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Stereodivergent *Baylis-Hillman* Reaction of a Chiral Acryloyl Imide Exploiting Ion-Chelation Effect: Mechanistic Insight on the Rearrangement of Trichloroacetimidates of the *Baylis-Hillman* Adducts to Trichloroacetamides

Eleonora Marcucci, Gianluca Martelli, Mario Orena*, and **Samuele Rinaldi**

Dipartimento di Scienze dei Materiali e della Terra, Università Politecnica delle Marche, Via Brecce Bianche, Ancona, Italy

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Summary. In the presence of *DABCO*, ethyl glyoxalate and (4*S*,5*R*)-1,5-dimethyl-3-acryloyl-4-phenylimidazolidin-2-one gave mixtures of the corresponding *Baylis-Hillman* adducts enriched in either isomer, depending on the absence or the presence of $LiClO_4$ in the reaction mixture. A diastereomeric mixture in 10:90 *dr* allowed to definitively establish the mechanism of the reaction leading to trichloroacetamides starting from trichloroacetimidates of the *Baylis-Hillman* adducts.

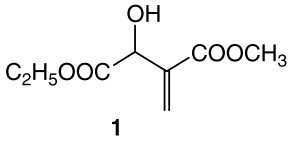
Keywords. Stereoselection; Chiral imide; Chelation; *Baylis-Hillman*; Rearrangement.

Introduction

Recently, we were involved in a programme dealing with the preparation of non-proteinogenic amino acids having conformational restrictions starting from *Baylis-Hillman* adducts [1], and we directed our attention towards adduct **1**, which allowed us to prepare (*R*,*S*)-β-methyleneaspartic acid [2, 3].

This product was also a key synthetic intermediate for both 3-hydroxy-[4a] and 3-aminopyrrolidin-2-ones [4b, c] in enantiomerically pure form after separation of equimolar diastereomeric mixtures of compounds bearing (*S*)-phenylethylamine as the chiral inductor. However, we considered it to be more useful to have in hands the enantiomerically pure form of **1** or an appropriate derivative, in order to avoid

* Corresponding author. E-mail: m.orena@univpm.it



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Scheme 1

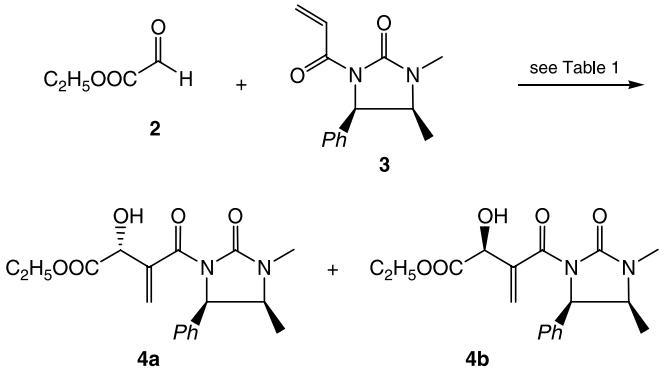
the use of chiral inductors such as the phenylethyl group, requiring relatively harsh conditions for cleavage.

Results and Discussion

A useful starting material for our goal could be the chiral imide **3** [5], where the acryloyl moiety bears (4*R*,5*S*)-3,4-dimethyl-5-phenyl-1,3-imidazolidin-2-one, an easily removable chiral auxiliary effective for the formation of stereogenic centres with high asymmetric induction [6, 7].

Thus, a series of reactions between ethyl glyoxalate (**2**) and imide **3** in the presence of *DABCO* were carried out under different conditions (Scheme 2, Table 1), and the highest diastereoselection was achieved by using *DMSO* as the solvent. In fact, the diastereomeric *Baylis-Hillman* adducts **4a** and **4b** were obtained in 85:15 diastereomeric ratio (*dr*), as evidenced by well defined ^{1}H ad ^{13}C NMR peak patterns of the reaction mixture which, however, was inseparable by column chromatography. On the other hand, we were pleased to observe that simply by adding a *Lewis* acid (*L*A) such $LiClO_4$ to the reaction mixture, a reversal of the diastereoselection occurred [8, 9]. In fact, when the reaction was carried out in *DCM* in the presence of 1 equiv. $LiClO_4$, the *Baylis-Hillman* adducts **4a** and **4b** were obtained in 10:90 *dr*, which significantly decreased on decreasing the amount of *L*A (Table 1) [10].

