5,6). Though the exact reason of why K^{t}OBu is so special in this annulation cascade is not apparent now, one must note that the choice of base is very critical as starting materials, intermediates, and product possess base sensitive reactive sites which could potentially lead to cumbersome outcomes. It is important to mention that the disubstitution in **2a** is essential for this annulation reaction as monosubstituted 2-methyl cyclopentene-1,3-dione failed to deliver the desired product with the recovery of both the starting materials (Table 1, below).

Scale-up was also suitable and the product **3a** was prepared in 1.2 g scale (72% yield, Scheme 2). At this juncture, we have also detected the formation of reduced products **1a**′, **2a**′, **2a**″, and **2a**‴ that favors a hydride-transfer mechanism[8] for the aromatization step to produce annulated product **3a** (also see, Scheme 6).

Having acquired the optimal conditions, we next examined the scope of the reaction (Table 2). This vinylogous annulation reaction was very general for a broad range of alkylidene malononitriles. Acyclic alkylidene malononitriles derived from substituted propiophenones having donating (**3b–c**, **3f–g**) and withdrawing (**3d–e**, **3h**) substituents in the aromatic ring uniformly delivered the desired products in very high yields. Sensitive functionalities such as allyl (**3f**), propargyl (**3g**), and styryl (**3l**) were undisturbed. Alkylidene malononitriles derived from acetophenone (**3i**), butyrophenone (**3j**), deoxybenzoin (**3k**), and 2-acetonaphthone (**3m**) also effectively participated in this reaction to furnish corresponding products in high yields. Product **3m** was also crystallized and X-ray analysis unambiguously established the structure of the annulated product.[9] Heteroaryl-substituted and bulky adamantyl-substituted alkylidene malononitriles were good substrates for this reaction, giving products **3n** and **3o** in 57% and 70% yields, respectively. Impor-

Table 2. Scope of the vinylogous annulation cascade.[a]

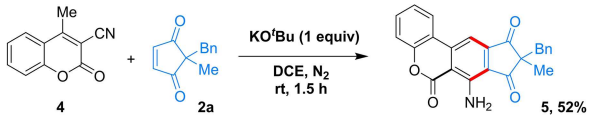


[a] Reaction conditions: **1a** (0.22 mmol), **2a** (0.36 mmol), KO^{t}Bu (1 equiv.), N_2, DCE (4 mL), rt, 1.5 h. Yields of isolated products were given.
[b] Reaction time was 1 h.

tantly, ferrocenyl functionalized product **3p** was also prepared in 74% yield. Reaction efficacy of cyclic alkylidene malononitriles was also investigated. Six-membered and five-membered alkylidene malononitriles prepared from α-tetralone (**3q**), 4-chromanone (**3r**), 4-thiochromanone (**3s**), 1-indanone (**3t**) and substituted 1,3-cyclopentanedione (**3u**) readily rendered expected products in good to high yields (51–78%).

Next, we explored the reaction scope with respect to 2,2-disubstituted cyclopentene-1,3-diones (Table 2). Pleasingly, annulation reactions with substrates bearing combination of a methyl and electronically distinct benzyl and allyl substituents at the quaternary center proceeded smoothly under the optimized conditions, rendering products **3aa**–**3ag** in very high yields (65–84%). Bioactive estrone derived alkylidene malononitrile also underwent facile annulation to offer **3ah** and **3ai** in 78% and 76% yields, respectively. Here, a diastereomeric ratio of 2:1 was observed for both cases. This late-stage functionalization of pharmaceutically important natural product is noteworthy.

Also, the reaction of 3-cyano-4-methylcoumarin **4** with cyclopentene-1,3-dione **2a** under the standard conditions was fruitful to forge annulated product **5** in 52% yield, demonstrating further scope of this vinylogous annulation cascade (Scheme 3).

