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Novel pyridine catalysed reactions of dimethyl acetylenedicarboxylate (DMAD) and arylmethylidenemalononitriles: a stereoselective synthesis of highly substituted buta-1,3-dienes

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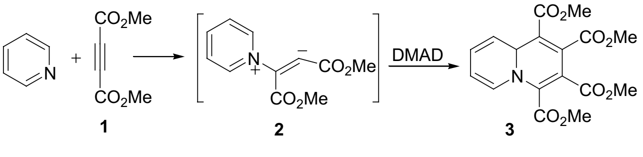
Abstract—A pyridine catalysed addition of dimethyl acetylenedicarboxylate to various arylmethylidenemalononitriles to afford highly substituted 1,3-butadienes with complete stereoselectivity is described.

The reaction of nucleophiles, nitrogen-containing heterocycles in particular, with activated acetylenes has been the subject of considerable research over the last several decades.[1] The earliest work in this area appears to be that of Diels and Alder, who in 1932 showed that pyridine reacts smoothly with dimethyl acetylenedicarboxylate (DMAD) **1** to form an adduct of unknown structure.[2] Decades later, the structure of the adduct was established as the 4*H*-quinolizine **3** by the systematic and elaborate investigations of Acheson and co-workers (Scheme 1).[3] The intermediacy of 1,4-dipolar species **2** was established by its intramolecular trapping with carbonyl groups by Winterfeldt.[1a,4] Reports of intermolecular trapping of the 1,4-dipole **2** with carbon dioxide and phenyl isocyanate, respectively, by Acheson and Plunkett[5] and Huisgen et al.[6] are also noteworthy.



Scheme 1.

In view of our general interest in multicomponent reactions (MCRs) involving zwitterionic species[7,8] we envisaged the possibility of trapping the 1,4-dipole with aryl aldehydes. In the event we did not observe the expected MCR product; instead the reaction afforded the corresponding aroyl fumarate with pyridine playing a mediator role for the formation of a carbon–carbon bond between the aldehyde and DMAD.[9] A similar reaction was also observed with *N*-tosylimines.[9c] In this context we recognised the potential of such a pyridine catalysed reaction of DMAD and suitable electrophilic alkenes to deliver highly substituted buta-1,3-dienes. The preliminary results of our investigations involving β-dicyanostyrenes leading to the formation of the expected buta-1,3-dienes are presented in this communication.

In an initial experiment, the reaction of DMAD **1** with benzylidenemalononitrile **4a** in the presence of pyridine (20 mol%) in dimethoxyethane afforded the highly substituted butadiene derivative **5a** in 61% yield (Scheme 2).

The product was characterised on the basis of spectroscopic data.[10] In the ^1H NMR spectrum the two carbomethoxy groups were observed at δ 3.83 and 3.77 as

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Keywords: Pyridine; Dimethyl acetylenedicarboxylate; Dipoles.

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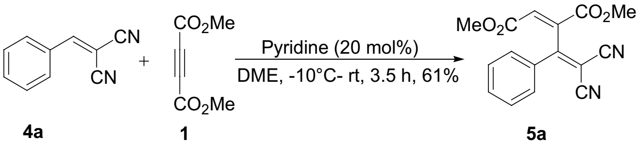


Scheme 2.

singlets, supporting the IR absorption at 1729 cm^{-1}. The olefinic proton resonated at δ 7.20. The ^{13}C signals for the two methoxycarbonyl groups were seen at δ 163.3 and 162.5. Single crystal X-ray analysis of **5h** provided the final confirmation of the structural assignment of the compounds in the series (Fig. 1).[11]

A variety of dicyanostyrenes were found to participate in the reaction affording the 1,3-dienes in good to excellent yields. The results are summarised in Table 1.

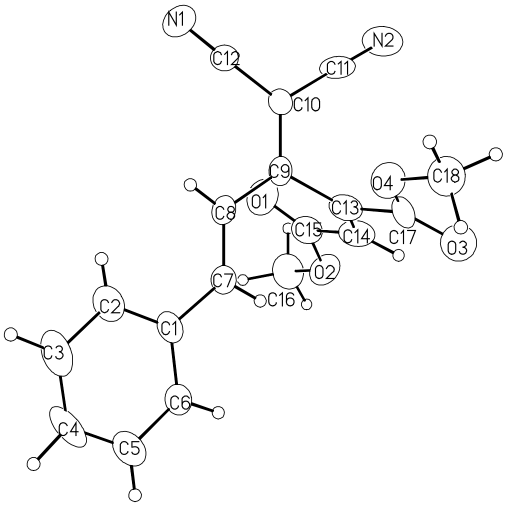
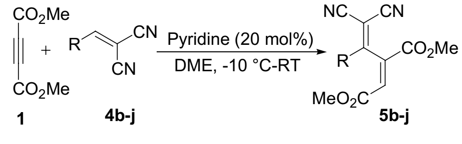
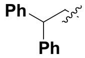


Figure 1. Single crystal X-ray structure of **5h**.

