



Thionyl chloride mediated dehydroxylation of 3-hydroxyindanones to indenones



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ABSTRACT

Quantitative transformation of 3-hydroxyindanones to indenones was achieved via SOCl_2 mediated dehydroxylation for the first time. Failure of both acid and base mediated dehydration of 3-hydroxyindanones encouraged us to devise a new protocol involving activation followed by elimination of the hydroxyl group. Thionyl chloride efficiently served the purpose and afforded the desired indenones in excellent yields.

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Introduction

Indenones are an important substructure in natural products, and in their related biologically active counterparts such as ligustrone A¹ and euplectin² (structurally related to the ligustrone molecule exhibiting cytotoxicity against the growth of murine P-815 mastocytoma cells). Indenones are used as alcoholic fermentation activators³ and potential estrogen binding receptors⁴ (Scheme 1).

Among a variety of substituted indenones, the chemistry of 2- and 3-aryindenone derivatives is of immense interest, not only for their interesting photophysical properties⁵ but also as synthetic precursors to more elaborate ring structures.⁶ Moreover, it could be a useful intermediate on routes to furanoindenones.⁷ Indenones can easily be converted to quinoline,^{6a,b} isoquinoline,^{6a,b} phthalazine,^{6c} chromone,^{6d–f} and isobenzofuran^{6g} derivatives via easy synthetic transformations. In our recent Letter, we isolated 3-aryindenone as the intermediate in the synthesis of the C-nor-D-homo steroid ring system.⁸

The straightforward synthesis of indenones involves the α -bromination of 1-indanones followed by dehydrobromination (Scheme 2, Eq. 1).⁹ Other common methods include the AlCl_3 -catalyzed addition of benzoyl chlorides to acetylenes (Scheme 2, Eq. 2) and the intramolecular Friedel–Crafts acylation of β -hydroxy- β -arylpropionyl chlorides and the modification of this approach

(Scheme 2, Eq. 1).¹⁰ A number of 2,3-disubstituted indenones have been prepared by the Pd-catalyzed reaction of *ortho*-bromo or *ortho*-iodobenzaldehyde with various internal acetylenes¹¹ as well as the Rh-catalyzed¹² reaction of aryl chlorides with internal acetylenes (Scheme 2, Eq. 2). Harrowven and co-workers¹³ synthesized a 3-aryindenone derivative (isolated from the fruits of *Viola sebifera*) by acid mediated aldol condensation of substituted *ortho*-arylpropionophenone.

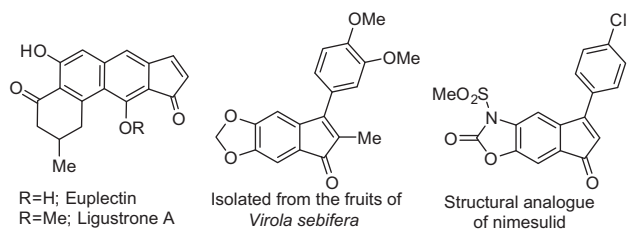
Gree and co-workers¹⁴ reported a two-step method to transform 3-hydroxyindanones to indenones via activation of the hydroxyl function by mesyl group and successive removal of it through β -elimination (Scheme 2, Eq. 3). However, the success of this methodology is highly dependent on the substituents present at C-2 or C-3 of the indane ring and lacks viability due to cumbersome reaction conditions. Although several methods for the preparation of indenones are known, most of them have some drawbacks in terms of substrate limitation, yield, insensitive reaction conditions, and lack of regioselectivity in product formation (Scheme 2).

Results and discussion

The present study was initiated in order to develop a more efficient and practical approach that would allow the regioselective preparation of indenones. After successful synthesis of an extensive range of substituted 3-hydroxyindanones through aldolization of *ortho*-diacylbenzene (Table 1, step-A),^{15,8} we here disclose an intriguing transformation of 3-hydroxyindanones **2** to indenones **3** via removal of the hydroxyl group. To serve this purpose, first

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Scheme 1. Important molecules containing the indenone core.

we examined conventional acid-mediated dehydration. Thus, 1 mmol of 5-bromo-3-hydroxyindanone (**2a**) was refluxed in DCE with 1 mmol of concentrated HCl. After 10 h, only 25% conversion of **2a** to the desired 5-bromoindenone (**3a**) was observed (Table 1, entry 1). In the next attempt, 1.5 mmol of P_2O_5 was used as the dehydrating agent under solvent-free conditions and the reaction mixture was heated at 100 °C. After 4 h of heating, substrate **2a** was recovered as such (Table 1, entry 2). Conventional base catalyzed dehydration protocol was also inefficient in converting **2a** to **3a** (Table 1, entries 3 and 4).

From the above unsuccessful attempts to dehydrate **2** to **3**, it could be assumed that the high energy barrier of this transformation is not permitting the reaction to proceed in the forward direction. Then, we envisioned decreasing the high energy barrier of this transformation by activating the hydroxyl group through $SOCl_2$, which forms a favorable six-membered transition state. To pursuit our goal, we treated 1 mmol of **2a** with 2.5 mmol of thionyl chloride as an alternative to inorganic acids in dichloromethane (DCM), and the reaction mixture was stirred at room temperature. After 72 h, 71% yield of **3a** was obtained (Table 1, entry 5). When the same reaction was performed in dichloroethane (DCE) at 60 °C, to our pleasure, **3a** was obtained in 93% yield within 2 h (Table 1, entry 6). DMSO proved to be inefficient as the reaction

medium as only a trace of **3a** was found (Table 1, entry 9). This may be due to the formation of a complex between $SOCl_2$ and DMSO. When a mixture of **2a** and 4.0 equiv of $SOCl_2$ was heated at 60 °C under solvent-free conditions **3a** was obtained in 82% yields (Table 1, entry 10). However, when 2.5 mmol of $SOCl_2$ in silica gel (200 mg) was used as the heterogeneous catalyst system instead of using $SOCl_2$ alone at 60 °C in a microwave (100 W) for 10 min **3a** was obtained only in 30% yield (Table 1, entry 11). PCl_5 in place of $SOCl_2$ proved to be completely inefficient in converting **2a** to **3a** (Table 1, entry 12).

