



A novel multicomponent reaction involving isoquinoline, allenolate and cyanoacrylates

Vijay Nair^{a,*}, Beneesh Pattoorpadu Babu^a, Vimal Varghese^a, C. R. Sinu^a, Rony Rajan Paul^a, E. R. Anabha^a, Eringathodi Suresh^b

^aOrganic Chemistry Section, National Institute for Interdisciplinary Science and Technology (CSIR), Trivandrum 695 019, India

^bAnalytical Science Division, Central Salt and Marine Chemicals Research Institute, Bhavnagar 364 002, India

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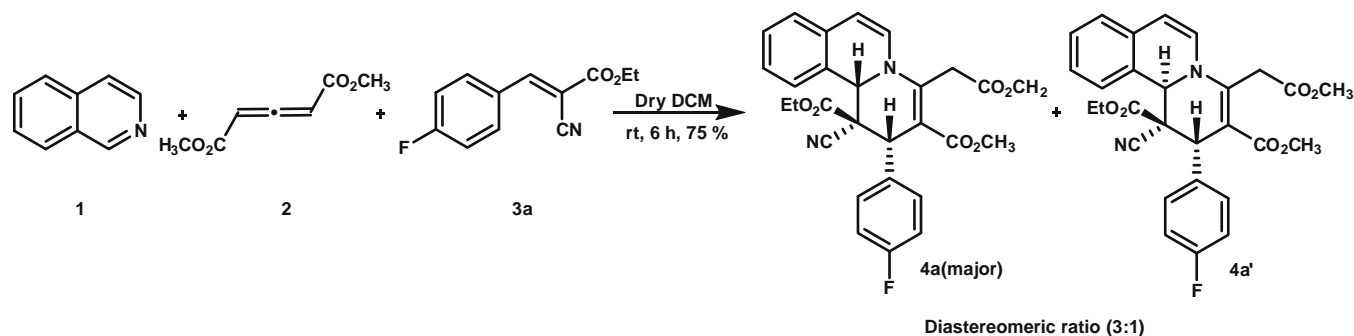
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ABSTRACT

Transient zwitterion generated from allenolate and isoquinoline was successfully intercepted with cyanoacrylates and arylidenemalononitriles to devise a novel multicomponent reaction under mild conditions.

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Scheme 1. Reaction with p-fluorophenylcyanoacrylate.

The formation of transient zwitterions by the addition of nucleophilic species such as phosphines, isocyanides, N-heterocycles, and nucleophilic carbenes to electrophilic π -systems has been known in the literature for a long time. As early as 1932, Diels and Alder reported that pyridine reacts with dimethyl acetylenedicarboxylate (DMAD) to afford a 1:2 adduct.¹ Three decades later, Acheson studied the reaction in detail and suggested that the initial event was the formation of a zwitterion between pyridine and DMAD.² Subsequently, Huisgen recognized this reaction as

the 1,4-dipolar variant of the classical Diels–Alder reaction.³ Further investigations by Huisgen, Acheson as well as Winterfeldt contributed significantly to the chemistry of zwitterions.⁴

Although isolated examples of the interception of zwitterions with dipolarophiles was already known in the literature,⁵ no attempts were made to trap them deliberately with a third component, a dipolarophile, to devise novel multicomponent reactions (MCRs).⁶ Investigations in our laboratory have led to the development of a number of novel MCRs mediated by transient zwitterions. A substantial part of our studies involved the zwitterions formed by the addition of nucleophiles such as pyridine, isoquinoline, and quinoline to acetylenic esters leading to novel heterocyc-

* Corresponding author. Tel.: +91 471 2490406; fax: +91 471 2491712.
E-mail address: vijaynair_2001@yahoo.com (V. Nair).

