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A simple protocol for the synthesis of a piperidine-2,6-dione framework from Baylis–Hillman adducts

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ABSTRACT

3-Hydroxy-2-methylenealkanenitriles, the Baylis–Hillman alcohols, derived from various aldehydes and acrylonitrile, have been conveniently transformed into 3-arylidene(or alkylidene)piperidine-2,6-diones in an operationally simple one-pot multi-step process involving Johnson–Claisen (J–C) rearrangement, partial hydrolysis, and cyclization. Rearranged Baylis–Hillman alcohols, (*E*)-2-hydroxymethyl-3-aryl-prop-2-enenitriles, have been converted into 4-aryl-3-methylidenepiperidine-2,6-diones in a similar reaction sequence. 4-Aryl-3,5-dimethylidenepiperidine-2,6-dione derivatives have been synthesized from Baylis–Hillman compounds, 3-aryl-4-cyano-2-methoxycarbonylpenta-1,4-dienes, obtained via the Baylis–Hillman reaction of methyl (2*Z*)-2-(bromomethyl)-3-arylprop-2-enoates with acrylonitrile, in a one-pot process.

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The piperidine-2,6-dione framework is a prominent skeleton present in a number of biologically active and natural products such as thalidomide[1a] (sedative, drug to prevent morning sickness of pregnant women), (+)-migrastatin[1b,c] (antitumor agent), lactimidomycin[1d,e] (antibiotic), dorrigocins A and B[1f,g] (antifungal, antibiotic), NK30424 A and B[1h,i] [inhibitors of lipopolysaccharide (LPS)-induced tumor necrosis factor (TNF)-α promoter activity], streptimidone[1j,k] (antibiotic), and sesbanimide[1l,m] (antitumor). Therefore the development of simple and facile methodologies for the synthesis of piperidine-2,6-dione frameworks represents an attractive and challenging area in synthetic organic and medicinal chemistry.[2] As part of our on-going research program on the applications of Baylis–Hillman adducts in heterocyclic chemistry,[3] we herein report a facile transformation of the Baylis–Hillman (B–H) adducts (or rearranged B–H adducts) into substituted piperidine-2,6-dione derivatives in an operationally simple procedure.

The Baylis–Hillman reaction has become a powerful synthetic tool in organic chemistry for the preparation of densely functionalized molecules via the construction of carbon–carbon bonds in an operationally simple one-pot atom economical procedure.[4,5] These densely functionalized molecules usually known as Baylis–Hillman adducts have been systematically employed in various organic transformations and also in the synthesis of natural products and bioactive molecules.[4,5]

A few years ago, we reported an interesting methodology for the synthesis of functionalized alkenes, that is, ethyl (4*Z*)-4-cyanoalk-4-enoates [with exclusive (*Z*)-selectivity] via the J–C rearrangement[5s] of the 2-methylene-3-hydroxyalkanenitriles, the Baylis–Hillman alcohols. We felt that the presence of two interesting functionalities (ester and nitrile) in appropriate positions in ethyl (4*Z*)-4-cyanoalk-4-enoates would make these derivatives attractive synthons for obtaining piperidine-2,6-dione derivatives via the partial hydrolysis of the cyano group into the amide group followed by cyclization. Today the science of synthesis demands the development of operationally simple one-pot processes for obtaining important molecules of medicinal relevance. We have, therefore, directed our attention toward the development of one-pot processes for the synthesis of piperidine-2,6-dione derivatives starting from the Baylis–Hillman alcohols derived from acrylonitrile and aldehydes (see retro-synthetic strategy: Scheme 1). In this direction, our real task would be the selection of an appropriate reagent to transform the nitrile group into the amide group, thus leading to cyclization.

The literature survey reveals that a combination of $FeCl_3$/acetic acid has been used for the preparation of cyclic amides from ketonitriles and imides from the compounds containing the ester and nitrile moieties in appropriate positions.[6] Batra and co-workers[7] used the combination of $FeCl_3$/propanonic acid for the conversion of 2-methylidene-3-(cyanoethoxycarbonyl)methyl-3-arylpropanoates, derived from the corresponding Baylis–Hillman acetates, into 3-methylidene-2,5-piperidinedione derivatives in two steps.

