JOC Article

Efficient Baylis−Hillman Reactions of Cyclic Enones in Methanol As Catalyzed by Methoxide Anion

Sanzhong Luo,[†] Xueling Mi,[‡] Hui Xu,[†] Peng George Wang,[§] and Jin-Pei Cheng*[,†,‡]

Center for Molecular Science, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100080, China, Department of Chemistry, State Key Laboratory of Elemento-organic Chemistry, Nankai University, Tianjin, 300071, China, and The State Key Laboratory of Microbial Technology, School of Life Science, Shandong University, Jinan, Shandong 250100, China

jpcheng@nankai.edu.cn

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The Baylis−Hillman reactions of cyclic enones with a variety of aldehydes were investigated. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was found to be a viable catalyst in promoting the reactions of sterically retarded substrates in methanol. The reactions showed clear solvent dependence and only occurred in hydroxylic solvents, especially in methanol. Further consideration on the steric character of DBU and its high basicity jointly with other experimental observations suggests that the methoxide anion should be the "true" Baylis−Hillman catalyst. This has been confirmed by the effectiveness of similar reactions directly employing methoxide as the catalyst. The reaction pathways of this type of catalysis are proposed to depend on the choice of substrates. Supporting experimental observations were demonstrated and discussed in relation to mechanistic considerations. This study also reveals that both DBU and sodium methoxide can be successfully applied as effective catalysts in methanol to promote the Baylis−Hillman reactions for a range of cyclic enones including cyclopent-2-enones, cyclohex-2-enones, γ-pyrone, and 1-benzopyran-4(4*H*)-ones.

Introduction

Baylis−Hillman reaction (or Morita−Baylis−Hillman reaction), a versatile carbon−carbon bond-forming reaction, has attracted tremendous research activities in the past decade. Considerable progress has been achieved in enlarging the substrate scope, developing effective catalysts, and establishing methodologies for asymmetric catalysis.[1,2] This type of reaction is generally initiated by a Michael addition of a nucleophile, i.e., the Baylis−Hillman catalyst. Among the traditional nucleophilic catalysts, tertiary amines and phosphines were the ones most frequently explored.[1c] Chalcogenide/$TiCl_4$ was also found to be an effective Baylis−Hillman catalyst in some cases.[3] Recently, the in situ generated halide ion was demonstrated to behave like a nucleophile when $TiCl_4$ or Et_2AlI alone was employed as a catalyst in certain Baylis−Hillman reactions.[4] A similar mechanism was also proposed when TiX_4 was used in combination with Bu_4NX, amine, or alcohol in the Baylis−Hillman reaction of methyl vinyl ketone.[5] In these cases, Lewis acids were considered to facilitate reactions by activating the substrates. More recently, the proazaphosphatrane sulfide/$TiCl_4$ combination was shown to be an excellent catalyst for a range of Baylis−Hillman substrates including enones, acrylonitrile, and acrylates.[6]

Previously, we found that imidazole and its derivatives could effectively catalyze Baylis−Hillman reactions of enones in aqueous media.[7] Remarkable rate enhancement was observed simply on conducting the reactions in weakly basic $NaHCO_3$ solution.[8] However, in our

[†] Chinese Academy of Sciences.
[‡] Nankai University.
[§] Shandong University.

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(2) For examples of asymmetric catalysis, see: (a) Mocquet, C. M.; Warriner, S. L. *Synlett* **2004**, 356. (b) McDougal, N. T.; Schaus, S. E. *J. Am. Chem. Soc.* **2004**, *125*, 12094. (c) Kawahara, S.; Nakano, A.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Org. Lett.* **2003**, *5*, 3013. (d) Shi, M.; Chen, L. H. *Chem. Commun*. **2003**, 1310. (e) Yang, K. S.; Lee, W. D.; Pan, J. F.; Chen, K. M. *J. Org. Chem.* **2003**, *68*, 915. (f) Shi, M.; Xu, Y. M. *Angew. Chem., Int. Ed*. **2002**, *41*, 4507. (g) Imbriglio, J. E.; Vasbinder, M. M.; Miller, S. J. *Org. Lett.* **2003**, *5*, 3741. (h) Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10219.

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(7) (a) Luo, S. Z.; Zhang, B.; He, J.; Janczuk, A.; Wang, P. G.; Cheng, J.-P. *Tetrahedron Lett.* **2002**, *43*, 7369. (b) Catri, R.; El Gaied, M. M. *Tetraheron Lett.* **2002**, *43*, 7835.

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SCHEME 1

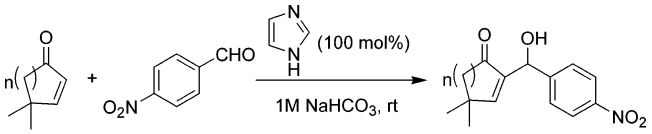
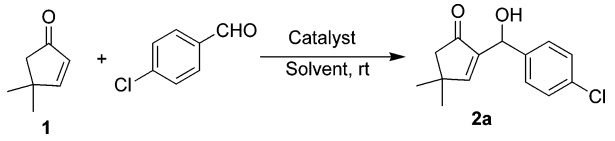


TABLE 1. Tertiary Amine Catalyzed Reactions of 4,4-Dimethylcyclopent-2-enone (1) with *p*-Chlorobenzaldehyde[a]



entry	catalyst (mol %)	solvent	time (h)	yield[b] (%)
1	DABCO (50)	MeOH	12	N.R.
2	DMAP (50)	MeOH	12	N.R.
3	3-quinuclidinone (50)	MeOH	20	N.R.
4	3-quinuclidinol (50)	MeOH	20	N.R.
5	quinuclidine (50)	MeOH	20	N.R.
6	Et_3N (50)	MeOH	12	N.R.
7	DBU (30)	MeOH	8	99
8	DBU (50)	MeOH	6	99
9	DBU (50)	EtOH	24	83
10	DBU (50)	DMF	16	N.R.
11	DBU (50)	MeCN	16	N.R.
12	DBU (50) + MeOH (50)	MeCN	24	N.R.
13	DBU (50) + phenol (50)	MeCN	24	N.R.

[a] Reactions were carried out on 0.5 mmol scale in 1 mL of solvent, molar ratio of aldehyde/enone = 1: 1.2. [b] Isolated yield based on aldehyde. N.R. = no reaction.

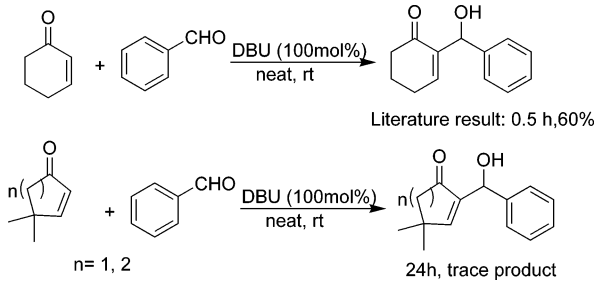
recent investigation of the similar reactions using hindered enones such as 4,4-dimethylcyclopentenone and 4,4-dimethylcyclohexenone, the reactions were observed to be substantially slower due probably to steric effects but were able to afford the desired Baylis–Hillman products in moderate yields (Scheme 1). Later, we found that DBU could accelerate the reaction very efficiently in methanol. This finding may be quite surprising especially when the steric character of DBU is considered. Consequently, we expanded the DBU-promoted reaction to a broader scope and found that it should be the methoxide anion rather than DBU that played the real role as an effective catalyst. Now we wish to report the details of this study.

Results and Discussion

The Catalysts. As mentioned, the imidazole-catalyzed Baylis–Hillman reactions of 4,4-dimethyl-substituted cyclic enones were substantially slower than those of the corresponding unhindered cyclic enones due to steric retardation. To improve the reaction, we examined a variety of tertiary amine catalysts taking the reaction of 4,4-dimethylcyclopent-2-enone with *p*-chlorobenzaldehyde as a model. The results are summarized in Table 1.

As shown in Table 1, among the amines examined, only DBU can effectively promote the reaction. In the presence of DBU (30 mol %), the reaction proceeded smoothly to give the desired Baylis–Hillman product in quantitative yield in 8 h (Table 1, entry 7). Increasing the loading of

SCHEME 2



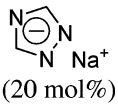
DBU shortened the reaction time to 6 h, but the product yield remained the same (Table 1, entry 8). The use of hydroxylic solvents was shown to be critical for DBU-promoted reactions. In CH_3CN and DMF, even with 50 mol % hydroxylic solvent added, no reactions were observed (Table 1, entries 10–13). Methanol was shown to be a superior medium to ethanol (Table 1, entries 8 and 9).