Such divergent reactivity patterns can be explained considering the conformational changes of the imide **3** both in the absence and in the presence of a *L*A, and it appears that the reaction outcome strongly relies upon conformational and configurational constraints. In fact, in the absence of a *L*A *DMSO* favors the conformation of the chiral imide **3** in which the carbonyl groups lie *anti* to each



2 3 4a 4b

Scheme 2

Table 1. The *Baylis-Hillman* reaction leading to diastereomeric adducts **4a** and **4b**[a]

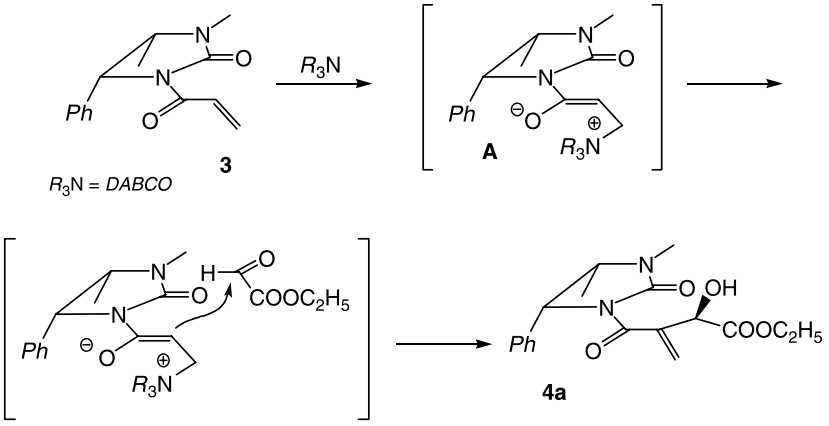
DABCO (mol%)	*L*A (mol%)	solvent	*t*/°C	yield/% (*dr* **4a**:**4b**)
30	–	*DCM*	0	58 (70:30)
50	–	*DCM*	rt	51 (80:20)
50	–	*DMSO*	rt	68 (85:15)
50	$LiClO_4$ (30)	*DCM*	0	52 (30:70)
50	$LiClO_4$ (30)	*DCM*	−18	68 (30:70)
50	$LiClO_4$ (50)	*DCM*	−18	66 (30:70)
50	$LiClO_4$ (100)	*DCM*	0	67 (10:90)
50	$Hg(CF_3COO)_2$ (50)	*DCM*	0	–[b]
50	LiBr (50)	*DCM*	0	–[b]
60	$Mg(ClO_4)_2$ (50)	*DCM*	rt	53 (40:60)

[a] Reactions carried out for 12 h by using 2.0 mmol of **2** and 1.0 mmol of **3**; both *DABCO* and *L*A amounts were referred to **3**; [b] no reaction

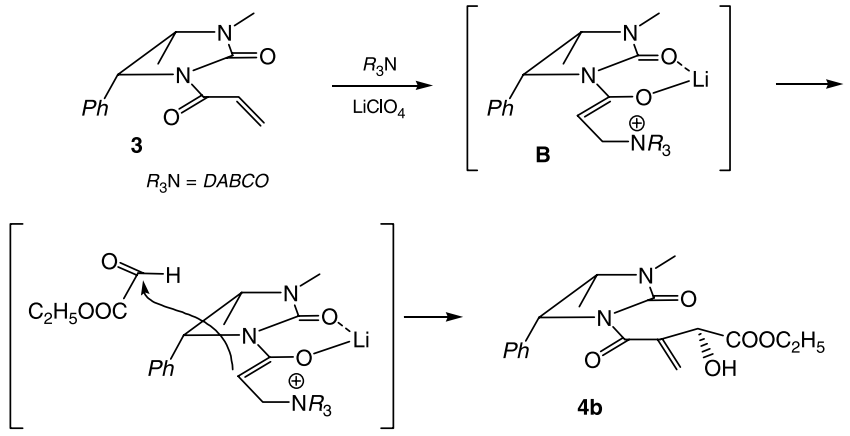
other, owing to its best solvating effect. Then, the control element influencing the stereochemical outcome is minimization of the steric interactions, and the attack of the enolate anion **A** to the aldehyde **2** occurs preferentially on the less hindered face of the imidazolidin-2-one ring, the aldehydic hydrogen being oriented towards the imidazolidinone ring. According to this mechanistic pathway, diastereomer **4a** must be the major product of the *Baylis-Hillman* reaction (Scheme 3).