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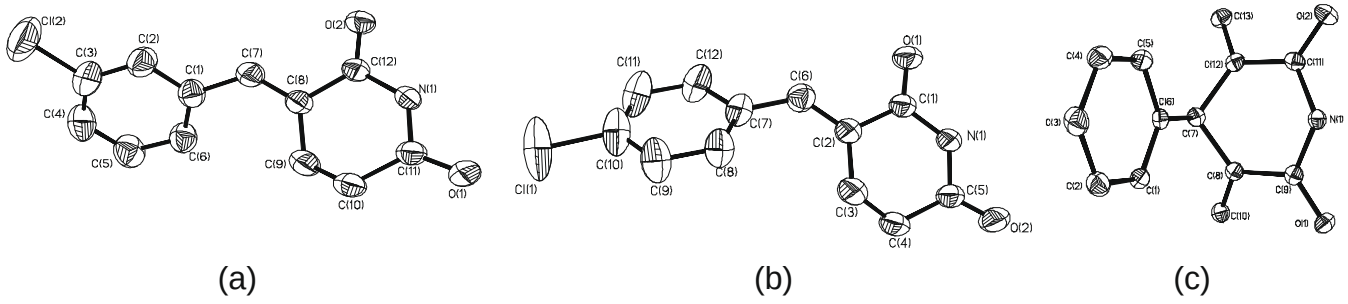
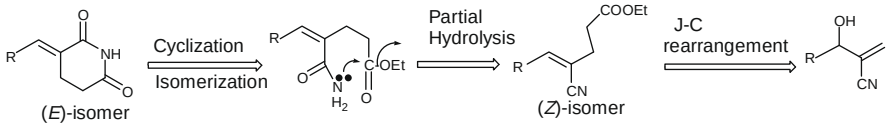


Figure 1. ORTEP diagrams of compounds (a) **2b**, (b) **2c**, and (c) **6a**[11] (hydrogen atoms were omitted for clarity).

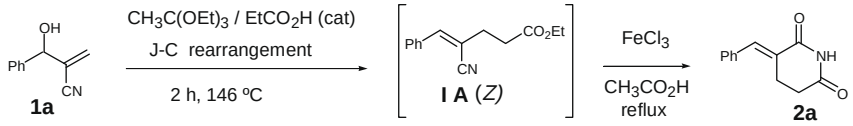


Scheme 1. Retro-synthetic strategy for the synthesis of 3-arylidene-(alkylidene)piperidine-2,6-dione framework.

Therefore it occurred to us that $FeCl_3$/acetic acid would serve as an appropriate reagent for the transformation of ethyl (4*Z*)-4-cyanoalk-4-enoates into a 3-benzylidenepiperidine-2,6-dione framework via selective hydrolysis and cyclization, in a one-pot process. We have thus first selected 3-hydroxy-2-methylene-3-phenylpropanoate (**1a**), the Baylis–Hillman alcohol obtained via the coupling of acrylonitrile and benzaldehyde, as a substrate for this purpose. In this direction, we have treated Baylis–Hillman alcohol **1a** (1 mmol) with triethyl orthoacetate (1 mL) at 146 °C in the presence of propanoic acid (3 drops) for 2 h. The excess orthoester and propanoic acid were removed under reduced pressure. The residue thus obtained was treated with anhydrous $FeCl_3$ (1 mmol) in acetic acid (5 mL) at reflux temperature for 10 h, to provide 3-benzylidenepiperidine-2,6-dione (**2a**) as a mixture of *E:Z* (78:22)[8] isomers as a colorless solid in 44% isolated yield, after work-up and purification by column chromatography (Scheme 1, Table 1, entry 1). It is indeed interesting to note that the (*Z*)-stereochemistry in the key intermediate **(IA)** has been converted into (*E*)-stereochemistry in the final product. It occurred to us that increasing the amounts of $FeCl_3$ might result in the total isomerization of the (*Z*)-double bond of the key intermediate into an (*E*)-double bond in the product. We have therefore conducted a number of experiments with increasing quantities of $FeCl_3$ to understand this aspect (Table 1). From Table 1, it is indeed, quite clear that the amount of $FeCl_3$ directs the fate of the stereochemistry of the product and we were pleased to note that $FeCl_3$ (5 mmol) (for 1 mmol of the Baylis–Hillman alcohol) provides 100% (*E*)-stereoselectivity.[8,9] Another interesting point in this strategy is that four steps (orthoester rearrangement, partial hydrolysis of the cyano group, cyclization, and isomerization) were performed in an operationally simple one-pot to produce 3-benzylidenepiperidine-2,6-dione (**2a**) with (*E*)-selectivity in good yields.

