

Multicomponent reactions based on nucleophilic carbenes and their applications in organic synthesis*

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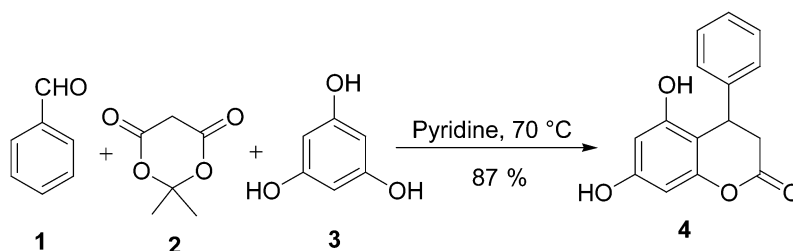
Abstract: Zwitterionic intermediates generated from the addition of nonprotic nucleophiles to activated acetylenes are intercepted with various third components constituting novel multicomponent organic transformations. Catalytic amounts of an organic base like pyridine were found to trigger reactions between an electrophilic acetylene and a variety of electrophiles. The reactions proceed through dipolar intermediates and show high stereoselectivity.

Keywords: Carbenes; multicomponent reactions; isocyanides; dipoles; zwitterions.

INTRODUCTION

One-pot reactions in which three or more starting materials react sequentially and lead to product(s) that retain all or most of the atoms of the starting materials are called multicomponent reactions (MCRs). These reactions are characterized by their convergence, ease of execution, high yields, efficiency, and atom economy [1]. The advent of Passerini [2] and Ugi [3] reactions established the special propensity of isocyanides to take part in MCRs. However, analogous nucleophilic carbenes and their synthetic equivalents have escaped deserving attention in this regard. The results of our detailed investigations on the MCRs of nucleophilic carbenes and related species are presented in the following sections.

The stepping stone to the realm of MCRs for us was a three-component coumarin synthesis developed in 1987 (Scheme 1), which proceeds via a domino Knoevenagel–Michael-type addition sequence [4].



Scheme 1

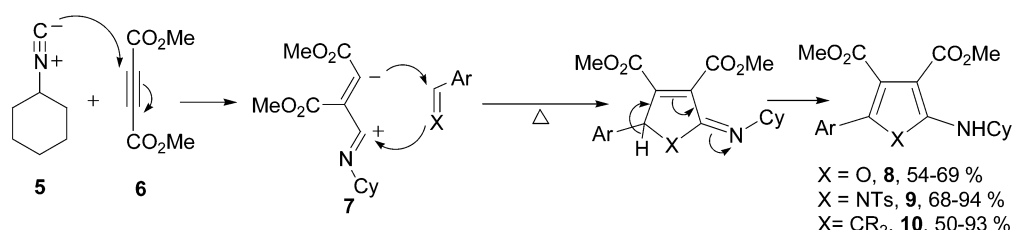
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Our investigations on the reactions of zwitterions generated by the addition of nucleophilic triggers to activated acetylenes revealed two distinct patterns of reactivity. Nucleophiles such as phosphines and pyridine played the role of a mediator in the reaction between two electrophiles, thus constituting novel syntheses of spiro lactones [5], benzoylfumarates [6], azadienes [7], and butadienes [8]. Nucleophiles like isocyanides, dimethoxycarbene, *N*-heterocyclic carbenes (NHCs), and isoquinoline participated in the reactions, providing a versatile array of MCRs [9].

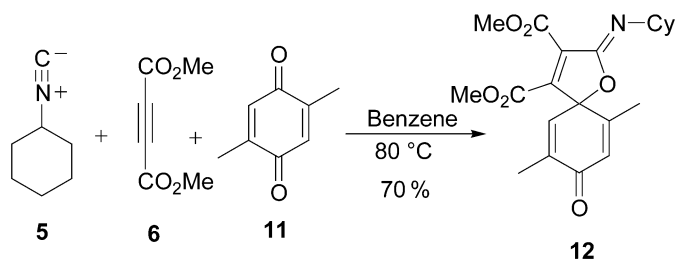
MULTICOMPONENT REACTIONS OF ISOCYANIDES

Although the addition of isocyanides to activated acetylenes such as dimethyl acetylenedicarboxylate (DMAD) to generate zwitterionic intermediates was studied in detail by Winterfeldt [10] in the 1970s, the synthetic potential of the intermediate remained unexploited. The intermediate **7** resembled a 1,3-dipole, and its trapping by a dipolarophile would constitute a three-component reaction which could potentially furnish five-membered hetero/carbocycles. Aldehydes, when reacted with cyclohexyl isocyanide and DMAD in refluxing benzene, afforded 2-aminofurans **8** in good to excellent yields [11]. When *N*-tosylimines were employed as the trapping agents for the dipole, aminopyrroles **9** were formed in excellent yields under milder conditions [12]. A facile synthesis of fully substituted cyclopentadienes **10** was effected by using olefinic dipolarophiles as the third reaction partner in the MCR (Scheme 2) [13].