On the contrary, the dramatic reversal of the diastereoface selectivity observed when a *L*A, such as $LiClO_4$, is present in the reaction mixture strongly supports the presence of the chelated intermediate **B** in which the carbonyl groups of the imide **3** are biased to lie *syn* (Scheme 4). In agreement with this hypothesis the adduct **4b** is the major product recovered from the reaction, arising from the attack of the enolate anion **B** to the aldehyde **2** (Scheme 4).

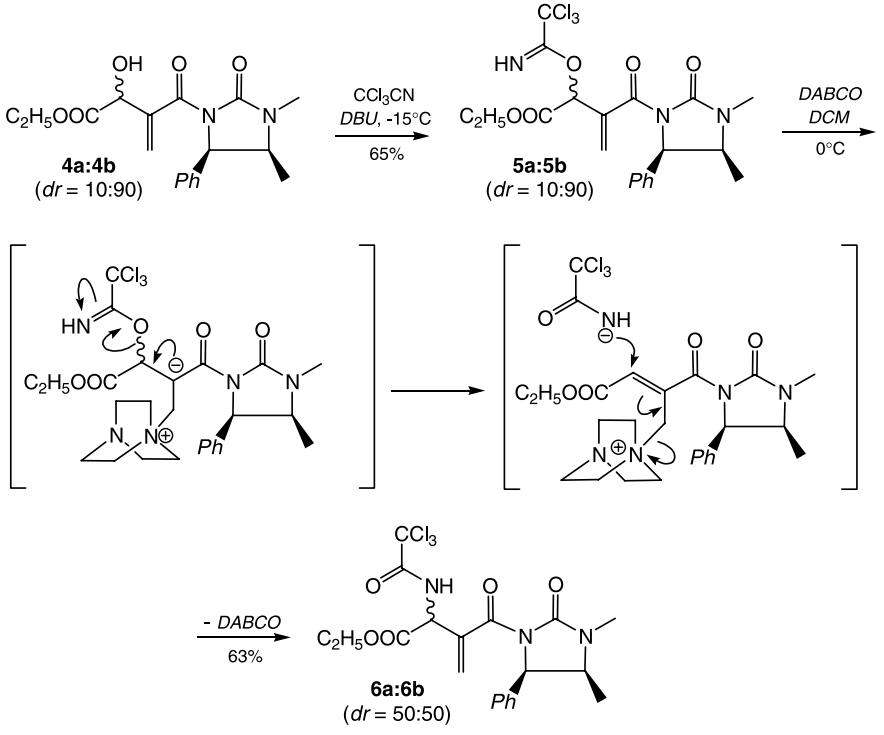
It is worth noting however, that $LiClO_4$ only was able to give a significant reversal of stereochemical outcome of the reaction. It changed only slightly in the presence of $MgClO_4$, whereas no conversion was observed when both $Hg(CF_3COO)_2$ or LiBr were used (Table 1) [10].



Scheme 3



Scheme 4



Scheme 5

Having in hands enriched diastereomeric mixtures of **4a** and **4b**, we thought that such a mixture could allow us to definitively ascertain the mechanism of the conversion of trichloroacetimidates of the *Baylis-Hillman* adducts into the corresponding trichloroacetamides we recently reported (Scheme 5) [1b]. According to our proposal, the conversion of trichloroacetimidate **5** [11] into trichloroacetylamino derivative **6** involves two subsequent, concerted S_N' reactions. In fact,

DABCO attacks first the conjugate double bond, and the process is concluded by the eventual removal of the *DABCO*, that acts as catalyst (Scheme 5) [1b].

A four-center, concerted mechanism [1b], which would proceed with inversion at the C-3 center, can be definitively excluded and a two-steps mechanism seems to be the sole occurring. In fact, the diastereomeric mixture 10:90 of the *Baylis-Hillman* adducts **4a** and **4b** was converted into a mixture of trichloroacetimidates **5a** and **5b** in 10:90 ratio (Scheme 5). By subsequent treatment with *DABCO* an equimolar diastereomeric mixture of the trichloroacetylamino derivatives **6a** and **6b** was obtained. Since the conjugate addition cannot proceed with asymmetric induction, the imidazolidin-2-one chiral auxiliary is not able to discriminate far from its stereogenic centres when an appropriate *Lewis* acid is missing [12]. This allows to discard the mechanism involving a four-centers transition state proceeding with inversion, which would give **6a** and **6b** as a 90:10 diastereomeric mixture.