With a view to understanding the generality of this reaction, we subjected representative Baylis–Hillman alcohols (**1b–g**), obtained via the reaction of acrylonitrile with various aldehydes, to this reaction strategy to provide (*E*)-3-arylidene (or alkylidene)piperidine-2,6-diones (**2b–g**) in 67-81% isolated yields (Scheme 1, Table 2). In order to extend the possibility of this strategy for obtaining more substituted imide derivatives, we performed the J–C rearrangement of the Baylis–Hillman alcohols **1a** and **1e** with triethyl orthopropanoate and then treated the in situ generated products with $FeCl_3$/acetic acid for 10 h under reflux to provide the compounds (*E*)-3-benzylidene-5-methylpiperidine-2,6-dione (**2h**) and (*E*)-3-(3-phenylpropylidene)-5-methylpiperidine-2,6-dione (**2i**) in 76% and 67% isolated yields, respectively (Table 2, entries 8 and 9). The structures of the compounds **2b** and **2c** were further confirmed by single crystal X-ray data.[11]

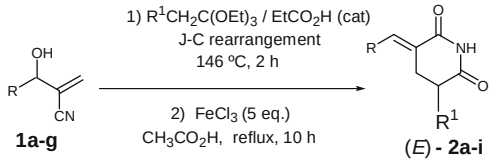
Table 1
Standardization of reaction conditions[a]



Entry	$FeCl_3$ (mmol)	Time (h)	**2a** (*E:Z*)[8]	Yield [b,c] **2a** (%)
1	1	10	78:22	44
2	2	10	82:18	80
3	3	10	91:09	82
4	4	10	96:04	81
5	5	02	65:35	45
6	5	04	88:12	60
7	5	06	92:08	70
8	5	08	96:04	82
9	**5**	**10**	**100:00**	**84**

[a] All reactions were carried out on a 1 mmol scale of B–H alcohol (**1a**).
[b] The compound **2a** was obtained as a colorless solid and fully characterized.
[c] Isolated yields based on B–H alcohols.

Table 2
Synthesis of (*E*)-3-arylidene(alkylidene)piperidine-2,6-diones (**2a–i**) from Baylis–Hillman alcohols (**1a–g**)[a]