It is known that DBU is a hindered and non-nucleophilic base with relatively strong basicity.[9] Recently, Aggarwal reported that DBU could act as a powerful Baylis–Hillman catalyst for a range of substrates including cyclohex-2-enone.[10] The reaction of cyclohex-2-enone with benzaldehyde afforded the Baylis–Hillman product in 60% yield in 1 h. However, in our trials under conditions similar to those in Aggarwal's work, the reaction of 4,4-dimethylcyclic enones with benzaldehyde was very sluggish, and only trace product was detected after 24 h with most of the starting materials decomposed (Scheme 2). The low reactivity of 4,4-dimethylcyclic enones may be ascribed to the steric effect of the two methyl groups at C4 position. This result, together with the inert character of DBU as a nucleophile in aprotic solvents as observed in this work (Table 1), indicates that DBU should be sensitive to steric effect. However, the steric issue cannot explain the fact that DBU was actually observed to be a highly effective catalyst in methanol (see Table 1). On the basis of the above observations, it can be envisioned that DBU is most likely not a direct Baylis–Hillman catalyst in methanol. Considering DBU's strong basicity, the methoxide anion, as in situ generated by DBU, should be the acting catalyst that directly initiated the reaction. This is also consistent with the present observations that the less basic tertiary amines (e.g., DABCO, DMAP, etc.) showed very low catalytic activity in Baylis–Hillman reactions (Table 1, entries 1–6).

To seek further evidence for the proposed methoxide anion catalysis, sodium methoxide was tested in the model reaction of 4,4-dimethylcyclopentenone and 4-chlorobenzaldehyde in methanol. To our delight, the reaction was found to proceed very smoothly and afforded the desired product with 98% yield after 3 h (Table 2, entry 1). Compared with DBU-promoted reaction, this reaction is slightly faster with 98% yield of the desired product. Other alkoxides as well as sodium 1,2,4-triazolium were also examined, but inferior results or decomposition were observed in these cases (Table 2, entries 3–6).

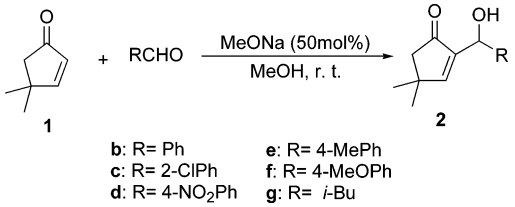
(9) (a) Oediger, H.; Möller, F.; Eiter, K. *Synthesis* **1972**, 591. (b) Ghosh, N. *Synlett* **2004**, 574.
(10) Aggarwal, V. K.; Mereu, A. *Chem. Commun*. **1999**, 2311.

TABLE 2. Alkoxide-Catalyzed Reactions of 4,4-Dimethylcyclopent-2-enone with *p*-Chlorobenzaldehyde[a]

Entry	Catalyst (50 mol%)	Solvent	Time (h)	Yield (%)[b]
1	MeONa	MeOH	3	98%
2	MeONa	MeCN	7	37%[c]
3	EtONa	EtOH	4	67%
4	*t*-BuOK	*t*-BuOH	1	Decomposition
5	$Ti(Oi\text{-}Pr)_4$	*i*-PrOH	12	No reaction
6	 (20 mol%)	MeOH	12	82%
7	K_2CO_3 (100 mol%)[d]	MeOH	3	88%

[a] Reactions were carried out on 0.5 mmol scale in 1 mL of solvent, molar ratio of aldehyde/enone = 1: 1.2. [b] Isolated yield based on aldehyde. [c] Uncharacterized byproducts observed. [d] In 2 mL of methanol.

SCHEME 3



Solvent effect was obvious in the methoxide-catalyzed reactions. In the presence of 50 mol % of sodium methoxide, the reaction in nonhydroxylic solvent MeCN gave only 37% yield along with some uncharacterized byproducts over 7 h (Table 2, entry 2). It is noteworthy that the inorganic base K_2CO_3 can also effectively catalyze the reaction (Table 2, entry 7). In the presence of K_2CO_3 (100 mol %), the reaction gave 88% yield over 3 h in methanol. It is known that K_2CO_3 is partially soluble in methanol in the form of potassium methoxide, which acts as the "real" catalyst to promote the reaction.[11] Thus, the use of K_2CO_3 may provide a convenient alternative to methoxide anion in synthetic applications.

Substrate Scopes. The catalytic conditions employed for investigating the scope and limitation of this version of reactions were usually 50 mol % of sodium methoxide or 50 mol % of DBU; in some cases, K_2CO_3 (100 mol %) was used for convenience.

Initially, the reactions of 4,4-dimethylcyclopent-2-enone with various aldehydes were investigated (Scheme 3, Table 3). Aromatic aldehydes bearing either an electron-withdrawing group or an electron-donating group all worked well under the current conditions. In the presence of sodium methoxide (50 mol %), the reactions proceeded very smoothly to afford the corresponding adducts with moderate to high isolated yields. Notably, the highly electron-rich *p*-methoxybenzaldehyde could also couple with enone **1** satisfactorily, providing the desired adducts in 33% yield after 24 h (Table 3, entry 5). Aliphatic aldehydes such as isovaleraldehyde worked well too, albeit with moderate yield (Table 3, entry 6). In all the cases tested, the Baylis–Hillman adducts were predominant with little or no aldol-type product detected.

TABLE 3. Sodium Methoxide Catalyzed Reactions of 4,4-Dimethylcyclopent-2-enone with Aldehydes[a]

entry	R	product	time (h)	yield[b] (%)
1	Ph	**2b**	4	91
2	2-ClPh	**2c**	3	90
3	$4\text{-}NO_2Ph$	**2d**	1	92
4	4-MePh	**2e**	12	77
5	4-MeOPh	**2f**	24	33
6	*i*-Bu	**2g**	11	56

[a] Reactions were carried out on 0.5 mmol scale in 1 mL of solvent, molar ratio of aldehyde/enone = 1:1.2 [b] Isolated yield based on aldehyde.

Reactions with 4,4-dimethylcyclohexenone (**3**) were also examined using sodium methoxide (100 mol %) as the catalyst. Unlike 4,4-dimethylcyclopent-2-enone (**1**), the reactions of enone **3** afforded the domino-Baylis–Hillman and aldol condensation product **5** besides the expected Baylis–Hillman adducts **4** (Scheme 4, Table 4). This difference in product formation between **1** and **3** may be rationalized by considering the steric hindrance of the α′ position. In cyclopent-2-enone **1**, the 5 (α′) position is steric hindered by the two neighboring methyl groups; thus, the α′-aldolization is forbidden. In cyclohex-2-enone **3**, the 6 (α′)-position is less hindered, and so a significant amount of subsequent Baylis–Hillman-aldol condensation product was obtained.[12] As shown in Table 4, the reactions were applied well for aromatic aldehydes. The use of K_2CO_3 or sodium methoxide gave similar results. In the cases of aliphatic aldehydes, self-condensation of aldehyde occurred due to the relatively low reactivity of 4,4-dimethylcyclohex-2-enone **3**, which led to poor results.

Next, the reaction was extended to a new class of cyclic enones, 1-benzopyran-4(4*H*)-ones and γ-pyrone. Since the α′-positions of these substrates are masked, the aldol pathway can thus be avoided and the reactions occurred very cleanly in methanol to give the desired Baylis–Hillman adducts under the catalysis of sodium methoxide (Scheme 5, Table 5). Most recently, Basavaiah reported that methanolic trimethylamine (100 mol %) could mediate the Baylis–Hillman reaction of 1-benzopyran-4(4*H*)-ones.[13] However, the reaction was applicable only to active aromatic aldehydes such as nitrobenzaldehydes and pyridinecarboxaldehydes and required very long reaction time which generally ranged from 2 to 5 days. In comparison with Basavaiah's results, the methoxide anion catalyzed Baylis–Hillman reaction of 1-benzopyran-4(4*H*)-ones produced higher yields of the desired adducts but in much shorter reaction time (see Table 5, entries 8 and 10). The reactions also worked well with less reactive aromatic aldehydes and aliphatic aldehydes, affording the desired Baylis–Hillman adducts in moderate to high yields (Table 5, entries 11, 16–18). Mean-

(11) $KHCO_3$ deposited upon the formation of KOMe was shown to be inert for catalysis. For solubility of K_2CO_3 in methanol, see: Platonov, A. Y.; Evdokimov, A. N.; Kurzin, A. V.; Maiyorova, H. D. *J. Chem. Eng. Data* **2002**, *47*, 1175.

(12) For steric effects in directing Baylis–Hillman reaction and Aldol reaction, see: Basavaiah, D.; Sreenivasulu, B.; Rao, A. J. *J. Org. Chem.* **2003**, *68*, 5983.

(13) For a recent example, see: Basavaiah, D.; Rao, A. J. *Tetrahedron Lett.* **2003**, *44*, 4365.

SCHEME 4

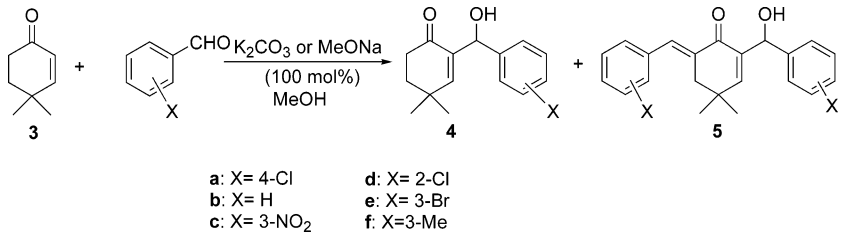
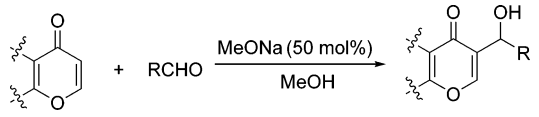


TABLE 4. Sodium Methoxide Catalyzed Reactions of 4,4-Dimethylcyclohex-2-enone with Aldehydes[a]

			yield[b] (%)			
entry	X	time (h)	**4**		**5**	
1	4-Cl	20	**4a**	37	**5a**	55
2	H	24	**4b**	26	**5b**	45
3	3-NO_2	6	**4c**	35	**5c**	51
4	2-Cl	20	**4d**	17	**5d**	41
5	3-Br	15	**4e**	36	**5e**	38
6	3-Me	36	**4f**	20	**5f**	16

[a] Reactions were carried out on 0.5 mmol scale in 1 mL of methanol, molar ratio of aldehyde/enone = 1:2.0; when K_2CO_3 was tried, the reaction was conducted in 2 mL of methanol. [b] Isolated yield based on aldehyde.

