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A Novel Multicomponent Reaction Involving Isocyanide, Dimethyl Acetylenedicarboxylate (DMAD), and Electrophilic Styrenes: Facile Synthesis of Highly Substituted Cyclopentadienes

Vijay Nair,* Rajeev S. Menon, P. B. Beneesh, V. Sreekumar, and S. Bindu

Organic Chemistry Division, Regional Research Laboratory (CSIR), Trivandrum, India

vijaynair_2001@yahoo.com

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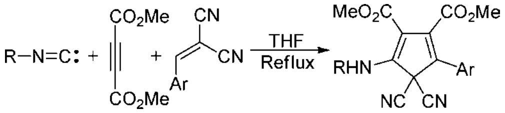
ABSTRACT



Alkyl isocyanides, DMAD, and various activated styrenes furnish fully substituted cyclopentadienes in a one-pot three-component reaction.

The advent of the Huisgen reaction,[1] which involves the cycloaddition of 1,3-dipoles to a variety of π-systems, heralded a new era in heterocyclic chemistry. Inter alia the phenomenal success of this reaction provided a rationale for generating a variety of unconventional dipoles, for example, zwitterionic species, and their trapping by dipolarophiles to afford heterocycles.

Zwitterionic species are known to arise from the addition of nucleophiles such as triphenylphosphine,[2] pyridine,[3] and a wide range of tertiary amines[4] to activated acetylenes.[5] Of special interest to us has been the zwitterion derived from isocyanide and DMAD.[6] Earlier attempts to trap this species with dipolarophiles to generate cyclic compounds have been essentially unsuccessful.[7] We have recently shown that this species can be efficiently trapped by dipolarophiles such as aryl aldehydes and *N*-tosylimines leading to a facile synthesis of furan and pyrrole derivatives, respectively.[8] Against this background, we surmised that the zwitterion might undergo cycloaddition to activated alkenes, thus constituting a synthesis of highly substituted cyclopentadienoid systems. Our preliminary results validating this concept are presented in this letter.

In a pilot experiment, *tert*-butyl isocyanide (**1**), DMAD (**2**), and 3-nitrobenzylidenemalononitrile (**3a**) were refluxed in THF for 24 h. Column chromatography of the reaction mixture on silica gel afforded the fully substituted cyclopentadiene derivative **4a** in 92% yield (Scheme 1).[9]

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(4) (a) Winterfeldt, E. *Chem. Ber.* **1964**, *97*, 1952. (b) Winterfeldt, E.; Dillinger, H. J. *Chem. Ber.* **1966**, *99*, 1558.

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(9) **Representative experimental procedure and spectral data:** To a refluxing solution of 1 mmol (142 mg) of DMAD **2** and 1.1 mmol (219 mg) of **3a** in THF was added 1 mmol (83 mg) of *tert*-butyl isocyanide **1** via a syringe. The reaction mixture was refluxed for 24 h, solvent was

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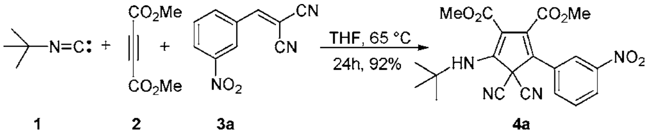
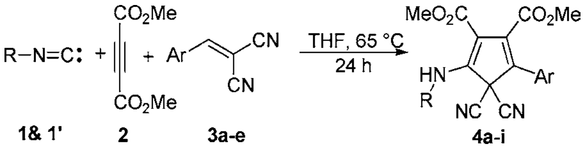
Scheme 1



The structure **4a** was assigned to the product on the basis of spectroscopic analysis. Two methoxycarbonyl groups resonated at δ 3.86 and 3.80 in the ^{1}H NMR spectrum. The ester carbonyl groups displayed ^{13}C resonance signals at δ 164.8 and 164.6 supporting the IR absorption at 1724 cm^{-1}. The IR absorption at 2246 cm^{-1} and the ^{13}C resonance signal at δ 110.7 were attributed to the cyano group. The amino proton appeared at δ 9.07 as a singlet, exchangeable with D$_2$O. The downfield shift and exchangeability of the NH proton was suggestive of intramolecular hydrogen bonding with the adjacent ester carbonyl group.

The isocyanide component of the multicomponent reaction (MCR) was variable; cyclohexyl isocyanide also rendered high-yielding reactions. The results are summarized in Table 1.

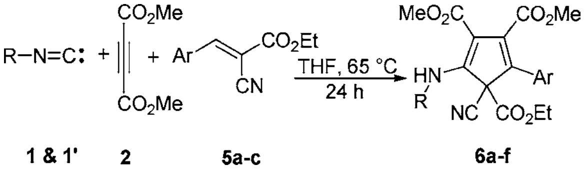
Table 1. Reaction of Isocyanides and DMAD with Dicyanostyrenes



entry	styrene	isocyanide	product	yield (%)
1	Ar = 3-nitrophenyl, **3a**	R = cyclohexyl	**4b**	79
2	Ar = 4-chlorphenyl, **3b**	R = *tert*-butyl	**4c**	91
		R = cyclohexyl	**4d**	68
3	Ar = phenyl, **3c**	R = *tert*-butyl	**4e**	78
		R = cyclohexyl	**4f**	74
4	Ar = methoxyphenyl, **3d**	R = *tert*-butyl	**4g**	93
		R = cyclohexyl	**4h**	87
5	Ar = *trans*-cinnamyl, **3e**	R = *tert*-butyl	**4i**	50

The alkene component of the MCR is also variable. When aryl cyanoacrylates were used in the reaction instead of arylidenemalononitriles, good to excellent yields of the products were obtained (Table 2).