To increase the applicability of this methodology, the reaction was directly performed by using **1a** as the starting substrate. **1a** was treated with catalyst **A** in DMSO, after full conversion of **1a** to **2a** (monitored by TLC); DMSO and the catalyst **A** was made free by pouring water to the reaction pot, and **2a** was extracted with DCM. After evaporating DCM the crude was dissolved in 5 mL of DCE, 2.5 equiv of $SOCl_2$ was added drop wise and heated at 60 °C for 2 h. Workup of the reaction provided **3a** in 92% yield (Table 1, entry 13). Further modifications of the reaction conditions could not furnish the desired product **3a** (Table 1, entries 14 and 15). Thus, Table 1, entry 13 was assumed to be the optimum reaction conditions, which was further used to generate a library of substituted indenones **3** in high yields (Table 2).

Mechanism of this transformation is illustrated in Scheme 3.¹⁶ If the substrate 3-hydroxyindanones contain α -H, β -elimination pathway is preferred to the conventional S_N1 pathway (that would lead to the formation of 3-chloroindanone derivative). To check the possibility of the formation of 3-chloroindanones we performed

Table 1
Optimization studies for Step-B^a

Entry	Promoter (mmol)	Solvent	Time (h)	Temp (°C)	Yield ^b (%)
1	HCl (1)	DCE	10	Reflux	25
2	P_2O_5 (1.5)	None	6	100	nr
3	NaOH (1.5)	H ₂ O	6	rt	nr ^c
4	NaOH (1.5)	H ₂ O	6	100	nr
5	$SOCl_2$ (2.5)	DCM	72	rt	71
6	$SOCl_2$ (2.5)	DCE	2	60	93
7	$SOCl_2$ (1.5)	DCE	2	60	52
8	$SOCl_2$ (2.5)	DCE	6	rt	20
9	$SOCl_2$ (2.5)	DMSO	6	60	Trace
10	$SOCl_2$ (4.0)	—	4	60	82
11 ^d	$SOCl_2/SiO_2$	—	10 min	60	30
12	PCl_5	DCE	3 h	60	—
13 ^e	$SOCl_2$ (2.5)	DCE	2	60	92
14 ^f	$SOCl_2$ (2.5)	DCE	6	60	—
15 ^g	AcOH (1.5)	DCE	6	60	nr

nr = no reaction.

Bold entry 13 signifies the optimized conditions.

^a 1 mmol of **2a** as the initial substrate in 5 mL solvent was used in each case (for entries 1–9).

^b Isolated yield of **3a**.

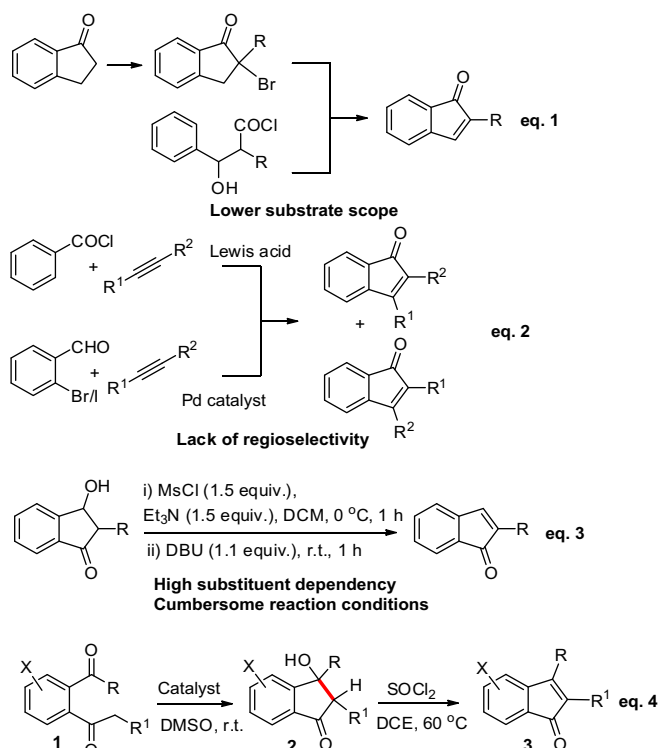
^c Under similar reaction conditions 3-phenyl-3-hydroxyindanone (**2i**) easily transformed to the corresponding indenone **3i** [Ref. 8].

^d The reaction was performed in microwave (100 W).

^e The reaction was performed directly by using **1a** (**1a** was reacted with catalyst **A** in DMSO to get **2a**, DMSO was then removed by pouring water to the reaction mixture and **2a** was extracted with DCM, evaporated, 5 mL of DCE was added to the crude, 2.5 mmol of $SOCl_2$ was added drop wise and heated to 60 °C).

^f $SOCl_2$ (2.5 mmol) was added drop wise to the DCE solution of **1a**, no trace of **3a** was obtained.

^g AcOH (1.5 mmol) was added drop wise to the DCE solution of **1a**.



Scheme 2. Comparison between literature Letters and this work.

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