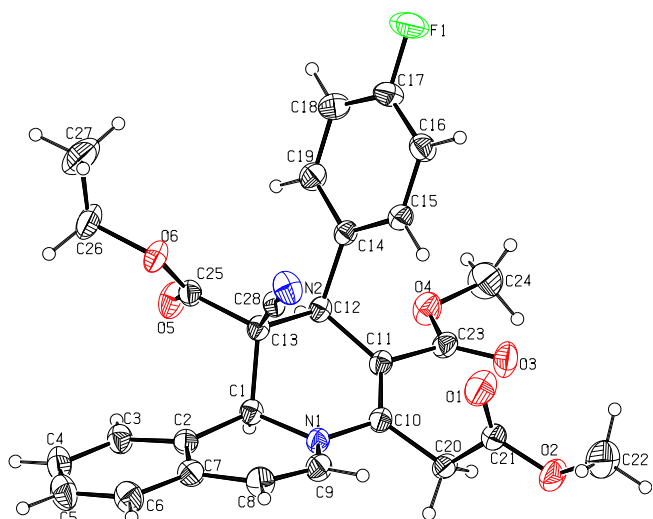


Figure 1. Single crystal X-ray structure of **4a**.

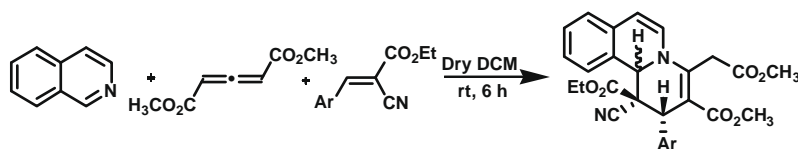
clic frameworks.⁷ In view of the success of these reactions, we were intrigued by the possibility of the addition of nucleophiles to allenates to generate zwitterions and the interception of the latter with electrophiles. Allenates are an important class of activated π -systems and the chemistry of the zwitterions from allenates

has received only scant attention until recently.⁸ Electron-deficient allenates have great affinity toward phosphines and the reactivity of this zwitterionic species was already studied in detail.⁹ At the same time the synthetic utility of the zwitterion from allenate and N-heterocycles remained unexplored. Herein, we report a novel MCR involving transient zwitterion generated from isoquinoline and allenate.

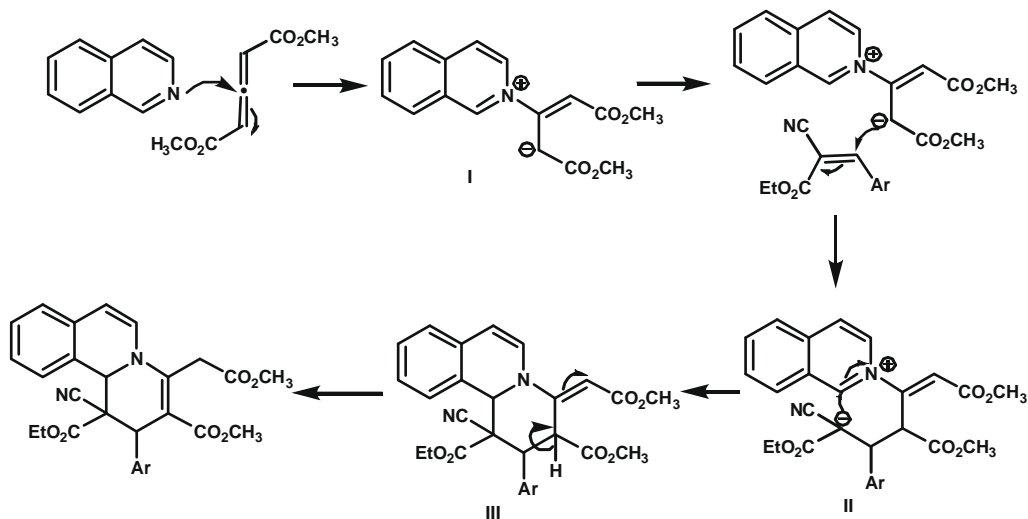
In a pilot experiment¹⁰, isoquinoline was added to a mixture of allenate **2** and cyanoacrylate **3a** in DCM, and the reaction mixture was stirred at room temperature for 6 h. Removal of the solvent followed by column chromatography of the residue on neutral alumina afforded a diastereomeric mixture (ratio 3:1) of the MCR product in 75% yield. The major isomer was then separated by fractional crystallization (Scheme 1).

