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First example of electrophile induced Baylis–Hillman reaction: a novel facile one-pot synthesis of indolizine derivatives†

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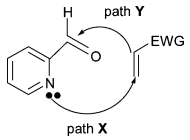
Treatment of pyridine-2-carboxaldehyde with activated alkenes such as alkyl vinyl ketones and cyclic enones in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) provides a novel facile one-pot synthesis of indolizine derivatives, thus for the first time describing an electrophile induced Baylis–Hillman reaction.

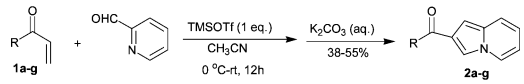
The Baylis–Hillman reaction is an atom economical carbon–carbon bond forming reaction involving the coupling of the α-position of activated alkenes with carbon electrophiles under the influence of catalysts/catalytic systems producing highly synthetically useful densely functionalized molecules, which have been extensively used in a number of stereoselective transformation methodologies and is of current interest.[1–3] Although a large variety of activated alkenes, various electrophiles and a number of catalysts/catalytic systems have been successfully employed, the electrophile induced Baylis–Hillman reaction has not been reported so far.[4] We herein report the first example of an electrophile induced Baylis–Hillman reaction *via* the treatment of activated alkenes with pyridine-2-carboxaldehyde under the influence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) in acetonitrile thus leading to the development of a novel convenient one-pot methodology for synthesis of indolizine derivatives.

The 1-azabicyclo(4.3.0)nonane (indolizine) framework occupies a special place in heterocyclic systems due to the presence of this structural assembly in a number of natural products of biological importance such as tabersonine,[5a] (−)-strychnine,[5b] (+)-vinblastine,[5c] (−)-monomorine,[5d] (−)-gephyrotoxin[5d] *etc*. A careful look at the indolizine framework would logically suggest that one step or one-pot simultaneous/tandem construction of the N–C bond and C–C bond onto six membered nitrogen heterocycles (piperidine/pyridine) in an appropriately organized manner using a suitable reagent would lead to the formation of the desired 1-azabicyclo(4.3.0)nonane framework (Scheme 1).[6,7]

The most generally accepted Baylis–Hillman reaction mechanism[1] (see the Electronic supplementary information (ESI)†) involves the initial Michael type addition of the tertiary amine (catalyst) to the activated alkene generating a zwitterionic enolate. This enolate adds to the electrophile in aldol fashion producing a zwitterion which then undergoes proton migration and subsequent elimination of the catalyst provides the densely functionalized molecules.[1] On careful examination of this mechanistic catalytic cycle, we envisioned that if the electrophile (aldehyde) also contains a nucleophilic-site such as a tertiary amine functionality and if the resulting new N–C bond (formed due to the attack of amine nitrogen onto the activated alkene) (path **X**) is allowed to stay intact by some means even after the construction of the required carbon–carbon bond *via* the attack of the resulting zwitterionic enolate onto the aldehyde functionality (path **Y**) this process might directly lead to the synthesis of the indolizine framework in a one-pot operation. In this direction it occurred to us that pyridine-2-carboxaldehyde, possessing the required sites of both electrophilicity and nucleophilicity, would be an appropriate candidate and the proper organization of pyridine-2-carboxaldehyde (electrophile) for self-inducing the Baylis–Hillman reaction with activated alkenes would in principle lead to the development of a simple synthesis of indolizine derivatives[7] in an operationally convenient one-pot procedure.

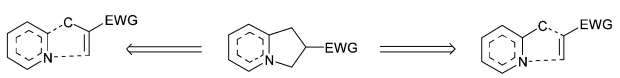


Accordingly, we have first carried out the reaction between pyridine-2-carboxaldehyde and methyl vinyl ketone in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf).[8] The best results were obtained when pyridine-2-carboxaldehyde (1 mmol) was treated with methyl vinyl ketone (**1a**) (1 mmol) in acetonitrile (containing 1% water, v/v) (2 mL) under the influence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) (1 mmol) at room temperature for 12 h, thus providing the desired 8-acetyl-1-azabicyclo(4.3.0)nona-2,4,6,8-tetraene (**2a**) in 38% isolated yield. Encouraged by this result, we have subjected various activated acyclic enones (**1b–g**) in this fascinating reaction to provide the corresponding indolizine derivatives (**2b–g**) in 43–55% isolated yields [eqn. (1) and Table 1]. With a view to examining the applicability of this methodology to cyclic enone systems, we have employed cyclohex-2-enone (**1h**) and 5,5-dimethylcyclohex-2-enone (**1i**) for the coupling reaction with pyridine-2-carboxaldehyde. Under similar conditions [as described in eqn. (1)], these



(1)

reactions did not provide the desired indolizine derivatives. Instead, we obtained only Baylis–Hillman alcohols (**3h** and **3i**) as evidenced by the ^{1}H NMR spectra of the crude product. However, during our attempts to isolate these alcohols in pure form through silica gel (Acme's, 100–200 mesh) column chromatography (20% EtOAc in hexanes) we have obtained indolizine derivatives 6-oxotricyclo(7.4.0.0^{2,7})trideca-2(7),8,10,12-tetraene (**2h**) and 4,4-dimethyl-6-oxotricyclo-(7.4.0.0^{2,7})trideca-2(7),8,10,12-tetraene (**2i**) in both cases (47% isolated yield in the case of **2h** and 40% isolated yield in the case of **2i**). These results clearly indicate that silica gel is affecting the dehydrative-cyclization to provide the desired indolizine derivatives. Indeed, we have confirmed this role of silica gel by treating the crude alcohols in ethyl acetate with silica gel (solid phase) for 6 h, at room temperature which provided the desired indolizines **2h** and **2i**, after usual work-up (^{1}H NMR spectrum



Scheme 1 Schematic representation for the synthesis of indolizine derivatives.