SCHEME 5



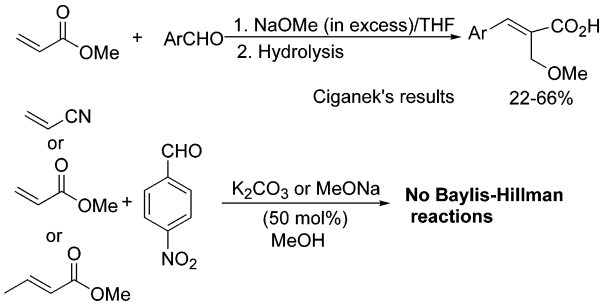
while, both of the chromone derivatives (**8** and **10**) were proved to be effective Michael acceptors under the present conditions. It is noted that even 5 mol % of sodium methoxide was able to facilitate efficient coupling of 1-benzopyran-4(4*H*)-one with nitrobenzaldehydes (Table 5, entries 8−10).

The Baylis−Hillman reaction of γ-pyrone proceeded smoothly giving moderate to good product yields in the presence of sodium methoxide (Table 5, entries 2, 4−7). Although there are two identical α-positions in γ-pyrone, only the mono-Baylis−Hillman adducts were obtained in the cases examined. Generally, 50 mol % of sodium methoxide were required to obtain good yields. In the presence of 10 mol % of sodium methoxide, the reaction between γ-pyrone and *p*-nitrobenzaldehyde afforded the Baylis−Hillman adduct in 40% yield after 2 h. The yield can be improved to 62% by loading 50 mol % of sodium methoxide (Table 5, entries 1 and 2). There was no further improvement on yield by loading more sodium methoxide or extending the reaction time.

As shown in Table 5, DBU also served as an efficient Baylis−Hillman catalyst for 1-benzopyran-4(4*H*)-ones and γ-pyrone (entries 3 and 12) in methanol. Comparable or even better results were obtained when DBU was used in place of sodium methoxide.

Isatin was reported as being able to serve as an electrophile in Baylis−Hillman reactions.[13,14] Accordingly, isatin was employed to couple with the chromone derivatives γ-pyrone **6** and cyclopentenone **1**. In the presence of 50 mol % of sodium methoxide, the reactions occurred

SCHEME 6



readily to provide the corresponding adducts in high yields (Table 6, entries 1−4).

Using sodium methoxide or potassium carbonate as catalyst, the reactions of common cyclic enones such as cyclopent-2-enone (**13**) and cyclohex-2-enone (**15**) were also investigated. As shown in Table 7, the reactions afforded reasonable yields of the desired Baylis−Hillman adducts within 1 h and demonstrated good applicability for a wide range of aldehydes. It should be pointed out that the Baylis−Hillman products were the dominant products although the reactions were generally not highly clean under the basic conditions. Decomposition was observed when extending the reaction time. In these cases, some non-Baylis−Hillman pathway may exist in the presence of methoxide anion (see discussion below). Nevertheless, the current reactions provide fast and convenient alternatives for the synthesis of densely functionalized cyclic allylic alcohols.

Previously, Ciganek reported that sodium methoxide in THF could mediate the coupling of methyl acrylate with aromatic aldehydes.[15] The reactions produced α-methoxymethylcinnamic acids (after hydrolysis) with moderate yields via Baylis−Hillman-type reactions (Scheme 6). In our studies, Baylis−Hillman substrates such as acrylates and acrylonitrile were also attempted. However, the examined reactions did not give any Baylis−Hillman products in methanol in the presence of sodium methoxide (50 mol %) (Scheme 6). This is consistent with Aggarwal's observation that sodium methoxide itself could not catalyze the Baylis−Hillman reaction of methyl acrylate in methanol.[16] All together, it seems likely that the α,β-unsaturated ketone structure may be essential for the success of methoxide anion catalysis in methanol.

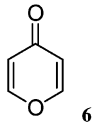
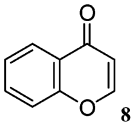
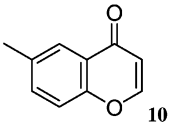
Mechanism Consideration. Among various nucleophiles exploited for Baylis−Hillman catalysis in the literature, oxy nucleophiles have rarely been attempted as catalysts.[15] Shi and co-workers previously reported that combination of titanium tetrachloride and oxy

(14) Garden, S. J.; Skakle, J. M. S. *Tetrahedron Lett.* **2002**, *43*, 1969−1972.

(15) Ciganek, E. *J. Org. Chem.* **1995**, *60*, 4635.

(16) Aggarwal, V. K.; Emme, I.; Fulford, S. Y. *J. Org. Chem.* **2003**, *68*, 692.

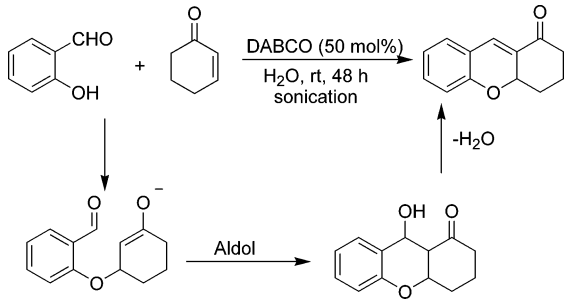
TABLE 5. Sodium Methoxide Catalyzed Reactions of 1-Benzopyran-4(4*H*)-ones and γ-Pyrone with Aldehydes[a]

Entry	Enone	R	Catalyst (mol%)	Product	Time (h)	Yield (%)[b]
1	 **6**	*p*-NO_2Ph	MeONa (10)	**7a**	2	40
2	**6**	*p*-NO_2Ph	MeONa (50)	**7a**	1	62
3	**6**	*p*-NO_2Ph	DBU (50)	**7a**	1	65
4	**6**	*p*-ClPh	MeONa (50)	**7b**	2	69
5	**6**	Ph	MeONa (50)	**7c**	12	50
6	**6**	*p*-MePh	MeONa (50)	**7d**	20	37
7	**6**	*i*-Bu	MeONa (50)	**7e**	15	63
8	 **8**	*p*-NO_2Ph	MeONa (5)	**9a**	2 (2 days)[c]	90 (86)[c]
9	**8**	*m*-NO_2Ph	MeONa (5)	**9b**	3	87
10	**8**	*o*-NO_2Ph	MeONa (5)	**9c**	2 (2 days)[c]	88 (81)[c]
11	**8**	*i*-Bu	MeONa (50)	**9d**	24	41
12	**8**	*i*-Bu	DBU (50)	**9d**	13	68
13	 **10**	*p*-NO_2Ph	MeONa (50)	**11a**	4	93
14	**10**	*m*-NO_2Ph	MeONa (50)	**11b**	4	83
15	**10**	*o*-NO_2Ph	MeONa (50)	**11c**	5	89
16	**10**	*p*-ClPh	MeONa (50)	**11d**	12	57
17	**10**	Ph	MeONa (50)	**11e**	14	49
18	**10**	*i*-Bu	MeONa (50)	**11f**	13	68

[a] Reactions were carried out on 0.5 mmol scale in 1 mL of solvent, molar ratio of aldehyde/enone = 1.0:1.0. [b] Isolated yield of pure product. [c] Data in parentheses refer to literature results.

compounds promoted the Baylis–Hillman reactions of methyl vinyl ketones.[5d] However, the oxy compound was not the real catalyst, and the reaction was most likely initialized by chloride ion from the neutral oxy-Ti complex. Most recently, the reaction of 2-hydroxybenzaldehyde and cyclohex-2-enone, a typical Baylis–Hillman coupling, was suggested to occur through a domino oxa-Micheal addition/aldol condensation pathway in the presence of DABCO under aqueous conditions.[17] The in situ generated phenoxide anion acted as the nucleophile to facilitate the coupling of aldehyde and enone in an intramolecular manner (Scheme 7).

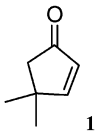
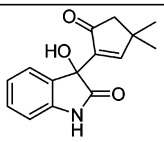
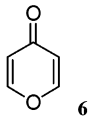
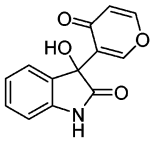
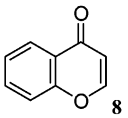
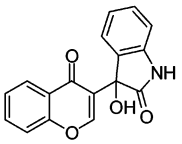
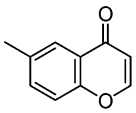
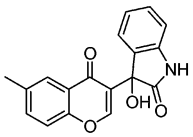
SCHEME 7



In the present study, sodium methoxide may act either as a nucleophile or a base when interacting with enone. Accordingly, there may be two alternative pathways accounting for the formation of the Baylis–Hillman product. As shown in Scheme 8 (taking the reaction of 2-cyclohexenone as an example), methoxide as a base may absorb a γ-proton to form the corresponding dienolate anion **II**, which is thermodynamically more stable than its cross-conjugated isomer **I** as generated by

(17) Bräse, S.; Lesh, B. *Angew. Chem., Int. Ed.* **2004**, *43*, 115.