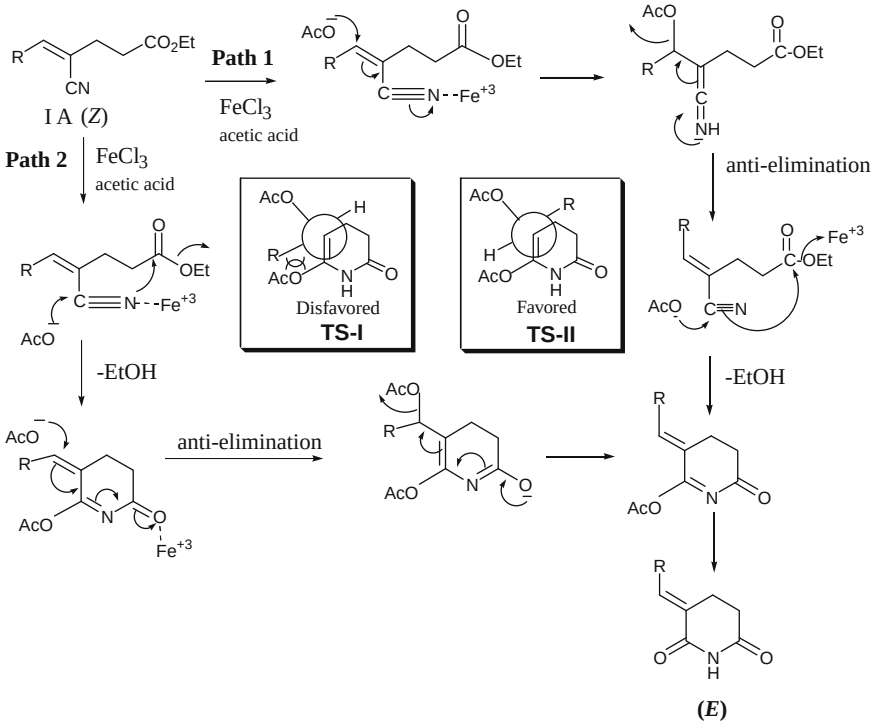
Entry	B–H alcohol	R	R^1	Product[b]	Yield[c] (%)
1	**1a**	C_6H_5	H	**2a**[9,10]	84
2	**1b**	3-ClC_6H_4	H	**2b**[d]	67
3	**1c**	4-ClC_6H_4	H	**2c**[d]	71
4	**1d**	4-MeC_6H_4	H	**2d**	77
5	**1e**	$C_6H_5CH_2CH_2$	H	**2e**	73
6	**1f**	C_7H_{15}	H	**2f**	75
7	**1g**	C_5H_{11}	H	**2g**	81
8	**1a**	C_6H_5	CH_3	**2h**	76
9	**1b**	$C_6H_5CH_2CH_2$	CH_3	**2i**	67

[a] All reactions were carried out on a 1 mmol scale of B–H alcohols (**1a–g**).
[b] All the compounds (**2a–i**) were obtained as colorless solids and fully characterized and the *E*-stereochemistry was assigned on the basis of ^{1}H NMR spectral analysis.[8]
[c] Isolated yields based on B–H alcohols.
[d] Structures of these molecules were also confirmed by single crystal X-ray data (Fig. 1).[11]

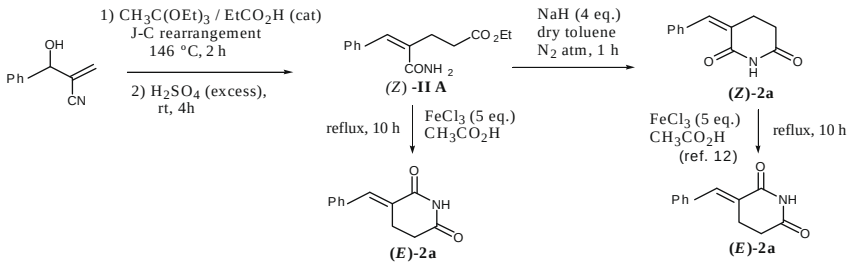
A possible mechanism for the interesting reversal of (*Z*)-stereochemistry in the key intermediate (**IA**) (J-C rearrangement product) into (*E*)-stereochemistry in the final product (imide) is presented in Scheme 2. $FeCl_3$ might first coordinate with the nitrogen of the nitrile group thus making its carbon more electrophilic. Then acetate ion might add on to the ene-nitrile via the 1,4-fashion first and then 1,2-fashion (**Path 1**) leading to the formation of an imide ring. Subsequent anti-elimination of the acetate might then give (*E*)-imide. Alternatively the acetate ion might add first in 1,2-fashion on to the ene-nitrile leading to the formation of (*Z*)-imide and then 1,4 addition of the acetate ion on the (*Z*)-imide (**Path 2**) followed by subsequent anti-elimination might provide (*E*)-imide. In order to understand the possibility of (*Z*)-imide [(***Z***)-**2a**] converting into (*E*)-imide we have prepared (*Z*)-3-benzylidenepiperidine-2,6-dione [(***Z***)-**2a** imide] via the treatment of the in situ generated (4*Z*)-4-cyano-5-phenylpent-4-enoate (**IA**) (the J–C rearrangement product) with H_2SO_4 [to provide-**IIA** amide (isolated)] followed by subsequent cyclization using NaH. The treatment of (***Z***)-**2a** (imide) with $FeCl_3$/acetic acid under reflux for 10 h provided (*E*)-3-benzylidenepiperidine-2,6-dione [(***E***)-**2a**] (probably thermodynamically more stable product[12]) (Scheme 3). We have also observed that the reaction of (4*Z*)-4-aminocarbonyl-5-phenylpent-4-enoate (**IIA**) with $FeCl_3$/acetic acid at reflux temperature for 10 h directly provided (*E*)-3-benzylidenepiperidine-2,6-dione [(***E***)-**2a**] (Scheme 3). These experiments, to some extent, demonstrate that the change of (*Z*)-stereochemistry into (*E*)-stereochemistry might be either due to the Michael addition of the acetate ion onto the (*Z*)-ene-nitrile or on to the (*Z*)-ene-imide[12] onto in situ formed (*Z*)-ene-amide followed by anti-elimination (Transition state models: **TS-I** and **TS-II**).