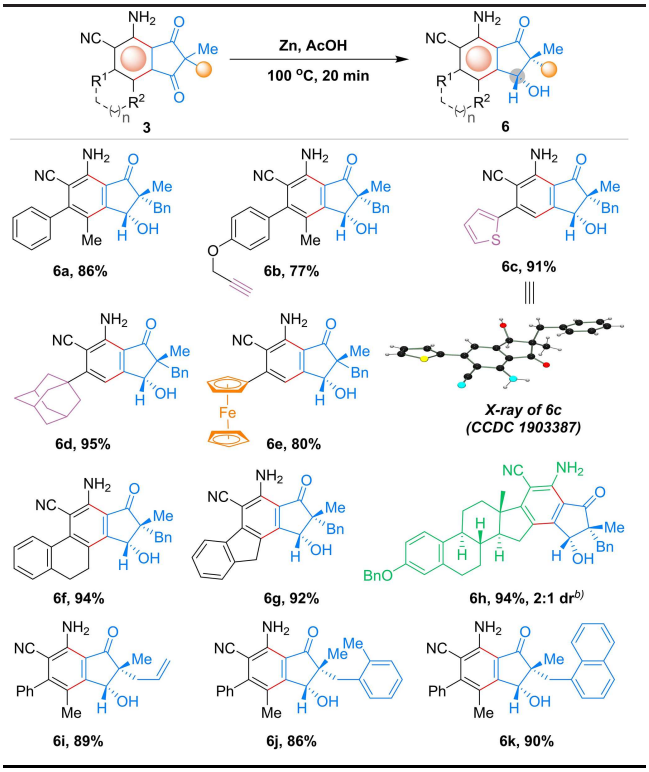


Scheme 3. Vinylogous annulation with coumarin derivative.

Following our synthetic planning, we then set out for the chemo- and regioselective reduction of annulated product **3** to access 3-hydroxy indanone Scaffold. To our delight, treatment the annulated product **3a** with Zn powder in AcOH at 100 °C for a short period of time (20 min) effected selective reduction of one keto-functionality to offer densely functionalized 3-hydroxy indanone **6a** as a single diastereomer in 86% isolated yield (Table 3).[10] This reduction conditions turned out quite general for a series of annulated product **3** bearing diverse substitutions and typically single diastereomer was obtained for the substrates examined (Table 3). Substrates having propargyl (**6b**), heterocyclic thienyl (**6c**), adamantyl (**6d**) and ferrocenyl (**6e**) groups gave desired product in very high yields. The single-crystal X-ray diffraction analysis of product **6c** confirmed its structure and relative configuration.[9] Fused polycyclic annulated products along with pharmaceutically relevant estrone derivative underwent smooth reduction to give desired products **6f–h** in excellent yields (>90%). Alteration of substitutions at the quaternary center did not hamper the reduction process and selectivity; single diastereomeric products with allyl (**6i**), 2-methylbenzyl (**6j**), and of 1-naphthalenemethyl (**6k**) groups were obtained in very high yields (86–90%). We believe the steric factor embedded in the substrates is responsible for the high diastereoselectivity observed in these cases.

The synthetic utility was further highlighted through the preparation of tetracyclic indenoquinoline[11] derivative. Accordingly, annulated product **3ac** having well-placed nitro-group was

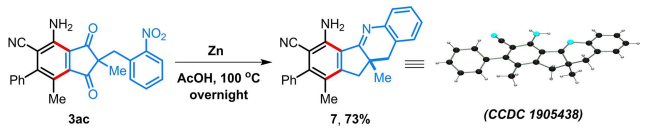
Table 3. Synthesis of 3-hydroxy indanones *via* stereoselective reduction.[a]



[a] Reaction conditions: **3** (0.2 mmol), Zn (16 equiv.), AcOH (2 mL), 100 °C, 20 min. Yields of isolated products were given.

[b] Reaction was performed with annulated product **3 ah** having 2:1 dr.