TABLE 6. Sodium Methoxide (50 mol %) Catalyzed Reactions of Isatin[a]

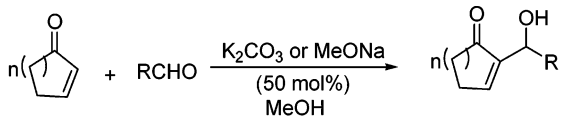
Entry	Enone	Product	Time (h)	Yield (%)[b]
1	 **1**	 **12a**	3	94
2	 **6**	 **12b**	3	84
3	 **8**	 **12c**	4	80
4	 **10**	 **12d**	2	77

[a] Reactions were carried out on 0.5 mmol scale in 1 mL of solvent, molar ratio of isatin/enone = 1:1.2. [b] Isolated yield of pure product after chromatography or recrystallization.

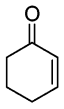
abstraction of an α′-proton.[18] The subsequent α-aldol reactions lead preferentially to Baylis−Hillman product under the experimental conditions (Scheme 8). When methoxide anion acts as a nucleophile, a slightly different mechanism should apply. In this connection, the Baylis−Hillman product should be obtained by following an oxa-Michael addition/aldol reaction pathway (**B**), reminiscent of the typical Baylis−Hillman process. However, the dual character of methoxide anion as a base and a nucleophile makes two reaction pathways less discernible.

On the basis of the short reaction time observed for the common enones **13** and **15**, it is very likely that a base initialized γ-dienolate anion intermediate (pathway **A**) is probably invoked in their reaction coordinates, of which the sequence of α-aldol reaction and isomerization provides the Baylis−Hillman adducts. This was further supported by the reaction of 3-methyl-2-cyclohexenone **17**. In the presence of potassium carbonate in methanol, the reaction of **17** with *p*-nitrobenzaldehyde afforded the γ-aldol condensation product **18** as the major product. A similar result was also observed in the reaction with *p*-chlorobenzaldehyde, which afforded the γ-aldol adduct **19** as the dominant product (Scheme 9). Thus, it is obvious that the reactions proceeded through γ-dienolate anion **III** to furnish the γ-aldol products. In these cases, where the α-position is less accessible than the γ-position, the reaction gives the γ-aldol product (**18** or **19**) as the dominant product. Presently, the oxa-Micheal addition/aldol pathway (**B**) cannot be ruled out for the reactions of **13** and **15**.

TABLE 7. Sodium Methoxide Catalyzed Reactions of Cyclopent-2-enone and Cyclohex-2-enone with Aldehydes[a]



n= 1, 2

Entry	Enone	R	Product	Time	Yield (%)[b]
1	 **13**	Ph	**14a**	10 min	94
2	**13**	*p*-ClPh	**14b**	10 min	72
3	**13**	*m*-BrPh	**14c**	10 min	90
4	**13**	*p*-NO_2Ph	**14d**	10 min	60[c]
5	**13**	*p*-MePh	**14e**	1 h	77
6	**13**	*p*-PhPh	**14f**	10 min	75
7	**13**	*p*-MeOPh	**14g**	4 h	41
8	**13**	*i*-Bu	**14h**	1 h	67
9	**13**	*n*-C_6H_{11}	**14i**	20 min	32
10	 **15**	Ph	**16a**	1 h	65
11	**15**	*p*-ClPh	**16b**	1 h	68
12	**15**	*m*-BrPh	**16c**	1h	74
13	**15**	*p*-NO_2Ph	**16d**	10 min	57[c]
14	**15**	*p*-MePh	**16e**	1h	60
15	**15**	*i*-Bu	**16f**	45 min	27

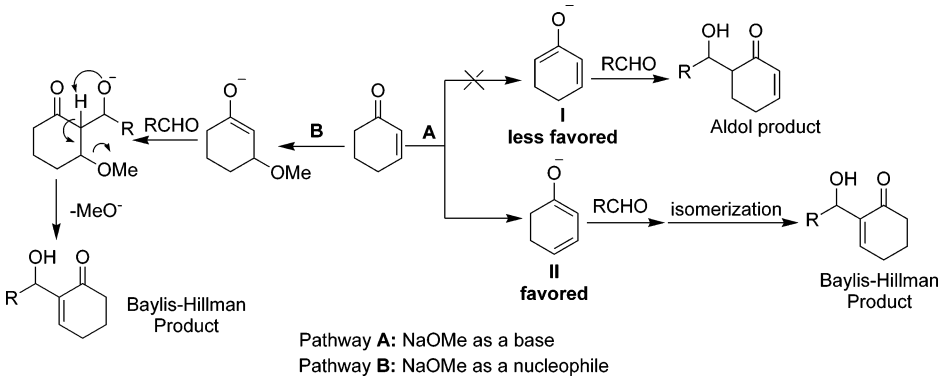
[a] Reactions were carried out on a 0.5 mmol scale in 1 mL of solvent, molar ratio of aldehyde/cyclopent-2-enone = 1.0:1.5; aldehyde/cyclohex-2-enone = 1.0:2.0. [b] Isolated yield of pure product. [c] Decomposition occurred upon extending the reaction time.

On the other hand, for enones **1**, **3**, **6**, **8**, and **10**, it is believed that the reactions should follow an oxa-Michael addition/aldol reaction pathway **B**, as their γ-positions are either masked (**1** and **3**) or heterosubstituted (**6**, **8**, and **10**). In these cases, the aldol reaction of methoxylated enolate with aldehydes and the subsequent elimination of methoxyl group afford the desired Baylis−Hillman adducts.[19] Methoxylated aldol products may also be produced in this process and were indeed obtained from the reaction of methyl vinyl ketone (MVK). The reaction of MVK with *p*-nitrobenzaldehyde was observed to give methoxylated aldol product **21** as a major product and

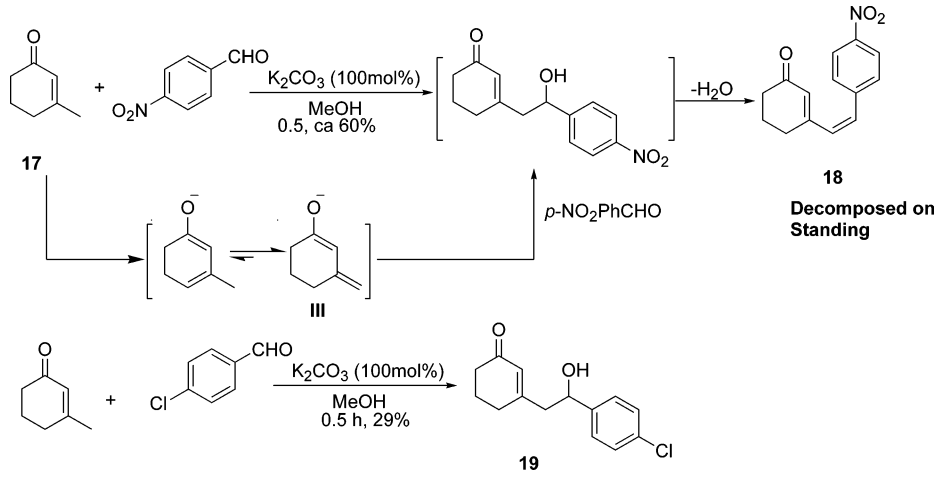
(18) (a) Lee, R. A.; McAndrews, C.; Patel, K. M.; Reusch, W. *Tetrahedron Lett.* **1973**, *14*, 965. (b) Lee, R. A.; Reusch, W. *Tetrahedron Lett.* **1973**, *14*, 969.

(19) Previously, it was reported that the sequential Michael addition of methoxide ion and elimination of the methoxy group with a base could be employed as an efficient method for protecting methylene lactone in the total synthesis of deoxocrispolide. Paquette, L. A.; Sturino, C. F.; Wang, X.; Prodger, J. C.; Koh, D. *J. Am. Chem. Soc.* **1996**, *118*, 5620.

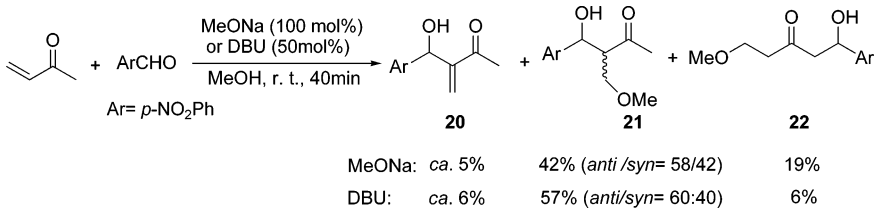
SCHEME 8



SCHEME 9



SCHEME 10



the Baylis–Hillman product **20** as a minor.[20] The methoxylated α′-aldol product **22** was also obtained as an additional minor product (Scheme 10). The use of DBU in this case gave similar product distribution, albeit with lower yield of **22**. These results further support the assumption that the Baylis–Hillman reactions of enones **1**, **3**, **6**, **8**, and **10** proceed via an oxa-Micheal addition/aldol pathway (**B**).