† Electronic supplementary information (ESI) available: Experimental procedures, analytical and spectral data for all the compounds **2a–i**. See http://www.rsc.org/suppdata/cc/b2/b211349j/

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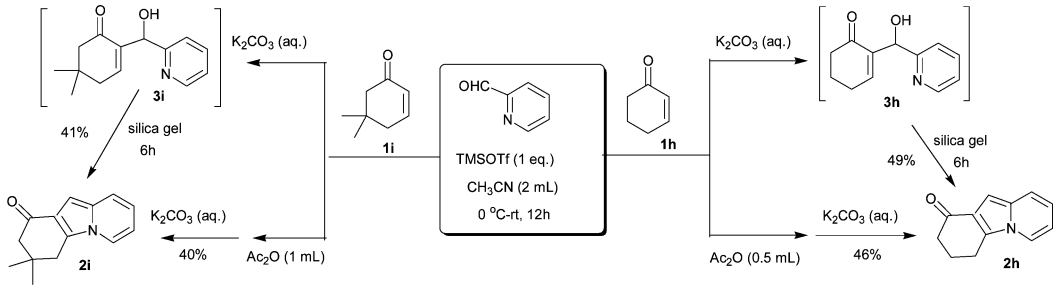


Scheme 2

Table 1 Electrophile induced Baylis–Hillman reaction[a,b]

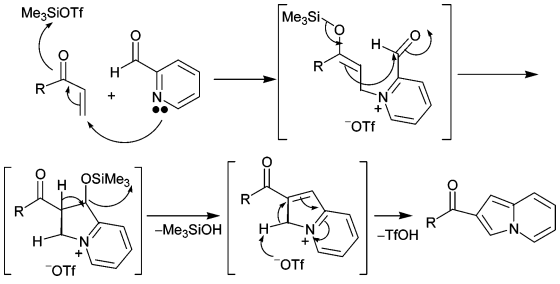
S. No.	Activated alkene	Product	mp/°C	Yield (%)[c]
1a	Methyl vinyl ketone	**2a**[9,d]	118–120[d]	38
1b	Ethyl vinyl ketone	**2b**	102–104	51
1c	Propyl vinyl ketone	**2c**	76	50
1d	Butyl vinyl ketone	**2d**	80–81	45
1e	Pentyl vinyl ketone	**2e**	85–86	55
1f	Hexyl vinyl ketone	**2f**	88	44
1g	Heptyl vinyl ketone	**2g**	90–91	43
1h	Cyclohex-2-enone	**2h**	86–88	49
1i	5,5-Dimethylcyclohex-2-enone	**2i**	132–134	41

[a] All reactions were carried out on 1 mmol scale of activated alkene. In the case of **1h** and **1i** the desired products were obtained only after treatment with silica gel. [b] All compounds (**2a–i**) were characterized by IR, ^{1}H NMR, ^{13}C NMR and elemental analyses. Further, the compounds **2a**, **2c**, **2e**–**2i** were also characterized by mass spectral analyses. [c] Isolated yields of the pure products after silica gel column chromatography. [d] This molecule is known in the literature and the reported[9] melting point is 127 °C.

of the crude product shows the complete conversion of alcohols into indolizines) followed by silica gel column chromatography in comparable yields (49% isolated yield in the case of **2h** and 41% isolated yield in the case of **2i**) (Scheme 2 and Table 1).

In order to directly obtain the indolizine derivatives **2h** and **2i** (without alcohol even in the crude product) we have performed these reactions in the presence of acetic anhydride.[7] The best results were obtained when pyridine-2-carboxaldehyde (1 mmol) was treated with cyclohex-2-enone derivatives (**1h** and **1i**) (1 mmol) in acetonitirle (2 mL) in the presence of acetic anhydride (0.5 mL in the case of **1h** and 1 mL in the case of **1i**) under the influence of TMSOTf (1 mmol) at room temperature for 12 h, thus providing the corresponding tricyclic molecules **2h** and **2i** in 46% and 40% isolated yields respectively (after usual work-up followed by silica gel column chromatography) (Scheme 2 and Table 1). A plausible mechanism for this one-pot synthesis of indolizine derivatives is described in Scheme 3.

In conclusion we have described, for the first time, an electrophile induced Baylis–Hillman reaction, thus providing a new dimension in the Baylis–Hillman chemistry leading to a novel facile convenient methodology for synthesis of indolizine



Scheme 3 Plausible mechanism for the electrophile induced Baylis–Hillman reaction.

derivatives in one-pot operation. Applications of these indolizine systems as suitable catalysts in the Baylis–Hillman reaction are under progress in our laboratory.

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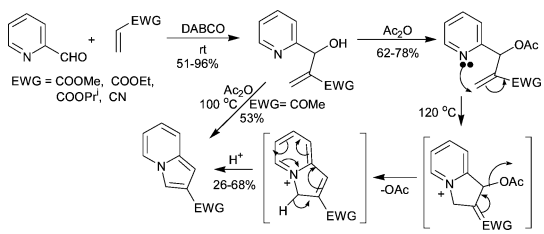

8 The addition of phenyl silyl selenide (ref. 8*a*) or pyridine (ref. 8*b*) to cyclohex-2-enone in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) provides the enol silyl ether, which further reacts with cyclic acetals in aldol fashion: (*a*) M. Suzuki, T. Kawagishi and R. Noyori, *Tetrahedron Lett.*, 1981, **22**, 1809; (*b*) F. Wang and R. Zibuck, *Synlett.*, 1998, 245.

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