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A convenient and mild one pot synthesis of cyclopentenone derivatives

Manjunath Moger, Ashok Kumar Pradhan, Rama Mohan Hindupur, Hari N. Pati *

Advinus Therapeutics Ltd, 21 & 22, Phase II, Peenya Industrial Area, Bangalore 560058, Karnataka, India

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Dedicated with profound love and gratitude to Prof. Bijay K. Mishra, Sambalpur University, on his 60th birthday

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Bronsted acid
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ABSTRACT

Developed a convenient and mild one pot synthesis of cyclopentenone derivatives using 1-acetyl-1-cyclohexene and wide range of aldehydes. Aromatic and heterocyclic aldehydes with electron donating and withdrawing groups were conveniently converted to the corresponding cyclopentenone derivatives.

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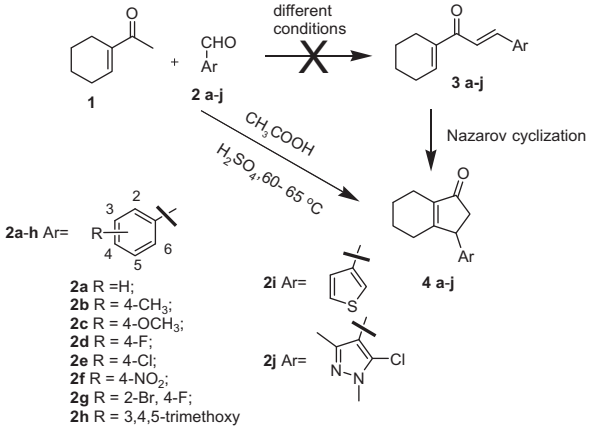
Cyclopentenones are five-membered carbocycles constituting α,β-unsaturated ketone system presenting a core part of various natural products[1] and synthetic intermediates. Reactions of these cyclopentenones result in the total synthesis of various natural products.[2] Among the few methods available,[3–5] Nazarov cyclization[6] of divinyl ketones is widely used to access cyclopentenones and its derivatives. For example, the cyclopentenone skeleton was assembled in the synthesis of complex molecules such as polyquinone, prostanoids,[7] and methylenomycin B, a natural cyclopentanoid antibiotic,[8] through Nazarov cyclization. Nazarov cyclization is the key step in the synthesis of complex molecules such as ligands of the $5HT_{1D}$ serotonin receptors.[9] In general, these reactions are catalyzed by Lewis acids[10] or Bronsted acids,[11,12] which facilitate the formation of pentadienyl cation of divinyl ketones leading to electrolytic cyclization forming cyclopentenone ring. But the synthesis of structurally diverse cyclopentenone derivatives by Nazarov cyclization strategy involves two stages: first, the synthesis of divinyl ketones and second, acid catalyzed conversion of divinyl ketones to cyclopentenone ring system. Instead, herein we report a simple and convenient one pot synthesis of cyclopentenone derivatives starting from 1-acetyl-1-cyclohexene and various aldehydes.

In continuation of our research in developing new synthetic methodologies, we were initially interested in the synthesis of divinyl ketones starting from 1-acetyl-1-cyclohexene (**1**) and various aromatic aldehydes (**2a–j**, Scheme 1). Several attempts were made for the synthesis of divinyl ketones using compound **1** and



Scheme 1. Synthesis of cyclopentenone derivatives **4a–j**.

* Corresponding author. Tel.: +91 99002 12096; fax: +91 80 2839 4015.
E-mail address: hari.pati@advinus.com (H.N. Pati).