In conclusion, we have shown, for the first time, that methoxide anion can effectively catalyze the Baylis–Hillman-type reaction of enones. For common enones such as cyclopent-2-enone and cyclohex-2-enone, the reactions occurred most likely through a γ-dienolate anion intermediate generated from deprotonation by the methoxide base, whereas for enones without γ-protons such as **1**, **3**, **6**, **8**, and **10** the reaction followed an oxa-Micheal addition/aldol pathway (**B**) with the methoxide anion as the nucleophile. DBU was shown to be effective in promoting this series of reactions in methanol, and the in situ generated methoxide anion accounted for its catalytic activity. Generally, the reactions are quite fast and afford the desired Baylis–Hillman products with moderate to good yields; thus, it provides a convenient and efficient approach for the synthesis of allylic alcohols under mild conditions.

Experimental Section

General Procedure. To a stirred mixture of sodium methoxide and aldehyde (0.5 mmol) in 2 mL of methanol was added the respective α,β-unsaturated ketones (0.6 mmol). The resulted mixture was stirred at room temperature. Upon completion or after the time indicated in the tables, the reaction was quenched with 1 N HCl and concentrated under reduced pressure. The residue was extracted with ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on

(20) Compound **20** and its methoxylated isomers **21** were isolated as inseparable mixtures and appeared as one point on TLC. However, their respective NMR signals were obviously discernible (see the Supporting Information), and the ratio was therefore estimated by the corresponding integration.

silca gel to afford the desired product. For the reactions in Tables 5 (entries 1−3, 8−10, and 13−15) and 6, the reaction mixture was filtered after the indicated time and the filtered solid was recrystallized from methanol−acetonitrile to afford the pure product. The filtrate was worked up as mentioned above to give another portion of pure product.

2-[(4-Chlorophenyl)hydroxymethyl]-4,4-dimethylcyclopent-2-enone (2a). Known compound.[21] Pale yellow solid. Mp: 49−50 °C. IR (KBr, cm^{-1}): 3426, 1697. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.20 (3H, s), 1.22 (3H, s), 2.34 (2H, s), 3.55 (1H, s), 5.50 (1H, s), 7.02 (1H, s), 7.29−7.36 (4H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 27.9, 39.2, 50.9, 68.8, 127.8, 128.6, 133.5, 139.8, 144.2, 168.2, 209.1. Anal. Calcd: C, 67.07; H, 6.03. Found: C, 67.01; H, 6.02.

2-(Hydroxyphenylmethyl)-4,4-dimethylcyclopent-2-enone (2b). Colorless syrup. IR (KBr, cm^{-1}): 3430, 1699. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.17 (3H, s), 1.19 (3H, s), 2.31 (2H, s), 3.28 (1H, br s), 5.49 (1H, s), 7.01 (1H, s), 7.28−7.35 (5H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 27.9, 28.0, 39.2, 50.9, 69.5, 126.5, 127.8, 128.5, 141.3, 144.5, 168.2, 209.3. HRMS for $C_{14}H_{17}O_2$ (M + 1): calcd 217.1223, found 217.1222.

2-[(2-Chlorophenyl)hydroxymethyl]-4,4-dimethylcyclopent-2-enone (2c). Colorless syrup. IR (KBr, cm^{-1}): 3396, 1705. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.18 (3H, s), 1.22 (3H, s), 2.38 (2H, s), 3.73 (1H, br s), 5.90 (1H, s), 6.87 (1H, s), 7.27−7.38 (3H, m), 7.63−7.65 (1H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 27.6, 27.9, 39.1, 50.7, 66.0, 127.0, 127.8, 129.3, 132.0, 138.5, 142.3, 169.0, 209.5. HRMS for $C_{14}H_{16}O_2$ Cl (M + 1): calcd 251.0833, found 251.0836.

2-[Hydroxy(4-nitrophenyl)methyl]-4,4-dimethylcyclopent-2-enone (2d). Pale yellow solid. Mp: 88−90 °C. IR (KBr, cm^{-1}): 3436, 1689. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.18 (3H, s), 1.19 (3H, s), 2.32 (2H, s), 3.50 (1H, br s), 5.60 (1H, s), 7.03 (1H, s), 7.54 (2H, d, J = 8.7 Hz), 8.17 (2H, d, J = 8.7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 27.7, 39.3, 50.7, 68.5, 123.6, 127.0, 143.4, 147.3, 148.4, 168.6, 208.8. HRMS for $C_{14}H_{15}NO_4$: calcd 261.1001, found 261.1005.

2-(Hydroxy-*p*-tolylmethyl)-4,4-dimethylcyclopent-2-enone (2e). Pale yellow syrup. IR (KBr, cm^{-1}): 3430, 1700. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.20 (3H, s), 1.22 (3H, s), 2.33 (2H, s), 2.36 (3H, s), 3.36 (1H, br s), 5.48 (1H, s), 7.05 (1H, s), 7.17 (2H, d, J = 7.8 Hz), 7.27 (2H, d, J = 7.8 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.1, 27.9, 39.0, 50.9, 69.4, 126.4, 129.1, 137.4, 138.3, 144.6, 167.9, 209.1. HRMS for $C_{15}H_{19}O_2$ (M + 1): calcd 231.1379, found 231.1383.

2-[Hydroxy(4-methoxyphenylmethyl)-4,4-dimethylcyclopent-2-enone (2f). Yellow syrup. IR (KBr, cm^{-1}): 3444, 1704. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.22 (3H, s), 1.24 (3H, s), 2.36 (2H, s), 3.50 (1H, br s), 3.84 (3H, s), 5.49 (1H, s), 6.91 (2H, d, J = 8.4 Hz), 7.04 (1H, s), 7.31 (2H, d, J = 8.4 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 28.0, 39.0, 50.9, 55.2, 69.3, 113.8, 127.7, 133.3, 144.6, 159.2, 167.8, 209.1. HRMS for $C_{15}H_{19}O_3$ (M + 1): calcd 247.1329, found 247.1329.

2-(1-Hydroxy-3-methylbutyl)-4,4-dimethylcyclopent-2-enone (2g). Pale yellow syrup. IR (KBr, cm^{-1}): 3436, 1698. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.93−0.95 (6H, m), 1.22 (6H, s), 1.43−1.48 (1H, m), 1.58−1.61 (1H, m), 1.75−1.81 (1H, m), 2.31 (2H, s), 2.51 (1H, br s), 4.46 (1H, dd, J = 4.5, 9.3 Hz), 7.16 (1H, s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.7, 23.3, 24.3, 27.9, 28.0, 38.9, 44.6, 50.8, 65.5, 144.8, 166.6, 209.7. HRMS for $C_{12}H_{21}O_2$ (M + 1): calcd 197.1536, found 197.1535.

2-(4-Chlorophenylhydroxymethyl)-4,4-dimethylcyclohex-2-enone (4a). Colorless syrup. IR (KBr, cm^{-1}): 34440, 1668. NMR ($CDCl_3$, 300 MHz): δ 1.12 (3H, s), 1.14 (3H, s), 1.82 (2H, t, J = 6.9 Hz), 2.41 (2H, d, J = 6.9 Hz), 3.50 (1H, br s), 5.41 (1H, s), 6.42 (1H, s), 7.23−7.29 (4H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 27.6, 27.8, 33.0, 34.9, 35.6, 72.0, 127.7, 128.5, 137.4, 140.4, 156.3, 200.1. HRMS for $C_{15}H_{17}ClO_2$: calcd 264.0917, found 264.0916.

2-(Hydroxyphenylmethyl)-4,4-dimethylcyclohex-2-enone (4b). Known compound.[22] Colorless syrup. IR (KBr, cm^{-1}): 3435, 1669. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.16 (3H, s), 1.18 (3H, s), 1.86 (2H, t, J = 6.6 Hz), 2.48 (2H, t, J = 6.6 Hz), 3.23 (1H, br s), 5.48 (1H, s), 6.49 (1H, s), 7.27−7.35 (5H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 28.0, 28.2, 33.3, 35.3, 36.0, 73.1, 126.7, 127.8, 128.7, 138.0, 142.2, 156.5, 200.5. HRMS for $C_{15}H_{18}O_2$: calcd 230.1307, found 230.1301.

2-[Hydroxy(3-nitrophenyl)methyl]]-4,4-dimethylcyclohex-2-enone (4c). Pale yellow syrup. IR (KBr, cm^{-1}): 3435, 2959, 1667, 1530, 1350. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.16 (3H, s), 1.18 (3H, s), 1.84 (2H, t, J = 6.9 Hz), 2.45 (2H, t, J = 6.9 Hz), 3.30 (1H, br s), 5.49 (1H, s), 6.56 (1H, s), 7.48 (1H, t, J = 7.8 Hz), 7.68 (1H, d, J = 7.8 Hz), 8.08 (1H, d, J = 7.8 Hz), 8.18 (1H, s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 27.6, 27.8, 33.1, 34.9, 35.6, 72.0, 121.3, 122.4, 129.3, 132.5, 136.9, 144.5, 148.3, 157.0, 200.0. HRMS for $C_{15}H_{18}O_4$ N (M + 1): calcd 276.1230, found 276.1227.