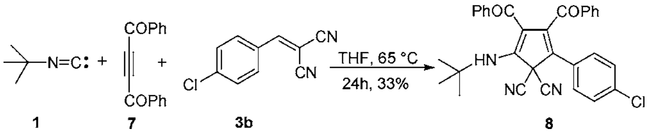
Table 2. Reaction of Isocyanides and DMAD with Aryl Cyanoacrylates



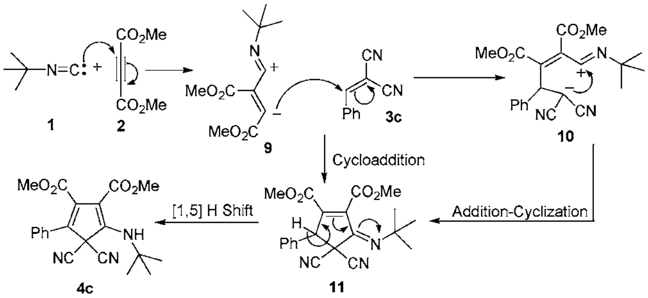
entry	styrene	isocyanide	product	yield (%)
1	Ar = 3-nitrophenyl, **5a**	R = *tert*-butyl	**6a**	67
		R = cyclohexyl	**6b**	77
2	Ar = 4-chlorphenyl, **5b**	R = *tert*-butyl	**6c**	73
		R = cyclohexyl	**6d**	54
3	Ar = phenyl, **5c**	R = *tert*-butyl	**6e**	70
		R = cyclohexyl	**6f**	50

The variability of the MCR with respect to the alkyne component was also tested. Dibenzoylacetylene[10] gave the corresponding cyclopentadiene derivative, albeit in low yield (Scheme 2).

Scheme 2



Scheme 3



A mechanistic rationalization for the reaction is given in Scheme 3. The initial event is the formation of the zwitterion **9** from the isocyanide **1** and DMAD (**2**). The zwitterion can add to the electrophilic carbon–carbon double bond of **3c** resulting in the formation of **10**, which then undergoes cyclization to deliver the primary adduct **11**. The latter then isomerizes to the final product **4c** via a [1,5] H shift. Although less likely, the alternate concerted 1,3-dipolar cycloaddition of the zwitterion to the styrene a la Huisgen reaction cannot be ruled out at the present time.

It is conceivable that the products **4** and **6** can be transformed to highly substituted cyclopentenones, which are

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removed on a rotary evaporator, and the residue was chromatographed on a silica gel column with a hexanes–ethyl acetate mixture (95: 5) to afford **4a** as a yellow crystalline solid (390 mg, 92%). Mp 160–161 °C. IR (KBr) ν_{max} 3431, 3213, 2986, 2955, 2246, 1724, 1667, 1589, 1537, 1444 cm^{-1}. ^{1}H NMR δ 9.07 (s, 1H, exchangeable with D$_2$O), 8.41 (s, 1H), 8.24 (d, J = 8.08 Hz, 1H), 7.92 (d, J = 7.82 Hz, 1H), 7.64 (uneven triplet, J_1 = 7.86 Hz, J_2 = 6.37 Hz, 1H), 3.86 (s, 3H), 3.80 (s, 3H), 1.68 (s, 9H). ^{13}C NMR δ 164.8, 164.6, 158.1, 148.7, 140.1, 133.2, 131.2, 130.2, 123.7, 123.1, 117.6, 110.7, 103.1, 57.3, 52.9, 51.9, 43.3, 31.3. Anal. Calcd for C$_{21}$H$_{20}$N$_4$O$_6$: C, 59.43; H, 4.75; N, 13.20. Found; C, 59.44, H, 4.75; N, 13.10.

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important structural fragments in organic synthesis. In this context a recent cyclopentenone synthesis involving the reaction of zirconecenediethyl in stoichiometric amounts with alkynes, benzylidene malononitrile, and isocyanates is noteworthy.[11]

In conclusion, we have devised a novel three-component one-pot reaction for the synthesis of fully substituted cyclopentadiene derivatives. It is noteworthy that all three components of the reaction are variable, thus making it a versatile process. The reaction belongs to a rare class of multicomponent cyclizations where a carbocycle is produced,[11,12] which contrasts with the majority of such reactions which deliver heterocycles.[13,14] It is likely that the scarcity of methods available for the synthesis of substituted cyclopentadiene derivatives combined with the operational simplicity of the present process will make it potentially attractive for this purpose in the future. Investigations aimed at exploring the scope of the reaction are currently underway.

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Supporting Information Available: General experimental procedures and IR, ^{1}H NMR, and ^{13}C NMR data for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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