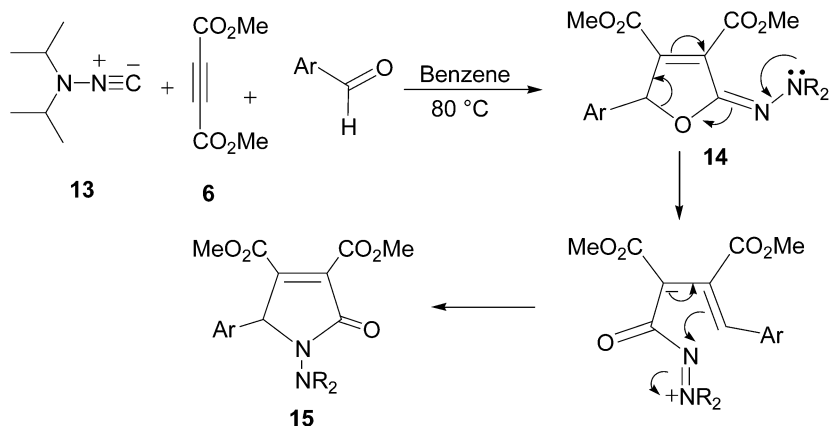
Scheme 2

In the context of our longstanding interest in the chemistry of quinonoid compounds [14], they were employed as the third component in the reaction, eventually constituting a three-component synthesis of novel spirocyclic iminolactones (Scheme 3) [15].



Scheme 3

When an aminoisocyanide **13** was employed in the MCR, the initially formed furanone hydrazone **14** underwent a transformation reminiscent of the Dimroth rearrangement to afford pyrrolinone derivative **15** as the final product (Scheme 4) [16].

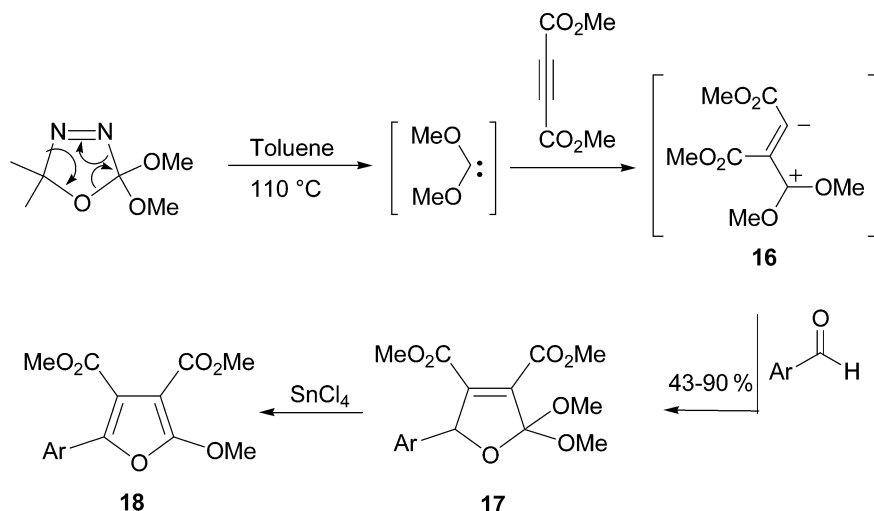


Scheme 4

MULTICOMPONENT REACTIONS OF DIMETHOXYCARBENE

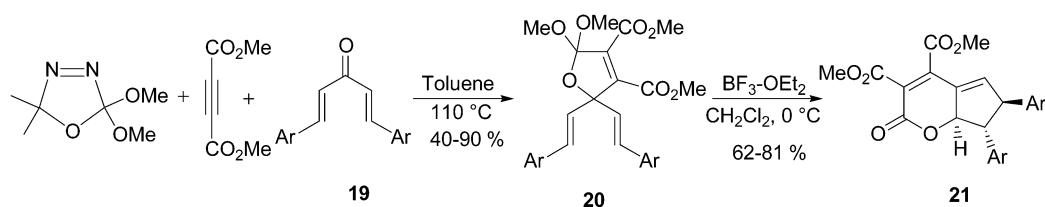
Dialkoxycarbenes constitute a very reactive class of intermediates, which were earlier studied by Hofmann's group [17] and later by Warkentin [18]. Despite the obvious resemblance to isocyanides, alkoxycarbenes eluded attention from the viewpoint of MCRs. Backed by our success in the area of isocyanide-based MCRs, we set about to explore the possibilities of using dialkoxycarbenes in such reactions.