In conclusion, starting from the chiral imide **3** we obtained in a stereodivergent mode mixtures of *Baylis-Hillman* adducts **4a** and **4b**, and to the best of our knowledge, this is the first case for a *Baylis-Hillman* reaction leading to a diastereomeric adduct where either isomer is prevalent depending on the absence or the presence of chelation effect. Starting from these mixtures the preparation of enantiomerically pure bioactive pyrrolidin-2-ones and pyrrolidines bearing both hydroxy and amino functionalities can be carried out after appropriate separation, and work towards this goal is currently underway in our laboratory.

Experimental

NMR spectra (200 MHz for ^{1}H, 50 MHz for ^{13}C, chemical shifts as ppm in the δ scale, coupling constants J in Hertz) were recorded at 25°C on a Varian Gemini 200 spectrometer. Optical rotations were measured on a Perkin Elmer 341 polarimeter. The samples were analyzed with a liquid chromatography Agilent Technologies HP1100 equipped with a Zorbax Eclipse XDB-C8 Agilent and Technologies column (flow rate 0.5 cm^3/min) and equipped with a diode-array UV detector (220 and 254 nm). Acetonitrile and methanol for HPLC were purchased from a commercial supplier. All the samples were prepared by diluting 1 mg in 5 cm^3 of a 1:1 mixture of H_2O and acetonitrile in pure acetonitrile or in pure methanol. The MSD1100 mass detector was utilized under the following conditions: mass range 100–2500 amu, positive scanning, energy of fragmentor 50 V, drying gas flow (N_2) 10.0 cm^3/min, nebulizer pressure 310 kPa, drying gas temperature 350°C, capillary voltage 4500 V. Elemental analyses (C, H, N) were conducted using a Carlo Erba 1106 elemental analyser, and their results were found to be in good agreement (±0.2%) with the calculated values. Column chromatography was performed using Kieselgel 60 Merck.

(4S,5R)-1,5-Dimethyl-3-acryloyl-4-phenylimidazolidin-2-one (**3**, $C_{14}H_{16}N_2O_2$)
The title compound was obtained as a solid (96%) following the procedure reported in Ref. [5b]; mp 138–140°C (Ref. [5b] 135–140°C); ^{1}H NMR and ^{13}C NMR spectra were found to be identical with the one described in Ref. [5]; $[\alpha]_D = -100.1°\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.0$, $CHCl_3$); ESI-MS: $m/z = 244.1$ $[M]^+$, 267.2 $[M + Na]^+$.

(4S,5R,3′R)-(3′-Ethoxycarbonyl-3′-hydroxy-2′-methylenepropanoyl)-3,4-dimethyl-5-phenylimidazolidin-2-one and its (4S,5R,3′S)-isomer (**4a** and **4b**, $C_{18}H_{22}N_2O_5$)
A solution containing 244 mg **3** (1.0 mmol) and 400 mg **2** (50% solution in toluene, 2.0 mmol), dissolved in 4 cm^3 solvent (see Table 1), in the absence or in the presence of the appropriate

Lewis acid (*L*A) (see Table 1) was stirred for 15 min at the temperature reported in Table 1. Then *DABCO* was added (see Table 1) and the mixture was stirred at the same temperature for a further 12 h. After dilution with 20 cm^3 ethyl acetate, the organic layer was washed first with 5 cm^3 0.5 *M* HCl and then with 30 cm^3 brine. After drying (Na_2SO_4) the solvent was removed under reduced pressure and the residue was purified by silica gel chromatography to give an inseparable mixture of **4a** and **4b** as a colorless oil (for yields and *dr* see Table 1). ESI-MS: $m/z = 346.2$ $[M]^+$, 369.2 $[M + Na]^+$.

