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The Huisgen 1,4-dipolar cycloaddition involving isoquinoline, dimethyl butynedioate and activated styrenes: a facile synthesis of tetrahydrobenzoquinolizine derivatives

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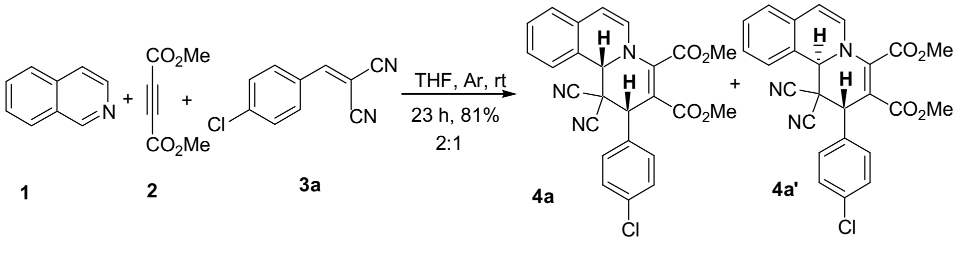
Abstract—A three-component reaction involving isoquinoline, dimethyl butynedioate and electrophilic styrenes is described. The reaction proceeds through a Huisgen 1,4-dipolar cycloaddition pathway.

The phenomenal success of the Huisgen reaction, involving the cycloaddition of 1,3-dipolar species to π-systems leading to five-membered heterocycles[1] paved the way for devising the homologous version of this reaction viz, 1,4-dipolar cycloaddition.[2] In his pioneering work, Huisgen demonstrated that the reaction of isoquinoline and dimethyl butynedioate generated a 1,4-dipolar intermediate, by trapping it with phenyl isocyanate, diethyl mesoxalate and dimethylazodicarboxylate.[3] Surprisingly, however, the synthetic potential of the 1,4-dipolar cycloaddition, vis-a-vis the 1,3-counterpart, remained uninvestigated. Recently, we showed that 1,4-dipoles can undergo cycloaddition to *N*-tosylimines and *o*-benzoquinones leading to 2*H*-pyrimido [2,1-*a*]isoquinoline[4] and spiro[1,3]oxazino[2,3-*a*]isoquinoline derivatives,[5] respectively.

In view of the success of the reaction, it was surmised that activated styrenes such as arylidenemalononitriles would participate in this reaction, and in the event would lead to the formation of tetrahydrobenzoquinolizine derivatives. Our preliminary results on this novel multicomponent reaction (MCR) are presented here.

In a pilot experiment, a solution of dimethyl butynedioate **2** and benzylidenemalononitrile **3a** in anhydrous THF was treated with an equimolar quantity of isoquinoline **1** at room temperature. Chromatographic separation of the reaction mixture afforded **4a** and **4a′** as a diastereomeric mixture in 81% yield (Scheme 1).[6]

The major diastereoisomer was isolated by repeated chromatography and characterized on the basis of spectroscopic analysis.[6] A strong absorption at 1742 cm^{-1} in the IR spectrum of **4a** indicated the presence of ester carbonyl groups, whereas the absorption at 2239 cm^{-1} corresponded to the cyano groups. In the ^{1}H NMR spectrum, the ring junction proton resonated at δ 5.33



Scheme 1. Reaction of isoquinoline and dimethyl butynedioate with dicyanostyrenes.

Keywords: Multicomponent reactions; Isoquinoline; Dimethyl acetylenedicarboxylate; 1,4-Dipolar cycloaddition.

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as a singlet and the other benzylic proton displayed a singlet at δ 4.58. The two methoxycarbonyl groups were visible at δ 4.00 and 3.49 as singlets. The hydrogens of the enamine double bond appeared as doublets at δ 6.36 (J = 7.84 Hz) and 5.79 (J = 7.84 Hz).

The relative stereochemistry of the major diastereoisomer **4a** was established by ^{1}H NOE difference spectroscopic studies. The major diastereomer was assigned cis stereochemistry since selective irradiation of H_a produced enhancements in the signals corresponding to H_b and H_c (Fig. 1).