With a view to providing a simple method for the synthesis of 4-aryl-3-methylidenepiperidine-2,6-dione derivatives, we subjected the rearranged Baylis–Hillman alcohols, (2*E*)-2-cyano-3-arylprop-2-en-1-ols[5r] (**3a–d**) (which were obtained from 3-hydroxy-2-methylene-3-arylpropionitriles via the treatment with 20% aq H_2SO_4 at reflux temperature for 2 h) to this strategy (the J–C rearrangement followed by partial hydrolysis and cyclization). The resulting products, 4-aryl-3-methylidenepiperidine-2,6-dione (**4a–d**) (Table 3, entries 1–4), were obtained in 64–70% isolated yields.

We have recently developed a simple methodology for the preparation of 4-cyano-2-methoxycarbonyl-3-arylpenta-1,4-dienes[5p] via the reaction of the Baylis–Hillman allyl bromides, that is, methyl (2*Z*)-2-(bromomethyl)-3-arylprop-2-enoates with acrylonitrile in the presence of DABCO. It occurred to us that these molecules might be appropriate starting materials for obtaining 4-aryl-3,5-dimethylidenepiperidine-2,6-dione derivatives. Accordingly we have subjected a representative class of Baylis–Hillman prod-

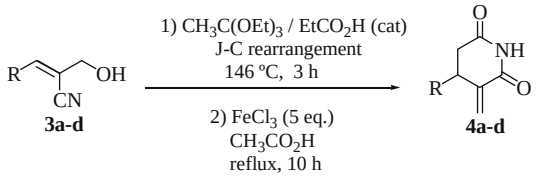


Scheme 2. A plausible mechanism for the formation of the (*E*)-3-arylidene(alkylidene)piperidine-2,6-dione framework.



Scheme 3. Conversion of (*Z*)-imide into (*E*)-imide and (Z)-amide into (*E*)-imide using $FeCl_3/CH_3CO_2H$.

Table 3
One-pot multi-step synthesis of 3-methylidene-4-arylpiperidine-2,6-diones (**4a–d**) from rearranged Baylis–Hillman alcohols (**3a–d**)[a]



Entry	B–H rearranged alcohol	R	Product[b]	Yield[c](%)
1	**3a**	C_6H_5	**4a**	63
2	**3b**	2-MeC_6H_4	**4b**	70
3	**3c**	4-MeC_6H_4	**4c**[10]	67
4	**3d**	4-$^iPrC_6H_4$	**4d**	64

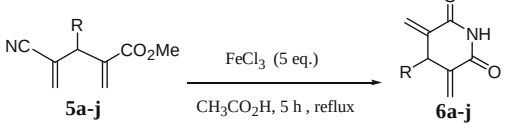
[a] All reactions were carried out on a 1 mmol scale of rearranged B–H alcohols (**3a–d**).
[b] All the compounds (**4a–d**) were obtained as colorless solids and fully characterized.
[c] Isolated yields based on rearranged B–H alcohols.

ucts, 4-cyano-2-methoxycarbonyl-3-arylpenta-1,4-dienes (**5a–j**) to this reaction strategy to provide 4-aryl-3,5-dimethylidene-piperidine-2,6-dione derivatives in 61–86% isolated yields (Table 4, entries 1–10).