Interception of the dipolar intermediate **16** generated from dimethoxycarbene and DMAD with a third component was successfully executed with aldehydes in a one-pot operation [19]. The dihydropyridinone derivatives formed could easily be converted to the corresponding furan derivatives **18** (Scheme 5).



Scheme 5

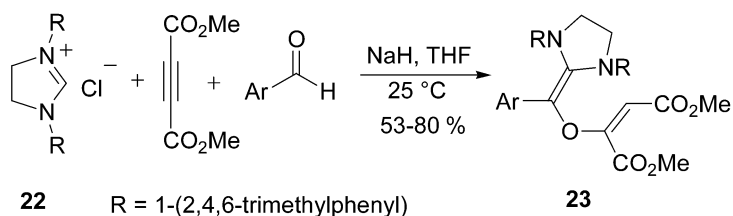
The synthetic potential of this MCR was illustrated by a stereoselective synthesis of bicyclic lactones. Divinyl ketones **19** underwent the MCR, providing easy access to divinyl dihydropyrans **20**, which on exposure to Lewis acid underwent an interrupted Nazarov reaction affording bicyclic γ -lactones **21** (Scheme 6) [20].



Scheme 6

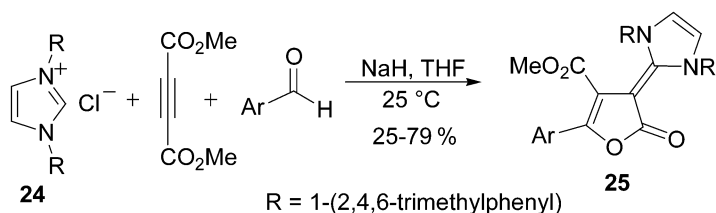
MULTICOMPONENT REACTIONS OF *N*-HETEROCYCLIC CARBENES

Ever since the isolation of a stable diaminocarbene by Arduengo in 1991, there has been growing interest in the exploration of the structure and chemical reactivity of NHCs [21]. But fundamental aspects like the chemical reactivity of NHCs with regard to MCRs have not been addressed. Our group reported the first-ever MCR of an NHC, wherein two classes of carbenes reacted differently. Imidazol-2-ylidene generated from **22** reacted with DMAD and aldehydes to afford 2-oxymaleates **23** with complete stereoselectivity (Scheme 7) [22].



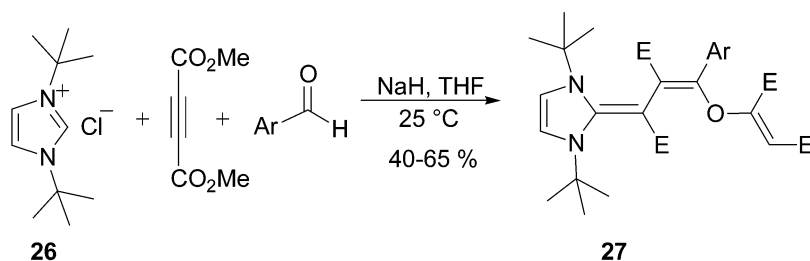
Scheme 7

When imidazol-2-ylidene derived from **24** was employed as the carbene component, the reaction took another course, resulting in the formation of furanone derivatives **25** (Scheme 8) [22].



Scheme 8

The difference in reactivity of NHCs generated from **22** and **24** can be attributed to the aromatic stabilization of the latter carbene, which favors the formation of a carbene-DMAD dipole, while the nonstabilized carbene generated from **22** adds to the aldehyde. Another interesting feature of the reactivity of NHCs in these reactions is the influence of the substituent on nitrogen. Very recently, we have observed that by merely changing the substituent on nitrogen from mesityl to *tert*-butyl, the reaction takes an entirely different course. When imidazol-2-ylidene generated from **26** was treated with DMAD (2 equiv) and aldehydes, a novel four-component reaction was observed (Scheme 9) [23]. It is especially noteworthy that both the unsymmetrical olefinic bonds are formed with complete stereoselectivity in the reaction.