2-(2-Chlorophenylhydroxymethyl)-4,4-dimethylcyclohex-2-enone (4d). Colorless syrup. IR (KBr, cm^{-1}): 3434, 1670. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.13 (3H, s), 1.15 (3H, s), 1.88 (2H, d, J = 6.9 Hz), 2.53−2.58 (2H, m), 3.04 (1H, br s), 5.89 (1H, s), 6.22 (1H, s), 7.25−7.38 (3H, m), 7.64 (1H, d, J = 7.8 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 27.2, 27.6, 32.8, 34.7, 35.5, 69.0, 125.8, 128.0, 128.5, 129.2, 132.2, 135.7, 138.3, 156.7, 200.5. HRMS for $C_{15}H_{18}O_2$ Cl (M + 1): calcd 265.0990, found 265.0989.

2-(3-Bromophenylhydroxymethyl)-4,4-dimethylcyclohex-2-enone (4e). Pale yellow syrup. IR (KBr, cm^{-1}): 3432, 1666. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.18 (3H, s), 1.19 (3H, s), 1.86 (2H, t, J = 6.9 Hz), 2.48 (2H, t, J = 6.9 Hz), 3.20 (1H, br s), 5.42 (1H, s), 6.50 (1H, s), 7.20−7.27 (2H, m), 7.40 (1H, d, J = 7.5 Hz), 7.51 (1H, s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 27.6, 27.8, 32.9, 34.8, 35.6, 72.2, 122.5, 124.9, 129.3, 129.8, 130.5, 137.1, 144.3, 156.5, 200.0. HRMS for $C_{15}H_{18}O_2Br$ (M + 1): calcd 311.0464, found 311.0463.

2-(Hydroxy-*m*-tolylmethyl)-4,4-dimethylcyclohex-2-enone (4f). Yellow syrup. IR (KBr, cm^{-1}): 3436, 1670. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.18 (3H, s), 1.19 (3H, s), 1.88 (2H, t, J = 6.9 Hz), 2.38 (3H, s), 2.50 (2H, t, J = 6.9 Hz), 2.95 (1H, br s), 5.47 (1H, s), 6.52 (1H, s), 7.09−7.14 (2H, m), 7.20−7.27 (2H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.4, 27.6, 27.8, 32.9, 34.9, 35.6, 72.6, 123.3, 127.0, 128.1, 137.6, 137.9, 141.7, 156.0, 200.1. HRMS for $C_{16}H_{20}O_2$ (M): calcd 244.1463, found 244.1458.

6-(4-Chlorobenzylidene)-2-[(4-chlorophenyl)hydroxymethyl]-4,4-dimethylcyclohex-2-enone (5a). Colorless syrup. IR (KBr, cm^{-1}): 3443, 1661, 1603, 1489. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.11 (3H, s), 1.13 (3H, s), 2.77 (2H, s), 3.63 (1H, br s), 5.55 (1H, s), 6.65 (1H, s), 7.28−7.38 (8H, m), 7.60 (1H, s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 28.7, 28.8, 34.0, 40.7, 72.4, 127.7, 127.9, 128.7, 128.8, 130.9, 133.3, 133.9, 134.5, 136.1, 138.5, 140.5, 155.6, 188.6. HRMS for $C_{22}H_{21}Cl_2O_2$ (M + 1) calcd 387.0913, found 387.0915.

6-Benzylidene-2-(hydroxyphenylmethyl)-4,4-dimethylcyclohex-2-enone (5b). Yellow syrup. IR (KBr, cm^{-1}): 3442, 1659, 1601. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.11 (3H, s), 1.14 (3H, s), 2.50 (1H, br s), 2.82 (2H, s), 5.59 (1H, s), 6.63 (1H, s), 7.28−7.42 (10H, m), 7.68 (1H, s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 29.1, 29.2, 34.3, 40.7, 73.6, 126.8, 127.6, 127.9, 128.5, 128.8, 130.0, 133.9, 136.0, 137.6, 139.0, 142.3, 155.8, 189.4. HRMS for $C_{22}H_{23}O_2$ (M + 1): calcd 319.1692, found 319.1688.

2-[Hydroxy(3-nitrophenyl)methyl]-4,4-dimethyl-6-(3-nitrobenzylidene)cyclohex-2-enone (5c). Yellow syrup. IR (KBr, cm^{-1}): 3442, 1662, 1612, 1528, 1350. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.16 (3H, s), 1.18 (3H, s), 2.82 (2H, s), 3.00 (1H, br s), 5.68 (1H, s), 6.83 (1H, s), 7.52−7.66 (4H, m), 7.74−7.80 (1H, m), 8.14−8.22 (3H, m), 8.29 (1H, s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 28.7, 28.8, 34.3, 40.2, 72.1, 121.4, 122.6, 123.3, 124.0, 129.4, 129.7, 132.6, 134.6, 135.4, 135.7, 137.0, 137.9, 144.3,

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148.3, 148.4, 156.6, 187.9. HRMS for $C_{22}H_{21}O_6N_2$ (M + 1): calcd 409.1394, found 409.1397.

6-(2-Chlorobenzylidene)-2-[(2-chlorophenyl)hydroxymethyl]-4,4-dimethylcyclohex-2-enone (5d). Colorless syrup. IR (KBr, cm^{-1}): 3434, 1663, 1619. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.10 (6H, s), 2.67 (2H, s), 3.10 (1H, br s), 5.99 (1H, s), 6.39 (1H, s), 7.21−7.48 (7H, m), 7.68 (1H, m), 7.77 (1H, s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 28.3, 28.4, 34.1, 40.4, 69.5, 126.4, 127.0, 128.3, 128.7, 129.4, 129.6, 129.7, 130.1, 132.5, 134.3, 134.4, 134.7, 135.1, 135.8, 138.5, 156.6, 189.0. HRMS for $C_{22}H_{21}O_2Cl_2$ (M + 1): calcd 387.0913, found 387.0908.

6-(3-Bromobenzylidene)-2-[(3-bromophenyl)hydroxymethyl]-4,4-dimethylcyclohex-2-enone (5e). Yellow syrup. IR (KBr, cm^{-1}): 3439, 1660, 1591. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.13 (3H, s), 1.15 (3H, s), 2.79 (1H, s), 5.55 (1H, s), 6.68 (1H, s), 7.21−7.34 (5H, m), 7.42−7.48 (3H, m), 7.57−7.59 (1H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 28.6, 28.8, 34.1, 40.2, 72.5, 122.6, 122.7, 125.0, 128.1, 129.5, 129.9, 130.0, 130.6, 131.5, 132.2, 134.6, 135.6, 137.6, 138.2, 144.3, 156.0, 188.4. HRMS for $C_{22}H_{21}O_2Br_2$ (M + 1): calcd 474.9903, found 474.9908.

2-(Hydroxy-*m*-tolylmethyl)-4,4-dimethyl-6-(3-methylbenzylidene)cyclohex-2-enone (5f). Yellow syrup. IR (KBr, cm^{-1}): 3443, 1661, 1604. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.14 (3H, s), 1.15 (3H, s), 2.38 (3H, s), 2.43 (3H, s), 2.83 (2H, s), 2.57 (1H, s), 6.65 (1H, s), 7.10−7.18 (4H, m), 7.23−7.30 (4H, m), 7.67 (1H, s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.3, 21.4, 28.6, 28.7, 33.8, 40.2, 73.1, 123.4, 126.5, 127.1, 128.1, 129.2, 130.3, 133.2, 135.5, 137.3, 137.9, 138.0, 138.5, 141.7, 155.2, 188.9. HRMS for $C_{24}H_{27}O_2$ (M + 1): calcd 347.2005, found 347.2007.

3-[Hydroxy(4-nitrophenyl)methyl]-4*H*-pyran-4-one (7a). Pale yellow solid. Mp: 163−164 °C. IR (KBr, cm^{-1}): 3403, 1649. ^1H NMR ($CDCl_3$, 300 MHz): δ 3.50 (1H, br, s), 5.86 (1H, s), 6.32 (1H, d, J = 5.7 Hz), 7.67 (2H, d, J = 8.7 Hz), 7.86 (1H, d, J = 5.7 Hz), 7.97 (1H, s), 8.18 (2H, d, J = 8.7 Hz). ^{13}C NMR (DMSO, 75 MHz): δ 66.5, 116.6, 123.4 (×2), 127.8 (×2), 131.9, 146.7, 151.0, 154.2, 156.9, 175.9. Anal. Calcd: C, 58.30; H, 3.67; N, 5.67. Found: C, 58.34; H, 3.66; N, 5.62.

3-[(4-Chlorophenyl)hydroxymethyl]-4*H*-pyran-4-one (7b). Pale yellow syrup. IR (KBr, cm^{-1}): 3351, 1655. ^1H NMR ($CDCl_3$, 300 MHz): δ 4.30 (1H, br s), 5.74 (1H, s), 6.35 (1H, d, J = 5.7 Hz), 7.30−7.37 (4H, m), 7.50 (1H, s), 7.74 (1H, d, J = 5.7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 69.3, 117.2, 127.9, 128.6, 131.6, 133.7, 138.6, 153.2, 155.6, 178.5. HRMS for $C_{12}H_9ClO_3$: calcd 236.0240, found 236.0248.