It is worth mentioning here that Kim and co-workers[6a,13] reported the synthesis of 3,5-dimethylidene-4-phenylpiperidine-2,6-dione and 3,5-dimethylidenepiperidine-2,6-dione (two examples) from the corresponding Baylis–Hillman products in two steps (via the treatment with sulfuric acid and followed by the treatment of the resulting amides with sodium bicarbonate in aqueous methanol). Our results clearly indicate that our one-pot procedure using $FeCl_3$/acetic acid offers better results than the two-step process mentioned above.

In conclusion, we have developed a convenient and simple one-pot multi-step procedure for the synthesis of (*E*)-3-arylidene(or alkylidene)piperidine-2,6-diones, 4-aryl-3-methylidenepiperidine-2,6-diones, and 4-aryl-3,5-dimethylidenepiperidine-2,6-diones thus demonstrating the importance of Baylis–Hillman adducts in organic synthesis.

Table 4
Synthesis of 4-aryl-3,5-dimethylidenepiperidine-2,6-dione (**6a–j**) from Baylis–Hillman compounds (**5a–j**) [a]



Entry	Substrate	R	Product[b]	Yield[c] (%)
1	**5a**	C_6H_5	**6a**[d,10]	82
2	**5b**	3-ClC_6H_4	**6b**	80
3	**5c**	3-BrC_6H_4	**6c**	86
4	**5d**	3-$OMeC_6H_4$	**6d**	61
5	**5e**	4-ClC_6H_4	**6e**	75
6	**5f**	4-BrC_6H_4	**6f**	76
7	**5g**	4-$OMeC_6H_4$	**6g**	63
8	**5h**	4-MeC_6H_4	**6h**	85
9	**5i**	4-EtC_6H_4	**6i**	70
10	**5j**	4-$^iPrC_6H_4$	**6j**	84

[a] All reactions were carried out on a 1 mmol scale of B–H compounds (**5a–j**).
[b] All the products (**6a–j**) were obtained as colorless solids and fully characterized.
[c] Isolated yields based on B–H products.
[d] The structure of this molecule was also confirmed by single crystal X-ray data (Fig. 1).[11,14]

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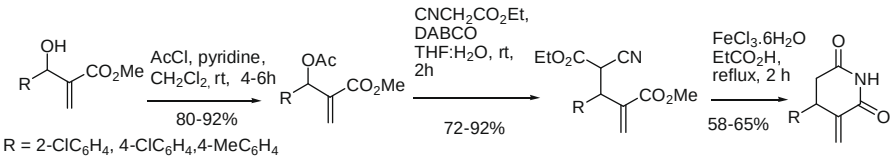
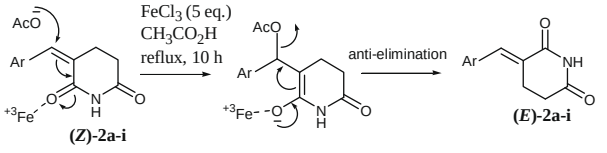
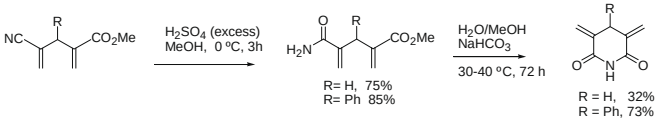
7. Batra prepared three 4-aryl-3-methylidenepiperidine-2,6-dione derivatives following the procedure given below (Ref.: Singh, V.; Yadav, G. P.; Maulik, P. R.; Batra, S. *Tetrahedron* **2006**, *62*, 8731–8739).