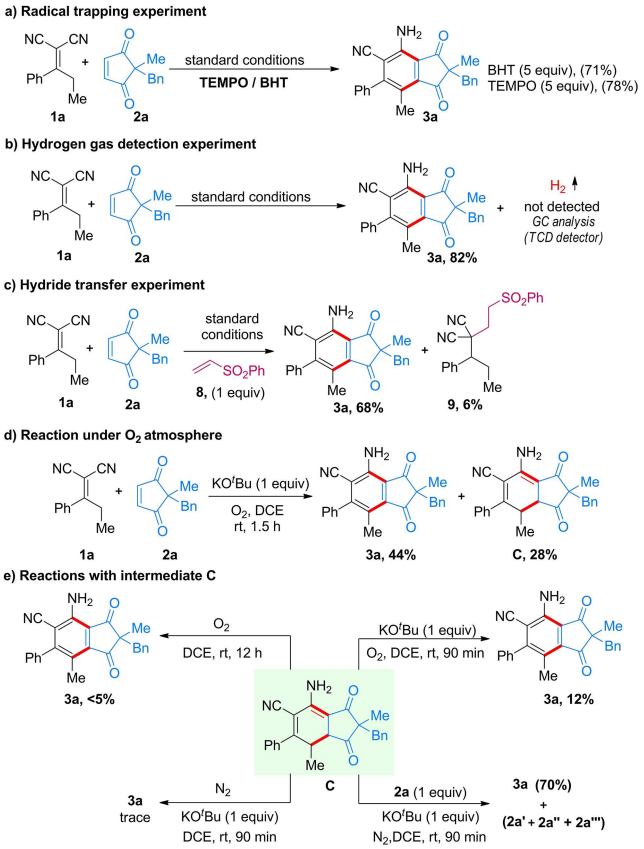
exposed to Zn/AcOH reduction conditions; complete reduction of both keto and nitro groups followed by intramolecular cyclization proceeded cleanly, furnishing compound **7** in 73% yield (Scheme 4). It is worth



Scheme 4. Synthesis of indenoquinoline derivative.

noting that, unlike other cases (Table 3), this cyclization cascade involved a reductive deoxygenation of aromatic ketone, which was confirmed through X-ray analysis.[9]

To gain insights of the reaction mechanism, various control experiments were conducted. Significant amount of product **3 a** was formed in the presence of radical scavengers like butylated hydroxyltoluene (BHT) or 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), refuting the involvement of a radical species in this process (Scheme 5a). The gas chromatography



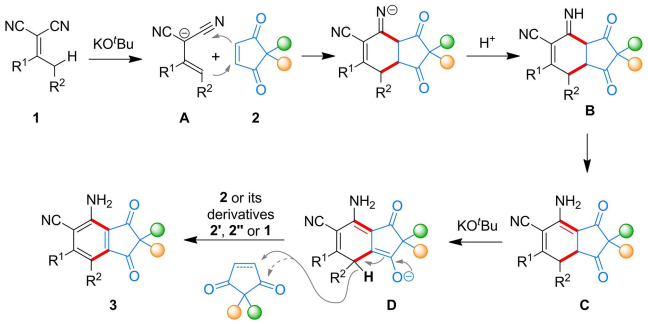
Scheme 5. Control experiments.

analysis of the benchmark reaction also disproved the liberation of hydrogen gas during the course of the reaction (Scheme 5b). Standard reaction of **1 a** and **2 a** in the presence of Michael acceptor vinyl sulfone **8** (1 equiv.) gave **9** in 6% yield (Scheme 5c). All these findings are in line with the propose hydride transfer mechanism.