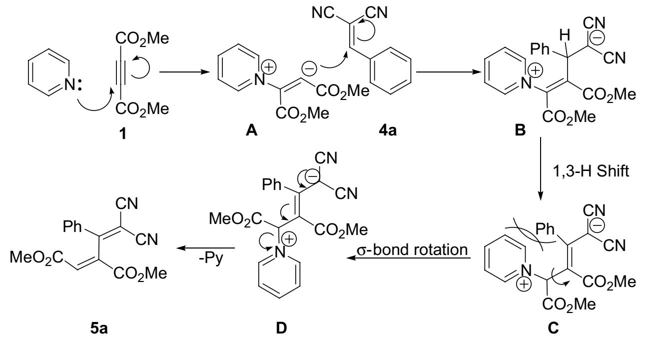
Table 1. Reaction of arylmethylidenemalononitriles with DMAD catalysed by pyridine[a]



Entry	Styrene, R =	Time, t (h)	Yield (%)[b]
1	4-Fluorophenyl, **4b**	3.5	82
2	3-Nitrophenyl, **4c**	3.5	71
3	4-Chlorophenyl, **4d**	3.5	87
4	1-Naphthyl, **4e**	3.5	92
5	3,4-Dichlorophenyl, **4f**	3.5	82
6	4-Methoxyphenyl, **4g**	12	78
7	*trans*-Cinnamyl, **4h**	3.5	45
8	 **4i**	3.5	43
9	3-Benzyloxyphenyl, **4j**	12	75

[a] See Ref. 10 for experimental details.

[b] Isolated yield.



Scheme 3.

Efforts to replace pyridine as the catalyst were unsuccessful; other catalysts such as *N*-methylimidazole and triphenylphosphine gave only traces of the desired product under similar conditions.

A mechanistic rationalisation for the reaction is provided in Scheme 3. The initially formed 1,4-dipole **A** can add to the electrophilic carbon–carbon double bond of **4a** to provide a new zwitterion **B**, which can undergo a [1,3]-H shift to provide **C**. The latter can exist in equilibrium with a more stable conformer **D**. Elimination of pyridine from **D** will deliver the butadiene **5a** with *E* configuration. It may be surmised that the stereoselectivity of the reaction is predicated on the elimination of pyridine occurring from the rotamer **D**, which is stereoelectronically disposed for the favourable *trans* elimination.

In conclusion, we have devised an easy method for the synthesis of highly substituted 1,3-butadienes, which are potential candidates for inverse electron demand Diels–Alder reactions. Further investigations aimed at defining the scope and limitations of the reaction are in progress.

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10. Representative experimental procedure and spectroscopic data for **5h**: A solution of DMAD (142 mg, 1 mmol) and **4h** (198 mg, 1.1 mmol) in dry DME (10 mL) under an argon atmosphere was cooled to −10 °C. To this, pyridine (16 mg, 0.2 mmol) was added and the reaction mixture was stirred for 3.5 h at rt. The solvent was then removed under vacuum and the residue on chromatographic separation on a silica gel column using hexanes–ethyl acetate (95:5) gave the product **5h** as a colourless crystalline solid (145 mg, 45%). Mp: 118–121 °C. IR (KBr) ν max: 3731, 3705, 2955, 2365, 2344, 2225, 1724, 1600, 1527, 1439, 1258, 1015 cm^{-1}. ^{1}H NMR: δ 7.55 (m, 2H), 7.46 (m, 4H), 7.30 (s, 1H), 6.90 (d, $J = 15.8$ Hz, 1H), 3.89 (s, 3H), 3.79 (s, 3H). ^{13}C NMR: δ 164.9, 163.0, 162.7, 145.1, 138.2, 134.1, 131.8, 129.0, 128.2, 128.0, 122.6, 112.3, 111.6, 53.9, 52.8. Anal. Calcd for $C_{18}H_{14}N_2O_4$: C, 67.07; H, 4.38; N, 8.69. Found: C, 67.23; H, 4.06; N, 8.76.
11. Single crystal X-ray structure data for **5h** have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 231299.