4a: ^{1}H NMR (200 MHz, $CHCl_3$): $\delta = 0.82$ (d, $J = 6.5$ Hz, CH–C*H*$_3$), 1.22 (t, $J = 7.2$ Hz, CH_2CH_3), 2.75 (br s, O*H*), 2.84 (s, N–C*H*$_3$), 3.94 (dq, $J = 6.5$ Hz, $J = 8.4$ Hz, C*H*–CH_3), 4.21 (q, $J = 7.2$ Hz, CH_2CH_3), 5.01 (s, C*H*OH), 5.26 (d, $J = 8.4$ Hz, *Ph*–C*H*), 5.47 (s, C=C*H*$_2$), 5.69 (d, $J = 1.3$ Hz, C=C*H*$_2$), 7.18–7.42 (m, Ar*H*) ppm; ^{13}C NMR (50 MHz, $CHCl_3$): $\delta = 13.8$, 14.6, 27.8, 54.0, 59.7, 61.6, 71.4, 119.2, 126.6, 128.1, 135.8, 142.5, 155.0, 167.0, 171.2 ppm.

4b: ^{1}H NMR (200 MHz, $CHCl_3$): $\delta = 0.82$ (d, $J = 6.5$ Hz, CH–C*H*$_3$), 1.07 (t, $J = 7.2$ Hz, CH_2CH_3), 2.75 (br s, O*H*), 2.84 (s, N–C*H*), 3.97 (dq, $J = 6.5$, 8.4 Hz, C*H*–CH_3), 4.11 (q, $J = 7.2$ Hz, CH_2CH_3), 5.04 (s, C*H*OH), 5.43 (d, $J = 8.4$ Hz, *Ph*–C*H*), 5.53 (s, C=C*H*$_2$), 5.76 (d, $J = 1.3$ Hz, C=C*H*$_2$), 7.18–7.42 (m, Ar*H*) ppm; ^{13}C NMR (50 MHz, $CHCl_3$): $\delta = 13.6$, 15.0, 28.1, 54.0, 58.7, 59.7, 71.1, 119.0, 126.9, 135.8, 142.8, 155.0, 167.0, 171.3 ppm.

(4S,5R,3′R)-(3′-Trichloroacetiminoxy-3′-hydroxy-2′-methylenepropanoyl)-3,4-dimethyl-5-phenylimidazolidin-2-one and its (4S,5R,3′S)-isomer (**5a** and **5b**, $C_{20}H_{22}Cl_3N_3O_5$)

To 490 mg of a mixture of *Baylis-Hillman* adducts **4a** and **4b** (1.0 mmol, *dr* = 10:90) dissolved in 0.5 cm^3 CCl_3CN, 0.2 cm^3 *DBU* were directly added (1 mm^3/s) under vigorous stirring. After 0.5 h the brown oil was directly purified by silica gel chromatography (cyclohexane:*DCM* = 30:70) and 318 mg of an inseparable mixture of diastereomeric trichloroacetimidates **5a** and **5b** (65%, *dr* = 10:90) was obtained as a colorless oil. ESI-MS: $m/z = 489.1$ $[M]^+$, 491.1 $[M + 2]^+$, 512.2 $[M + Na]^+$, 514.2 $[M + 2 + Na]^+$.

5a: ^{1}H NMR (200 MHz, $CHCl_3$): $\delta = 0.82$ (d, $J = 6.6$ Hz, CH–C*H*$_3$), 1.26 (t, $J = 7.2$ Hz, CH_2CH_3), 2.82 (s, N–C*H*$_3$), 3.98 (dq, $J = 6.6$, 8.1 Hz, C*H*–CH_3), 4.24 (q, $J = 7.2$ Hz, CH_2CH_3), 5.28 (d, $J = 8.1$ Hz, *Ph*–C*H*), 5.62 (s, C=C*H*$_2$), 5.90 (s, C=C*H*$_2$), 6.13 (s, C*H*O), 7.13–7.42 (m, Ar*H*), 8.49 (s, C=N*H*); ^{13}C NMR (50 MHz, $CHCl_3$): $\delta = 14.0$, 15.0, 26.9, 54.3, 60.0, 61.9, 75.4, 91.6, 120.7, 126.9, 127.2, 128.1, 128.3, 128.5, 136.0, 154.8, 161.1, 166.9.

5b: ^{1}H NMR (200 MHz, $CHCl_3$): $\delta = 0.82$ (d, $J = 6.6$ Hz, CH–C*H*$_3$), 1.01 (t, $J = 7.2$ Hz, CH_2CH_3), 2.82 (s, N–C*H*$_3$), 3.98 (dq, $J = 6.6$, 8.1 Hz, C*H*–CH_3), 4.14 (q, $J = 7.2$ Hz, CH_2CH_3), 5.45 (d, $J = 8.3$ Hz, Ph–C*H*), 5.66 (s, C=C*H*$_2$), 5.93 (s, C=C*H*$_2$), 6.16 (s, C*H*O), 7.13–7.42 (m, Ar*H*), 8.49 (s, C=N*H*); ^{13}C NMR (50 MHz, $CHCl_3$): $\delta = 13.9$, 15.2, 29.7, 54.3, 59.1, 60.0, 79.1, 120.5, 127.1, 128.0, 128.1, 128.3, 128.5, 128.6, 138.3, 154.8, 161.1, 165.8.