The reaction was found to be general with respect to various arylidenemalononitriles affording diastereomeric mixtures of the corresponding tricyclic derivatives **4b–k** in moderate yields and **4b′–g′** in low yields (Table 1). The diastereomeric ratios of the products were determined on the basis of ^{1}H NMR spectroscopy of the mixtures.

The stereochemistry of **4h** was assigned as cis by ^{1}H NOE difference spectroscopic studies. Selective irradiation of H_a produced enhancements in the signals corresponding to H_b and H_c (Fig. 2).

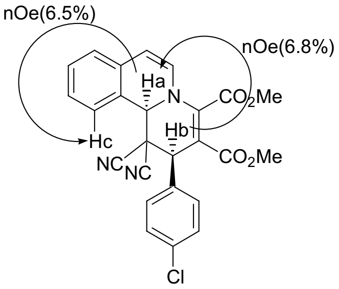


Figure 1. Selected NOE correlations for the major diastereoisomer **4a**.

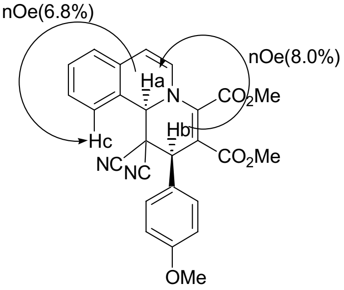
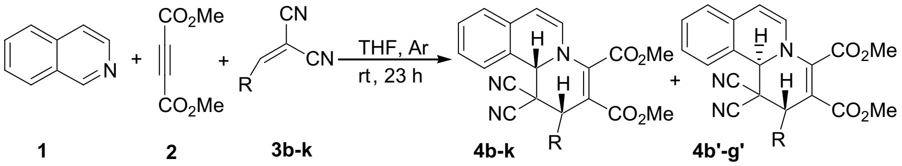


Figure 2. Selected NOE correlations for **4h**.

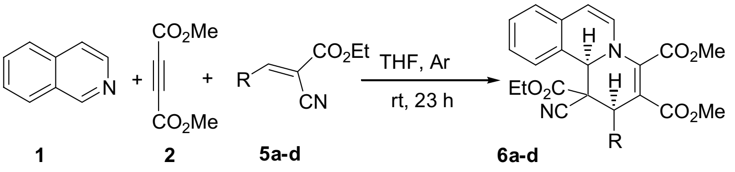
Table 1. Reaction of isoquinoline and dimethyl butynedioate with various dicyanostyrenes



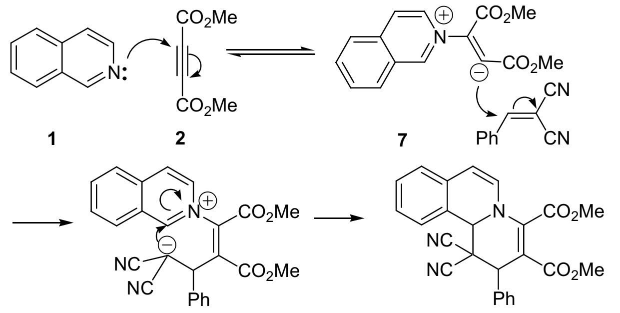
Entry	Styrene	Products (cis:trans)	Isolated yield (%)
1	R = 3-chlorophenyl, **3b**	**4b**:**4b′**	51:15 (2:1)
2	R = 3-nitrophenyl, **3c**	**4c**:**4c′**	55:10 (2:1)
3	R = 4-methylphenyl, **3d**	**4d**:**4d′**	52:19 (2:1)
4	R = 4-fluorophenyl, **3e**	**4e**	42 (1:1)
5	R = phenyl, **3f**	**4f**:**4f′**	49:13 (2:1)
6	R = naphthyl, **3g**	**4g**:**4g′**	64:25 (2:1)
7	R = 4-methoxyphenyl, **3h**	**4h**	53[a]
8	R = 4-(trifluoromethyl)phenyl, **3i**	**4i**	48[a]
9	R = *trans*-cinnamyl, **3j**	**4j**	58[a]
10	R = Ph$_2$CH–, **3k**	**4k**	43[a]

[a] Only one diastereoisomer formed. Diastereomeric ratio in parentheses.