The structure of the major isomer **4a** was assigned on the basis of conventional spectroscopic analysis. IR spectrum of the compound showed strong carbonyl absorption at 1737 and 1705 cm^{-1} . ^1H NMR spectrum of compound **4a** displayed the characteristic singlet proton signals at δ 5.17 and 5.02. The two methoxy protons showed their resonating signals as sharp singlets at δ 3.84 and 3.37. All other signals were also in good agreement with the proposed structure. The ester carbonyl groups displayed ^{13}C resonance signals at δ 169.5, 166.5, and 165.9. The IR absorption at 2243 cm^{-1} as well as the ^{13}C resonance signal at δ 105.5 was attributed to the cyano group. Finally unambiguous evidence for the structure of **4a** was obtained by single crystal X-ray analysis (Fig. 1). The trans relationship of the minor isomer was established from NOE analysis.

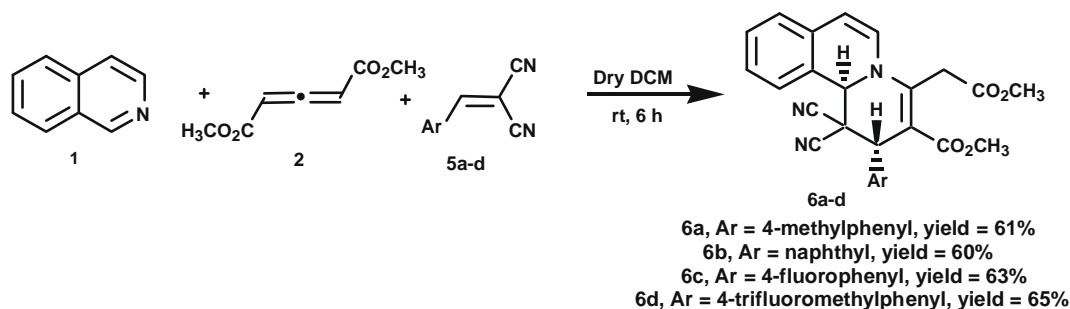
Table 1
Scope of the reaction



Entry	Ar	Product	Yield (%)	Ratio
1	4-Nitrophenyl (3b)	4b	74	(3:1)
2	3-Chlorophenyl (3c)	4c	69	(3:1)
3	Naphthyl (3d)	4d	76	(4:1)
4	Phenyl (3e)	4e	75	(3:1)
5	4-Trifluoromethylphenyl (3f)	4f	72	(4:1)
6	4-Methoxyphenyl (3g)	4g	56	(3:1)



Scheme 2. Proposed mechanism.



Scheme 3. Reaction with arylidene malononitrile.

The reaction appears to be general with a number of substituted cyanoacrylates and the MCR product was formed in moderate to good yield as diastereomeric mixture. The results are summarized in Table 1. Stereoselective formation of the MCR product can be attributed to the relative stability of the intermediate carbanion.

A mechanistic rationalization for this reaction is given in Scheme 2. It is conceivable that the initial event is the formation of zwitterion **I** from isoquinoline and allenolate. It then adds to cyanoacrylate to afford the dipolar intermediate **II**, which on cyclization followed by hydrogen shift afforded the MCR product.

Subsequent investigations showed that a similar reaction occurred with isoquinoline–allenolate zwitterion and arylidene malononitriles. Illustrative examples are presented in Scheme 3. The trans stereochemistry of the product was assigned on the basis of NOE analysis.

In conclusion we have devised a new multicomponent reaction for the synthesis of highly functionalized pyrido[2,1-*a*]isoquinoline derivative. In this strategy allenolate functioned as a three-carbon analogue of DMAD. This is the first MCR involving a zwitterion generated from isoquinoline and allenolate.