3-(Hydroxyphenylmethyl)-4*H*-pyran-4-one (7c). Pale yellow syrup. IR (KBr, cm^{-1}): 3384, 1652. ^1H NMR ($CDCl_3$, 300 MHz): δ 4.53 (1H, br s), 5.79 (1H, s), 6.35 (1H, d, J = 5.7 Hz), 7.32−7.44 (5H, m), 7.48 (1H, s), 7.72 (1H, d, J = 5.7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 69.9, 117.2, 126.6, 128.0, 128.5, 132.0, 140.0, 153.4, 155.5, 178.7. HRMS for $C_{12}H_{10}O_3$: calcd 202.0630, found, 202.0623.

3-(Hydroxy-*p*-tolylmethyl)-4*H*-pyran-4-one (7d). Yellow syrup. IR (KBr, cm^{-1}): 3408, 1650. ^1H NMR ($CDCl_3$, 300 MHz): δ 2.34 (3H, s), 4.30 (1H, br s), 5.76 (1H, s), 6.36 (1H, d, J = 5.7 Hz), 7.17 (2H, d, J = 7.8 Hz), 7.30 (2H, J = 7.8 Hz), 7.48 (1H, s), 7.73 (1H, d, J = 5.7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.1, 69.8, 117.2, 126.6, 129.3, 132.1, 137.0, 137.8, 153.5, 155.6, 178.8. HRMS for $C_{13}H_{12}O_3$: calcd 216.0786, found 216.0785.

3-(1-Hydroxy-3-methylbutyl)-4*H*-pyran-4-one (7e). Yellow syrup. IR (KBr, cm^{-1}): 3411, 1652. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.94−0.97 (6H, m), 1.49−1.55 (1H, m), 1.69−1.85 (2H, m), 3.50 (1H, br s), 4.58−4.63 (1H, m), 6.35 (1H, d, J = 5.7 Hz), 7.74 (1H, d, J = 5.7 Hz), 7.76 (1H, s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.6, 23.1, 24.4, 44.4, 66.8, 117.2, 131.7, 151.8, 155.2, 178.7. HRMS for $C_{10}H_{14}O_3$: calcd 182.0943, found 182.0939.

3-[Hydroxy(4-nitrophenyl)methyl]-4*H*-chromen-4-one (9a). Known compound.[13,23] Pale yellow solid. Mp: 186−187 °C (lit.[13] mp 186−187 °C). IR (KBr, cm^{-1}): 3390, 1627. ^1H NMR (DMSO, 300 MHz): δ 5.88 (1H, s), 6.26 (1H, d, J = 4.2 Hz), 7.45 (1H, t, J = 7.5 Hz), 7.63 (1H, d, J = 8.4 Hz), 7.70 (2H, d, J = 8.7 Hz), 7.78 (1H, J = 7.5, 8.4 Hz), 7.98 (1H, d, J = 7.5 Hz), 8.14 (2H, d, J = 8.7 Hz), 8.44 (1H, s). ^{13}C NMR (DMSO, 75 MHz): δ 67.0, 118.7, 123.5, 125.2, 125.8, 126.6, 128.1, 134.3, 134.6, 146.8, 151.5, 154.8, 156.1, 175.4. Anal. Calcd: C, 64.65; H, 3.73; N, 4.71. Found: C, 64.68; H, 3.75; N, 4.62.

3-[Hydroxy(3-nitrophenyl)methyl]-4*H*-chromen-4-one (9b). White solid. Mp: 134−136 °C. IR (KBr, cm^{-1}): 3379, 1627. ^1H NMR (DMSO, 300 MHz): δ 5.83 (1H, s), 6.20 (1H, d, J = 4.2 Hz), 7.39 (1H, t, J = 7.5 Hz), 7.49−7.59 (2H, m), 7.69−7.74 (1H, m), 7.82 (1H, d, J = 7.5 Hz), 7.91−7.94 (1H, m), 8.00−8.03 (1H, m), 8.22 (1H, m), 8.40 (1H, m). ^{13}C NMR (DMSO, 75 MHz): δ 67.1, 118.9, 121.7, 122.6, 123.7, 125.4, 126.0, 126.8, 130.0, 133.9, 134.8, 146.4, 148.0, 154.9, 156.3, 175.7. Anal. Calcd: C, 64.65; H, 3.73; N, 4.71. Found: C, 64.77; H, 3.73; N, 4.68.

3-[Hydroxy(2-nitrophenyl)methyl]-4*H*-chromen-4-one (9c). Known compound.[13,23] Pale yellow solid. Mp 148−149 °C (lit.[13] mp 150−152 °C). IR (KBr, cm^{-1}): 3381, 1638. ^1H NMR (DMSO, 300 MHz): δ 6.30 (1H, d, J = 4.8 Hz), 6.38 (1H, d, J = 4.2 Hz), 7.45−7.54 (2H, m), 7.64−7.73 (3H, m), 7.78−7.83 (1H, m), 7.88−7.92 (1H, m), 7.98−8.01 (1H, m), 8.26 (1H, s). ^{13}C NMR (DMSO, 75 MHz): δ 62.8, 118.9, 124.4, 125.4, 126.0, 126.6, 129.0, 129.7, 133.4, 134.8, 137.3, 148.9, 154.6, 156.3, 175.7. Anal. Calcd: C, 64.65; H, 3.73; N, 4.71. Found: C, 64.59; H, 3.72; N, 4.66.

3-(1-Hydroxy-3-methylbutyl)-4*H*-chromen-4-one (9d). Yellow syrup. IR (KBr, cm^{-1}): 3439, 1640. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.96−0.99 (6H, m), 1.58−1.62 (1H, m), 1.76−1.87 (1H, m), 3.50 (1H, br s), 4.73−4.77 (1H, m), 7.40−7.46 (2H, m), 7.64 (1H, t, J = 4.2 Hz), 7.89 (1H, s), 8.21 (1H, d, J = 8.1 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.8, 23.3, 24.7, 45.1, 67.3, 118.1, 123.9, 125.2, 125.6, 126.3, 133.8, 152.3, 156.3, 178.2. HRMS for $C_{14}H_{16}O_3$: calcd 232.1099, found 232.1100.

3-[Hydroxy-(4-nitrophenyl)methyl]-6-methyl-4*H*-chromen-4-one (11a). White solid. Mp: 198−199 °C. IR (KBr, cm^{-1}): 3387, 1630. ^1H NMR (DMSO, 300 MHz): δ 2.40 (3H, s), 5.90 (1H, s), 6.26 (1H, d, J = 4.2 Hz), 7.54−7.64 (2H, m), 7.72 (2H, d, J = 8.7 Hz), 7.79 (1H, s), 8.17 (2H, d, J = 8.7 Hz), 8.42 (1H, s). ^{13}C NMR (DMSO, 75 MHz): δ 20.9, 67.1, 118.7, 123.5, 123.7, 124.6, 126.7, 128.3, 135.6, 135.9, 147.0, 151.8, 154.6, 154.8, 175.5. Anal. Calcd: C, 65.59; H, 4.21; N, 4.50. Found: C, 65.55; H, 4.23; N, 4.40.

3-[Hydroxy-(3-nitrophenyl)methyl]-6-methyl-4*H*-chromen-4-one (11b). White solid. Mp: 153−154 °C. IR (KBr, cm^{-1}): 3377, 1627. ^1H NMR (DMSO, 300 MHz): δ 2.38 (3H, s), 5.91 (1H, s), 6.26 (1H, d, J = 4.5 Hz), 7.52−7.62 (3H, m), 7.78 (1H, s), 7.88 (1H, d, J = 7.5 Hz), 8.08 (1H, d, J = 7.5 Hz), 8.29 (1H, s), 8.44 (1H, s). ^{13}C NMR (DMSO, 75 MHz): δ 20.9, 67.1, 118.7, 121.6, 122.5, 123.4, 124.6, 126.7, 130.0, 133.8, 135.5, 135.8, 146.5, 148.0, 154.6, 154.7, 175.6. Anal. Calcd: C, 65.59; H, 4.21; N, 4.50. Found: C, 65.25; H, 4.15; N, 4.46.

3-[Hydroxy(2-nitrophenyl)methyl]-6-methyl-4*H*-chromen-4-one (11c). Pale yellow solid. Mp: 183−184 °C. IR (KBr, cm^{-1}): 3332, 1638. ^1H NMR (DMSO, 300 MHz): δ 2.36 (3H, s), 6.25 (1H, d, J = 4.2 Hz), 6.35 (1H, s), 7.45−7.52 (2H, m), 7.56−7.69 (3H, m), 7.74 (1H, s), 7.86 (1H, d, J = 8.1 Hz), 8.19 (1H, s). ^{13}C NMR (DMSO, 75 MHz): δ 19.4, 61.3, 117.2, 121.8, 122.9, 123.2, 125.0, 127.5, 128.2, 131.9, 134.1, 134.3, 136.0, 147.4, 152.9, 153.1, 174.1. Anal. Calcd: C, 65.59; H, 4.21; N, 4.50. Found: C, 65.52; H, 4.19; N, 4.46.

3-[Hydroxy(4-chlorophenyl)methyl]-6-methyl-4*H*-chromen-4-one (11d). White solid. Mp: 122−123 °C. IR (KBr, cm^{-1}): 3423, 1629. ^1H NMR ($CDCl_3$, 300 MHz): δ 2.46 (3H, s), 4.15 (1H, br s), 5.87 (1H, s), 7.34−7.52 (6H, m), 7.63 (1H, s), 7.99 (1H, s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.8, 69.9, 117.8, 123.4, 124.8, 125.7, 127.9, 128.6, 133.6, 135.3, 135.4, 139.2, 153.2, 154.6, 178.2. Anal. Calcd: C, 67.89; H, 4.36. Found: C, 67.55; H, 4.40.