Notably, reaction of **1 a** with **2 a** was sluggish under oxygen atmosphere, and the intermediate **C** was isolated in 28% yield along with product **3 a** (Scheme 5d). When isolated intermediate **C** was exposed to molecular oxygen, formation of product **3 a** was not significant even after prolonging the reaction time (Scheme 5e, left). Improvement was also insignificant when the reaction under oxygen atmosphere was performed in the presence of KO^{t}Bu; **3 a** was obtained in only 12% yield and TLC showed the presence of unreacted intermediate **C** (Scheme 5e, right). Further, treatment of intermediate **C** with KO^{t}Bu under nitrogen atmosphere did not produce product **3 a**. However, when the same reaction was executed in the presence of hydride acceptor **2 a**, product **3 a** was isolated in

70% yield (Scheme 5e, below). These findings clearly validate a base promoted hydride transfer mechanism under nitrogen atmosphere for the aromatization step and distinct our methodology from others where O_2 was claimed to be crucial for the aromatization step. Notably, this base promoted hydride transfer under nitrogen atmosphere is also in line with the prior work by Nikolai et al..[8c]

Based on the above control experiments, a plausible reaction mechanism is proposed in the Scheme 6.



Scheme 6. Plausible reaction mechanism.

Deprotonation of alkylidene malononitrile **1** with KO ^{t}Bu produces enolate **A**. It reacts with cyclopentene-1,3-dione **2** and gives **B** after proton transfer from the reaction medium. Intermediate **B** isomerises to more stable intermediate **C**. Further deprotonation generates the enolate **D**, which triggers the hydride transfer to acceptors (**1**, **2** or derivatives of **2**) to deliver the product **3**.

In conclusion, we have developed a succinct synthesis of pharmaceutically important 3-hydroxy indanone derivatives based on KO^{t}Bu promoted vinylogous annulation cascade of alkylidene malononitrile with 2,2-disubstituted cyclopentene-1,3-dione, followed by Zn/AcOH reduction strategy. Here, the annulation step involved in the construction of aromatic ring, which is distinctive to prior synthetic approaches. The protocol is operationally simple, scalable, and features broad substrates scope to offer desired products as a single diastereomer in very high yields. The reaction condition was also operative for vinylogous annulation cascade of 3-cyano-4-methylcoumarine. Notably, this strategy bodes well in diversification of bioactive estrone and rapid synthesis of an indenoquinoline derivative. Mechanistic investigations favor a hydride transfer mechanism for the aromatization step instead of radical mechanism. Further, applications of the vinylogy concept are currently underway in our laboratory.

Experimental Section

General procedure of vinylogous annulation cascade reaction: The alkylidene malononitriles **1** (0.22 mmol, 1 equiv.), cyclopentene-1,3-diones **2** (0.36 mmol, 1.6 equiv.), and anhydrous potassium tert-butoxide (1 equiv.) were taken in a 16× 100 mm oven dried reaction tube equipped with a magnetic stir. The reaction tube was capped with a rubber septum, evacuated and backfilled with nitrogen gas. Then, dry DCE (4 mL) was added via syringe. The mixture was allowed to stir at room temperature for 1–1.5 h. After completion (TLC monitored), the crude reaction mixture was loaded directly onto silica gel column and purified with a gradient eluent of hexane and ethyl acetate to provide pure 1,3-indandiones **3**.

General procedure for the synthesis of 3-hydroxy indanones: The compound **3** (0.1 mmol, 1 equiv.) and zinc (16 equiv.) were taken in a 50 mL round bottom flask equipped with a magnetic stir. Acetic acid (2 mL) was added and the flask was capped with a rubber septum. The mixture was allowed to stir at 100 °C for 20 minutes. Then the crude reaction mixture was quenched carefully with saturated $NaHCO_3$ solution (aq) and was extracted three times with EtOAc (10 mL × 3). The combined organic layers was washed with brine and dried over anhydrous Na_2SO_4. The volatiles were carefully evaporated and the crude reaction mixture was loaded directly onto silica gel column and purified with a gradient eluent of hexane and ethyl acetate to provide pure 3-hydroxy indanones **6**.

Acknowledgements

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