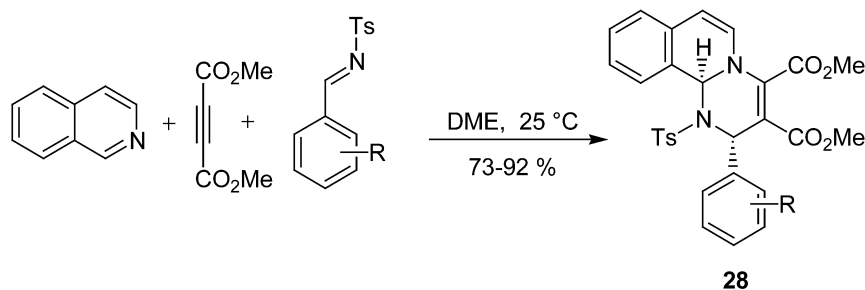


Scheme 9

This seemingly random reactivity pattern of NHCs is a subject of our current investigation.

MULTICOMPONENT REACTIONS OF ISOQUINOLINE

The 1,4-dipole generated from isoquinoline and DMAD [24] was attractive from a synthetic viewpoint since it offered multitudes of possibilities for construction of heterocycles of complex structure in a single step from readily available compounds. In the initial phase of our study, it was observed that treating a mixture of DMAD and *N*-tosylimines with isoquinoline in DME afforded pyrimido-isoquinoline derivatives **28** in excellent yields and good diastereoselectivity (Scheme 10) [25].



Scheme 10

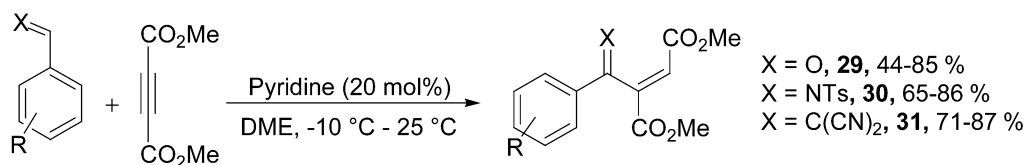
When aldehydes were employed as the third components in this reaction, excellent yields of oxazino-isoquinolines were obtained. With 1,2- and 1,4-quinones as the third component, spirooxazino-isoquinolines were isolated as the final product [26].

TWO-COMPONENT REACTIONS TRIGGERED BY NUCLEOPHILES

From the work of Huisgen [27], Winterfeldt [28], Acheson [29], Tebby [30], and others, it is known that nucleophiles like phosphines and pyridine also can generate reactive dipoles by addition to activated acetylenes. The attempted trapping of these dipoles by various third components did not result in the expected products; instead, the nucleophile simply mediated the reaction between the acetylene and the intended trap for the dipole. Further experiments were carried out, and it was observed that only catalytic amounts of the nucleophile were required for these transformations.

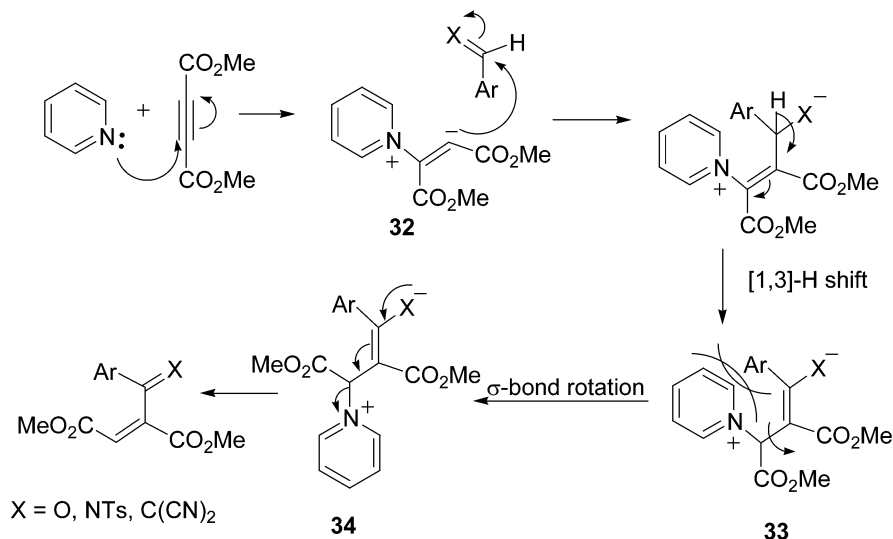
From a synthetic viewpoint, the most important dipolar species that we have come across is the one generated from pyridine and DMAD. Aromatic aldehydes reacted smoothly with DMAD in the presence of catalytic amounts of pyridine to afford high yields of benzoylfumarates with complete stereoselectivity (Scheme 11) [6]. Similarly, reaction of *N*-tosylimines with DMAD was also catalyzed by pyridine to afford highly functionalized 1-azadienes in excellent yields [7]. The reaction of pyridine-