(4S,5R,3′R)-(3′-Trichloroacetylamino-3′-hydroxy-2′-methylenepropanoyl)-3,4-dimethyl-5-phenylimidazolidin-2-one and its (4S,5R,3′S)-isomer (**6a** and **6b**, $C_{20}H_{22}Cl_3N_3O_5$)

To 293 mg **5a** and **5b** (0.6 mmol, *dr* = 10:90) dissolved in 4 cm^3 *DCM*, 44 mg *DABCO* (0.4 mmol) were added at 0°C and the mixture was subsequently stirred for 6 h at rt. After dilution with 20 cm^3 ethyl acetate, the organic layer was washed with 5 cm^3 1 *M* HCl and 10 cm^3 brine. The solvents were dried (Na_2SO_4) and removed under reduced pressure to give a residue which was purified by silica gel chromatography (cyclohexane:ethyl acetate = 20:80) to give 185 mg of an inseparable mixture of diastereomeric trichloroacetamides **6a** and **6b** (63%, *dr* = 50:50) as a colorless oil. ESI-MS: $m/z = 489.1$ $[M]^+$, 491.1 $[M + 2]^+$, 512.2 $[M + Na]^+$, 514.2 $[M + 2 + Na]^+$.

6a: ^{1}H NMR (200 MHz, $CHCl_3$): $\delta = 0.80$ (d, $J = 6.6$ Hz, CH–C*H*$_3$), 1.22 (t, $J = 7.1$ Hz, CH_2CH_3), 2.80 (s, N–C*H*$_3$), 3.97 (dq, $J = 6.6$, 8.7 Hz, C*H*–CH_3), 4.22 (q, $J = 7.1$ Hz, CH_2CH_3), 5.15 (d, $J = 8.7$ Hz, EtOOC–C*H*–N), 5.28 (s, C=C*H*$_2$), 5.29 (d, $J = 8.0$ Hz, *Ph*–C*H*), 5.82 (s, C=C*H*$_2$), 7.12–7.21 (m, Ar*H*), 7.25–7.41 (m, Ar*H*), 8.24 (d, $J = 8.7$ Hz, N*H*); ^{13}C NMR (50 MHz, $CHCl_3$): $\delta = 13.6$, 15.4, 29.5, 54.2, 59.6, 59.9, 78.4, 120.4, 127.3, 127.9, 128.5, 128.7, 129.5, 129.6, 138.7, 154.6, 161.7, 165.4.

6b: ^{1}H NMR (200 MHz, $CHCl_3$): $\delta = 0.80$ (d, $J = 6.6$, CH–CH_3), 1.10 (t, $J = 7.1$ Hz, CH_2CH_3), 2.80 (s, N–CH_3), 3.97 (dq, $J = 6.6$, 8.7 Hz, CH–CH_3), 4.18 (q, $J = 7.1$ Hz, CH_2CH_3), 5.07 (d, $J = 8.7$ Hz, EtOOC–CH–N), 5.24 (d, $J = 8.0$ Hz, *Ph*–CH), 5.36 (s, C=CH_2), 5.77 (s, C=CH_2), 7.12–7.21 (m, ArH), 7.25–7.41 (m, ArH), 8.24 (d, $J = 8.7$ Hz, NH); ^{13}C NMR (50 MHz, $CHCl_3$): $\delta = 13.8$, 15.4, 29.9, 53.9, 59.2, 60.4, 79.3, 120.5, 127.1, 128.0, 128.1, 128.3, 129.5, 129.6, 138.5, 154.2, 161.3, 165.9.

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[10] It is worth mentioning that the *Baylis-Hillman* reaction of the imide **3** gives satisfactory results only starting from ethyl glyoxalate **2**. In fact even electrophilic aldehydes such as 4-nitrobenzaldehyde and 2,4-dinitrobenzaldehyde failed to give any results, and starting materials were invariably recovered

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