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- Typical experimental procedure:** (a) Reaction with cyanoacrylate: Isoquinoline **1** (64.5 mg, 0.5 mmol) was added to a mixture of allenolate **2** (78 mg, 0.5 mmol) and cyanoacrylate **3a** (165 mg, 0.75 mmol) in dry dichloromethane at room temperature and stirred for 6 h. Solvent was then removed in a rotary evaporator and the residue was subjected to column chromatography on a neutral alumina column using 80:20 hexane–ethyl acetate solvent mixture to afford diastereomeric mixture of the MCR product **4a** (189 mg, 75%) as white solid. The major isomer was then separated by crystallization from hexane–dichloromethane solvent mixture. IR (KBr): 2980, 2941, 2243, 1737, 1705, 1600, 1519, 1429, 1348, 1265, 1211, 1136 cm^{-1} . ^1H NMR (CDCl_3/TMS): δ 7.26–7.22 (m, 3H), 7.07 (t, 2H, $J = 7.8$ Hz), 6.95 (t, 3H, $J = 8.8$ Hz), 6.57 (d, 1H, $J = 7.9$ Hz), 5.74 (d, 1H, $J = 7.9$ Hz), 5.17 (s, 1H), 5.02 (s, 1H), 4.23 (d, 1H, $J = 17.6$ Hz), 4.14–4.08 (m, 1H), 4.01–3.92 (m, 1H), 3.84 (s, 3H), 3.70 (d, 1H, $J = 17.6$ Hz), 3.38 (s, 3H), 1.01 (t, 3H, $J = 7.2$ Hz). ^{13}C NMR (CDCl_3): δ 169.5, 166.5, 165.9, 162.1, 145.9, 134.1, 131.1, 129.6, 129.5, 127.5, 126.8, 126.4, 125.6, 124.1, 115.7, 115.4, 114.9, 112.5, 105.5, 64.1, 63.4, 58.3, 52.5, 51.2, 49.7, 37.3, 13.6. LRMS-FAB: ($\text{M}+\text{H}$) $^+$ Calcd for $\text{C}_{28}\text{H}_{25}\text{FN}_2\text{O}_6$: 505.18. Found: 505.36. (b) Reaction with arylidene malononitrile: Isoquinoline **1** (64.5 mg, 0.5 mmol) was added to a mixture of allenolate **2** (78 mg, 0.5 mmol) and arylidene malononitrile **5a** (126 mg, 0.75 mmol) in dry dichloromethane at room temperature and was stirred for 6 h. The MCR product was readily precipitated as white amorphous solid. Solvent was then removed in a rotary evaporator and the residue was washed with methanol and dried. It was then dissolved and reprecipitated from hot chloroform to afford the MCR product **6a** (138 mg, 61%) as a single diastereomer. IR (KBr): 3026, 2946, 2241, 1751, 1705, 1595, 1568, 1431, 1321, 1236, 1207, 1105 cm^{-1} . ^1H NMR (CDCl_3/TMS): δ 7.32 (d, 2H, $J = 8.1$ Hz), 7.26–7.22 (m, 3H), 7.16 (d, 2H, $J = 3.6$ Hz), 7.07 (d, 1H, $J = 7.5$ Hz), 6.59 (d, 1H, $J = 7.8$ Hz), 5.87 (d, 1H, $J = 7.8$ Hz), 5.00 (s, 1H), 4.69 (s, 1H), 4.23 (d, 1H, $J = 17.1$ Hz), 3.94 (d, 1H, $J = 17.1$ Hz), 3.80 (s, 3H), 3.54 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (CDCl_3): 169.4, 165.6, 146.6, 133.9, 132.7, 131.7, 130.4, 129.1, 128.7, 127.1, 126.5, 125.9, 125.7, 125.4, 122.6, 113.5, 11.7, 106.2, 64.6, 52.6, 51.3, 45.9, 45.7, 37.3, 21.2. LRMS-FAB: ($\text{M}+\text{H}$) $^+$ Calcd for $\text{C}_{27}\text{H}_{23}\text{N}_3\text{O}_4$: 454.18. Found: 454.29.