DMAD dipole with activated olefins constituted a completely stereoselective synthesis of highly substituted butadienes in excellent yields [8].



Scheme 11

Mechanistically, these reactions proceed through the initial formation of the 1,4-dipole **32** from pyridine and DMAD. Its addition to the carbonyl compound/olefin and subsequent [1,3]-H shift produces the intermediate **33**. Elimination of pyridine from the sterically less hindered conformation **34** affords the product (Scheme 12).

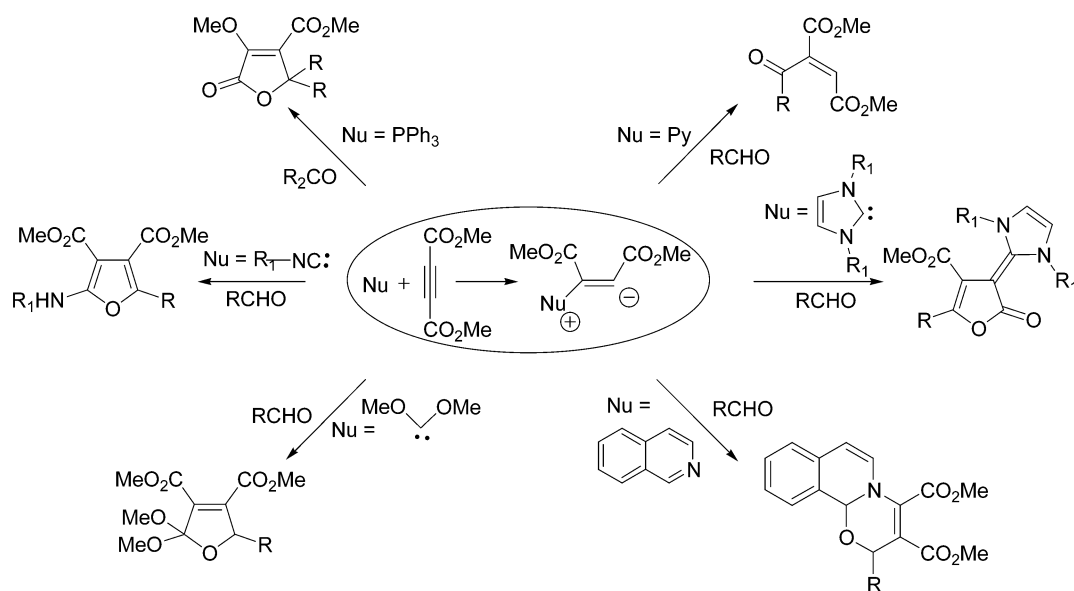


Scheme 12

SUMMARY

The conceptual framework that is pivotal to the design of the reactions described in the previous sections is depicted in Scheme 13.

Central to this versatile class of reactions is the generation of reactive dipolar species from the addition of nonprotic nucleophiles to activated acetylenes. The pronounced affinity of these dipolar species toward carbon electrophiles was exploited to develop many novel organic transformations. The fate of the dipolar species seems to be largely determined by the nature of the nucleophile used. Pyridine and phosphine were especially noticeable as nucleophiles in the sense that they acted as catalytic mediators for a number of two-component reactions where two electrophiles were assembled together under surprisingly mild conditions. Other nucleophiles like isocyanides, dimethoxycarbene, diaminocarbenes, and isoquinoline initiated novel MCRs, providing access to densely functionalized carbocycles and heterocycles. The available array of carbon electrophiles and variations possible in the nucleophile when combined with the inherent sensitivity of the MCRs toward subtle structural modifications of the substrates render them exceedingly versatile [9].



Scheme 13

These reactions are especially noteworthy for the rapid generation of molecular complexity, operational simplicity, and efficiency. The generously functionalized products are amenable to further transformations, making them potentially attractive synthetic intermediates.

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