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3-(Hydroxyphenylmethyl)-6-methyl-4*H*-chromen-4-one (11e). Pale yellow syrup. IR (KBr, cm^{-1}): 3424, 1642. ^1H NMR ($CDCl_3$, 300 MHz): δ 2.45 (3H, s), 3.10 (1H, br s), 5.92 (1H, s), 7.30−7.40 (4H, m), 7.47−7.49 (3H, m), 7.59 (1H, s), 7.99 (1H, s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.5, 69.0, 116.5, 122.0, 123.5, 124.7, 125.1, 126.5, 127.1, 133.6, 133.9, 139.2, 152.0, 153.2, 176.9. HRMS for $C_{17}H_{14}O_3$: calcd 266.0943, found 266.0937.

3-(1-Hydroxy-3-methylbutyl)-6-methyl-4*H*-chromen-4-one (11f). Pale yellow solid. Mp: 67−69 °C. IR (KBr, cm^{-1}): 3352, 1634. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.97−1.00 (6H, m), 1.58−1.65 (1H, m), 1.78−1.88 (2H, m), 2.46 (3H, s), 3.00 (1H, br s), 4.70−4.75 (1H, m), 7.34−7.51 (2H, AB peaks), 7.88 (1H, s), 7.99 (1H, s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.8, 21.7, 23.1, 24.6, 44.9, 67.3, 117.7, 123.5, 124.7, 125.8, 135.0, 151.9, 154.4, 178.2. Anal. Calcd: C, 73.15; H, 7.37. Found: C, 73.28; H, 7.33.

3-(4,4-Dimethyl-1-oxocyclopent-2-en-2-yl)-3-hydroxyindolin-2-one (12a). Orange powder. IR (KBr, cm^{-1}): 3427, 3300, 1729, 1688. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.22 (6H, s), 2.36 (2H, s), 6.90 (1H, d, J = 7.5 Hz), 7.05−7.08 (1H, m), 7.27−7.31 (3H, m), 8.18 (1H, br s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 27.8, 27.9, 39.3, 50.9, 75.0, 110.5, 123.3, 124.9, 129.4, 130.3, 140.6, 140.8, 140.9, 169.2, 207.8. HRMS for $C_{15}H_{15}N$ Na O_3 (M + Na): calcd 280.0950, found 280.0951.

3-Hydroxy-3-(4-oxo-4*H*-pyran-3-yl)indolin-2-one (12b). Yellow solid. IR (KBr, cm^{-1}): 3412, 3201, 1725, 1641. ^1H NMR (DMSO, 300 MHz): δ 6.19 (1H, d, J = 6.0 Hz), 6.50 (1H, br s), 6.79−6.87 (2H, m), 6.98−7.01 (1H, m), 7.15−7.21 (1H, m), 8.18 (1H, d, J = 6.0 Hz), 8.43 (1H, s), 10.36 (1H, s). ^{13}C NMR (DMSO, 75 MHz): δ 73.1, 109.4, 116.0, 121.2, 123.4, 129.2, 129.9, 130.8, 143.4, 154.5, 156.6, 175.1, 176.4. HRMS for $C_{13}H_{10}NO_4$ (M + 1): calcd 244.0604, found 244.0604.

3-Hydroxy-3-(4-oxo-4*H*-chromen-3-yl)-1indolin-2-one (12c). Brown solid. IR (KBr, cm^{-1}): 3437, 3243, 1705, 1645. ^1H NMR (DMSO, 300 MHz): δ 6.70 (1H, br s), 6.82−6.87 (2H, m), 7.05 (1H, d, J = 7.5 Hz), 7.21 (1H, t, J = 7.5 Hz), 7.47 (1H, t, J = 7.5 Hz), 7.70−7.73 (1H, m), 7.80−7.89 (2H, m), 8.63 (1H, s), 10.5 (1H, s). ^{13}C NMR (DMSO, 75 MHz): δ 70.9, 107.0, 116.0, 118.8, 120.4, 121.1, 122.1, 122.3, 123.1, 126.8, 128.8, 131.9, 140.9, 152.4, 153.4, 171.9, 174.3. HRMS for $C_{17}H_{11}NNaO_4$ (M + Na): calcd 316.0580, found 316.0579.

3-Hydroxy-3-(6-methyl-4-oxo-4*H*-chromen-3-yl)indolin-2-one (12d). Known compound.[13] Yellow solid. IR (KBr, cm^{-1}): 3381, 3264, 1702, 1637. ^1H NMR (DMSO, 300 MHz): δ 2.37 (3H, s), 6.68 (1H, s), 6.85 (2H, t, J = 7.2 and 7.5 Hz), 7.04 (1H, d, J = 7.2 Hz), 7.21 (1H, t, J = 7.5 Hz), 7.62−7.65 (3H, m), 8.59 (1H, s), 10.45 (1H, s). ^{13}C NMR (DMSO, 75 MHz): δ 19.6, 72.4, 108.6, 117.3, 120.3, 121.7, 122.6, 123.0, 123.4, 128.3, 130.4, 134.2, 134.5, 142.5, 153.2, 153.8, 173.5, 175.9. HRMS for $C_{18}H_{13}NNaO_4$ (M + Na): calcd 330.0737, found 330.0732.

(*Z*)-3-[2-(4-Nitrophenyl)vinyl]cyclohex-2-enone (18). Known compound.[24] Brown syrup. IR (KBr, cm^{-1}): 1657, 1594, 1513, 1341. ^1H NMR ($CDCl_3$, 300 MHz): δ 2.10−2.19 (2H, m), 2.49−2.53 (2H, m), 2.63−2.67 (2H, m), 6.17 (1H, s), 7.04 (2H, s), 7.63−7.67 (2H, m), 8.23−8.27 (2H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): d 22.2, 24.9, 37.7, 124.2, 127.7, 130.0, 132.4, 133.6, 142.2, 147.6, 155.8, 200.2. HRMS for $C_{14}H_{14}NO_3$ (M + 1): calcd 244.0968, found 244.0967.

3-[2-(4-Chlorophenyl)-2-hydroxyethyl]cyclohex-2-enone (19). Pale yellow syrup. IR (KBr, cm^{-1}): 3407, 1655. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.87−1.93 (2H, m), 2.21−2.29 (4H, m), 2.44−2.61 (3H, m), 4.83 (1H, m), 5.86 (1H, s), 7.20−7.27(4H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): d 22.6, 30.2, 37.2, 47.6, 71.8, 127.1, 128.0, 128.8, 133.7, 142.1, 162.4, 199.9. HRMS for $C_{14}H_{15}ClNaO_2$ (M + Na): calcd 273.0653, found 273.0658.

4-Hydroxy-3-methoxymethyl-4-(4-nitrophenyl)butan-2-one (21). Pale yellow syrup, inseparable *anti* and *syn* diastereoisomer mixture. IR (KBr, cm^{-1}): 3431, 1710, 1521, 1348. ^1H NMR ($CDCl_3$, 300 MHz): δ 2.16 (1.14H, minor, *syn* isomer, −C*H*$_3$), 2.21 (1.86H, major, *anti* isomer, −C*H*$_3$), 3.05−3.09 (1H, m), 3.26 (1.86H, major, *anti* isomer, −OC*H*$_3$), 3.31 (1.14H, minor, *syn* isomer, −OC*H*$_3$), 3.34−3.39 (1H, m), 3.49−3.54 (1H, m), 3.63−3.66 (1H, m), 5.14 (0.62H, *anti* isomer, −C*H*OH, d, J = 7.2 Hz), 5.26 (0.38H, *syn* isomer, −C*H*OH, d, J = 5.1 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): *anti* isomer, δ 31.4, 59.1, 59.2, 70.9, 71.9, 123.7, 127.2, 147.5, 149.3, 210.9; *syn* isomer, δ 31.1, 58.4, 59.2, 70.3, 72.5, 123.6, 126.9, 147.3, 149.1, 209.5. HRMS for $C_{12}H_{15}O_5NNa$ (M + Na): calcd 276.0842, found 276.0843.

1-Hydroxy-5-methoxy-1-(4-nitrophenyl)pentan-3-one (22). Known compound.[25]Yellow syrup. IR (KBr, cm^{-1}): 3433, 1710, 1520, 1348. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.60 (1H, br s), 2.70 (2H, t, J = 6.0 Hz), 2.86 (2H, d, J = 6.0 Hz), 3.33 (3H, s), 3.66 (2H, t, J = 6.0 Hz), 5.28 (1H, t, J = 6.0 Hz), 7.53 (2H, d, J = 8.7 Hz), 8.20 (2H, d, J = 8.7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 43.4, 51.6, 58.9, 67.4, 68.9, 123.9, 126.4, 147.3, 150.0, 209.3. HRMS for $C_{12}H_{16}O_5N$ (M + 1): calcd 254.1023, found 254.1025; for $C_{12}H_{15}O_5NNa$ (M + Na): calcd 276.0842, found 276.0842.

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Supporting Information Available: NMR spectra for all the new compounds and spectra data for the known compounds **14a**−**i**, **16a**−**f**, and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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