Table 2. Reaction of isoquinoline and dimethyl butynedioate with aryl cyanoacrylates



Entry	Styrene	Product	Yield (%)
1	R = 3-chlorophenyl, **5a**	**6a**	46
2	R = 4-fluorophenyl, **5b**	**6b**	33
3	R = 3-nitrophenyl, **5c**	**6c**	51
4	R = 4-nitrophenyl, **5d**	**6d**	45



Scheme 2. Mechanism of the formation of isoquinoline-fused tricyclic systems.

The alkene component of the MCR is variable. The reaction afforded single diastereomers, albeit in lower yields, when aryl cyanoacrylates were used instead of arylidenemalononitriles. The results are summarized in Table 2. Surprisingly, no reaction occurred when benzylidenemalonate was used as the third component.

Mechanistically, the reaction may be considered to proceed via the initial formation of the 1,4-dipolar intermediate **7** from isoquinoline **1** and butynedioate **2** followed by its trapping with arylidenemalononitriles, presumably by a two step process, to give the final product (Scheme 2).

In conclusion, we have devised a novel three-component reaction for the synthesis of tetrahydrobenzoquinolizine derivatives via 1,4-dipolar cycloaddition under mild conditions. Further work is underway in this area.

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6. Representative experimental procedure and spectroscopic data for compounds **4a** and **4a′**: a solution of dimethyl butynedioate (232 mg, 1.63 mmol) and **3a** (200 mg, 1 mmol) in dry THF (10 mL) was stirred under an argon atmosphere. To this, isoquinoline (140 mg, 1 mmol) was added and the reaction mixture was stirred for 23 h at rt. The solvent was then removed under vacuum and the residue, on chromatographic separation on silica gel using hexane–ethyl acetate (85:15), gave the products **4a** (56%) and **4a′** (25%) as a pale yellow crystalline solids. Data for compound **4a**: mp 121–123 °C. IR (KBr) ν_{max}: 2955, 2239, 1742, 1715, 1607, 1526, 1438, 1357, 1236 cm^{-1}. ^{1}H NMR [300 MHz, CDCl$_3$–CCl$_4$, 7:3 (v/v)]: δ 7.52 (d, $J = 7.43$ Hz, 1H), 7.45–7.38 (m, 4H), 7.30–7.25 (m, 2H), 7.10 (d, $J = 7.84$ Hz, 1H), 6.36 (d, $J = 7.84$ Hz, 1H), 5.79 (d, $J = 7.84$ Hz, 1H), 5.33 (s, 1H), 4.58 (s, 1H), 4.00 (s, 3H), 3.49 (s, 3H). ^{13}C NMR (75 MHz): δ 164.2, 133.8, 130.7, 129.3, 128.4, 127.6, 126.1, 125.7, 122.2, 114.2, 113.5, 112.0, 110.2, 109.5, 109.3, 108.2, 107.5, 107.2, 106.6, 104.9, 96.1, 63.3, 53.7, 52.1, 50.7. HRMS: (EI) calculated for C$_{25}$H$_{18}$N$_3$O$_4$Cl: 459.0986. Found: 459.0979. Data for compound **4a′**: IR (KBr) ν_{max}: 2955, 2239, 1742, 1715, 1607, 1526, 1438, 1357, 1236 cm^{-1}. ^{1}H NMR [300 MHz, CDCl$_3$–CCl$_4$, 7:3 (v/v)]: δ 7.48 (d, $J = 7.12$ Hz, 1H), 7.37–7.18 (m, 4H), 7.16–7.13 (m, 2H), 7.10 (d, $J = 7.84$ Hz, 1H), 6.28 (d, $J = 7.76$ Hz, 1H), 5.79 (d, $J = 7.84$ Hz, 1H), 5.09 (s, 1H), 4.56 (s, 1H), 3.98 (s, 3H), 3.58 (s, 3H). ^{13}C NMR (75 MHz): δ 164.2, 132.5, 130.7, 128.1, 128.5, 127.6, 126.1, 125.7, 122.2, 114.2, 113.1, 112.1, 111.2, 109.4, 109.2, 108.5, 107.3, 107.2, 106.4, 104.5, 96.5, 63.0, 53.5, 52.2, 50.5.