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Table 1
Optimization of reaction condition with various acids for synthesis of cyclopentenone derivative

Entry	Acid	Solvent	Temp (°C)	Time (h)	Yield[a] (%)
1	EtOH/HCl (10%)	Ethanol	60	16	No reaction
2	—	Polyphosphoric acid (PPA)	80	16	No reaction
3	$SOCl_2$ (1.0 equiv)	Dichloromethane	0	1	Intractable product
4	—	Acetic acid	60	16	No reaction
5	—	H_2SO_4	0-25	1	Decomposition
6	H_2SO_4 (1.0–5.0 equiv)	Toluene	60	8	5
7	H_2SO_4 (1.0 equiv)	Acetic acid	60	16	60
8	Triflic acid (1.0 equiv)	Acetic acid	60	16	No reaction
9	H_2SO_4 (1.0 equiv)	Acetic acid	70	8	40
10	H_2SO_4 (1.0 equiv)	Acetic acid	50	16	No reaction
11	H_2SO_4 (0.5 equiv)	Acetic acid	60	16	No reaction
12	H_2SO_4 (1.5 equiv)	Acetic acid	60	8	50
13	H_2SO_4 (2.0 equiv)	Acetic acid	60	8	20

[a] Isolated yields.

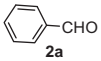
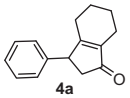
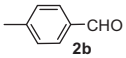
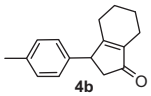
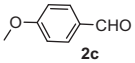
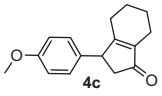
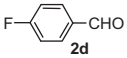
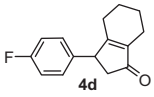
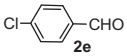
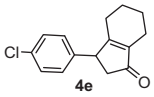
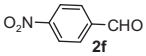
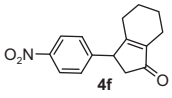
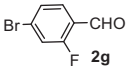
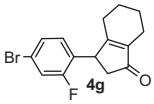
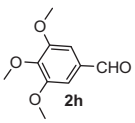
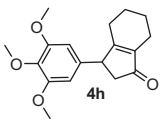
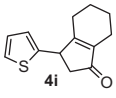
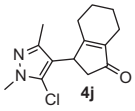
compounds **2a–j** in the presence of aqueous or alcoholic solutions of NaOH. However, the attempts were unsuccessful, as under these conditions, intermediates formed during the aldol addition did not undergo dehydration. Similarly, reactions using LDA or LiHMDS as base followed by acidic work-up resulted in the formation of β-hydroxy ketones that did not undergo dehydration in the presence of several acidic reagents such as $SOCl_2$, $POCl_3$, polyphosphoric acid, and H_2SO_4.

The expected α,β-unsaturated product was not obtained even under acidic reaction conditions employing ethanolic HCl, PPA, and H_2SO_4. Interestingly, the reaction of **1** and **2e** using acetic acid and catalytic amount of sulfuric acid under heating conditions furnished unprecedented cyclopentenone derivative **4e** instead of the expected divinyl ketone in low yields.

Encouraged by these results, we decided to optimize the reaction conditions and investigate the scope of this one pot synthetic methodology for cyclopentenone derivatives using variety of aldehydes **2a–j**.

For optimization of reaction condition, we chose 4-chlorobenzaldehyde **2e** as a model substrate and treated with compound **1** under various acidic conditions as shown in Table 1. The reaction in ethanolic HCl, PPA, and CH_3COOH did not proceed and unreacted

Table 2
Reaction of various aldehydes with 1-acetyl-1-cyclohexene (**1**) in optimized conditions to obtain cyclopentenone derivatives **4a–j**

Entry	Substrate	Time (h)	Product	Yield[a] (%)
1	 **2a**	6	 **4a**	62
2	 **2b**	6	 **4b**	54
3	 **2c**	6	 **4c**	58
4	 **2d**	8	 **4d**	62
5	 **2e**	8	 **4e**	70
6	 **2f**	16	 **4f**	55
7	 **2g**	10	 **4g**	60
8	 **2h**	6	 **4h**	74
9	**2i**	6	 **4i**	58
10	**2j**	8	 **4j**	60

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