8. It has been well known in the literature that in the ^{1}H NMR spectrum of the trisubstituted alkenes the chemical shifts of the vinylic β-protons cis to the carbonyl (ketone, ester, acid, and amide) group and those of the corresponding vinylic β-protons trans to the carbonyl group are well differentiated. The vinylic β-protons cis to the carbonyl group appear downfield in comparison with that of trans β-protons. [see Ref: (a) Jackman, L. M.; Sternhell, S. *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, 2nd ed., Pergamon: Oxford, 1969; Vol. 5. (b) Tobey, S. W. *J. Org. Chem.* **1969**, *34*, 1281]. In the case of compound **2a** (R = Phenyl) the *E*:*Z* ratio was determined by the integration values of the singlets at δ 7.90 [vinylic β-protons cis to the carbonyl group (*E*-alkene) and δ 6.97 [vinylic β-protons trans to the carbonyl group (*Z*-alkene)]. In the case of **2a**–**d**, **h** (R = aryl) vinylic β-protons appeared at ~δ 7.86 (as a singlet) while in the case of **2e**–**g**, **i** (R = alkyl or 2-phenylethyl) vinylic β-protons appeared at ~δ 7.01 (as triplets).
9. *Representative procedure*: Synthesis of (*E*)-3-benzylidene-piperidine-2,6-dione (**2a**): To a stirred solution of 3-hydroxy-2-methylene-3-phenylpropanenitrile (**1a**, 1 mmol, 0.159 g) in triethyl orthoacetate (1 mL), propanoic acid (3 drops) was added and the reaction mixture was heated at 146 °C for 2 h. The reaction mixture was cooled to room temperature and the excess orthoester and propanoic acid were distilled off under reduced pressure. The residue, thus obtained, was dissolved in acetic acid (5 mL). Anhydrous $FeCl_3$ (5 mmol, 0.812 g) was added and the reaction mixture was heated under reflux for 10 h. Then the reaction mixture was cooled to room temperature and acetic acid was removed under reduced pressure. The residue was dissolved in dichloromethane (5 mL) and poured into aqueous 4 N HCl (5 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic layer was washed successively with saturated $NaHCO_3$ solution, water, and dried over anhydrous Na_2SO_4. The solvent was removed and the residue was purified by column chromatography (silica gel, 35% ethyl acetate in hexanes) to provide (*E*)-3-benzylidenepiperidine-2,6-dione (**2a**) as a colorless solid (0.169 g) in 84% yield. Mp: 198–200 °C, (Lit.[2f,10] 209–210 °C) IR (KBr): *ν* 3200–2900 (multiple bands), 1730, 1691, 1624 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.64 (t, 2H, *J* = 6.8 Hz), 2.98–3.06 (m, 2H)*, 7.37–7.50 (m, 5H), 7.90 (s, 1H), 8.03 (br s, 1H); ^{13}C NMR (100 MHz, 20% DMSO-d_6 in $CDCl_3$): δ 21.30, 30.29, 126.21, 127.43, 127.86, 128.55, 133.53, 137.26, 166.00, 171.37; LC–MS (*m*/*z*): 200 $(M-H)^-$, Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.69; H, 5.56; N, 6.92. (* *This multiplet almost looks like an unresolved dd*).
10. These compounds are known in the literature. Spectral data are reported. Our spectral data are in agreement with those of the literature (for **2a** see Ref. 2d,f, for **4c** see Ref. 7, for **6a** see Ref. 6a).
11. Detailed X-ray crystallographic data are available from the CCDC, 12 Union road, Cambridge CB2 1EZ, UK for compounds **2b** (CCDC #689771), **2c** (CCDC #689772), **6a** (CCDC #689773).
12. The plausible mechanism for the conversion of (*Z*)-imide into thermodynamically more stable (*E*)-imide is shown below.



13. Kim's two-step procedure: two examples only reported (Ref: see 6a).



14. The single crystal revealed the presence of two molecules in the asymmetric unit. For clarity we have shown one molecule in the ORTEP diagram.