

# Strategies for Heterocyclic Construction via Novel Multicomponent Reactions Based on Isocyanides and Nucleophilic Carbenes

VIJAY NAIR,\* C. RAJESH, A. U. VINOD, S. BINDU, A. R. SREEKANTH, J. S. MATHEN, AND LAKSHMI BALAGOPAL

Organic Chemistry Division, Regional Research Laboratory (CSIR), Trivandrum 695 019, India

Received October 23, 2002

## ABSTRACT

This Account focuses mainly on our recent endeavors in the area of multicomponent reactions (MCRs) involving zwitterionic species generated by the addition of isocyanides and nucleophilic carbenes such as dimethoxycarbene and *N*-heterocyclic carbenes to activated alkynes. The strategy employed encompasses the interception of 1:1 zwitterionic species, generated in situ with a wide range of electrophiles. The new MCRs developed offer an efficient and convenient entry into several heterocycles of biological and synthetic importance.

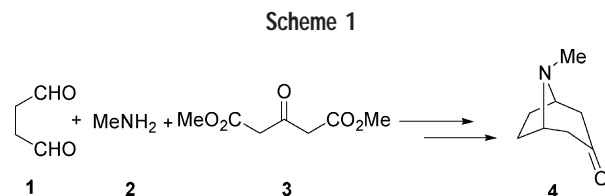
## Introduction

Multicomponent reactions (MCRs), defined as one-pot reactions in which at least three functional groups join through covalent bonds, have been steadily gaining importance in synthetic organic chemistry.<sup>1</sup> The reagents employed may be different molecules or they may be different functional groups of the same reagent. Speed, diversity, efficiency, and environmental amiability are

Vijay Nair has Ph.D degrees from the Banaras Hindu University (1967, with Professor R. H. Sahasrabudhey) and the University of British Columbia (1969, with Jim Kutney). Subsequent to obtaining these degrees, he was a postdoctoral fellow with Josef Fried at the University of Chicago, with Peter Yates in Toronto, and with Gilbert Stork at Columbia University. After a 16-year career (Senior Research Chemist and Principal Scientist) with Lederle Laboratories (American Cyanamid Co.) in Pearl River, NY, he returned to his native Kerala State in India and joined the Regional Research Laboratory (CSIR) in 1990 as its Deputy Director, where he established an Organic Synthesis Division. During 1997–2001 he was the Director of the Institute. Presently he is continuing as a Director-Grade Scientist. Dr. Nair's research interests are in the areas of oxidative electron-transfer mediated C–C and C–heteroatom bond-forming reactions, multicomponent reactions, heterocyclic synthesis, and medicinal chemistry. Dr. Nair has lectured extensively at universities in Germany, Japan, the United States, and India. He is a Fellow of the Indian Academy of Sciences.

C. Rajesh obtained his M.Sc. degree in chemistry from Mahatma Gandhi University, Kottayam. He completed his Ph.D (2002) under the supervision of Dr. Vijay Nair at the Regional Research Laboratory (CSIR). Subsequently he has been a postdoctoral fellow at the University of Pennsylvania, Philadelphia, with Professor Jeff Winkler.

A. U. Vinod obtained his M.Sc in chemistry from Calicut University. His doctoral thesis was completed under the supervision of Dr. Vijay Nair, and he obtained the Ph.D from Mahatma Gandhi University (2003). Currently Vinod is a postdoctoral fellow with Professor David Crich at the University of Illinois in Chicago.



some of the key features of this class of reactions. The history of MCRs dates back to 1838, when Laurent and Gerhardt prepared “benzoylazotid” from bitter almond oil and ammonia.<sup>2</sup> Robinson’s tropinone synthesis from succinic dialdehyde, methylamine, and dimethyl acetonedicarboxylate provides a spectacular example of the application of MCRs in natural product synthesis (Scheme 1).<sup>3</sup>

Although several classes of compounds take part in MCRs, the most successful ones are isocyanide-based MCRs like the Passerini three-component reaction (P-3CR)<sup>4</sup> and the Ugi four-component reaction (U-4CR).<sup>5</sup> This is attributable, mainly, to the presence of formal divalent carbon in these species (Scheme 2).

We have a long-standing interest in this field; the observation that the methylene derivatives resulting from the addition of aldehydes to Meldrum’s acid can be intercepted by phloroglucinol being the starting point.<sup>6</sup> In this article, we provide an account of some of our recent efforts to develop novel multicomponent reactions for heterocyclic construction by means of isocyanides as well as nucleophilic carbenes.

## Background

Among the plethora of methods available for heterocyclic construction, the generation of 1,3-dipolar species and their trapping by suitable  $\pi$  systems leading to five-membered heterocycles occupies a prime position, attributable in a large measure to the monumental contri-

\* To whom correspondence should be addressed. Fax: 91-471-2491712. Tel.: 91-471-2490406. E-mail: vijaynair\_2001@yahoo.com.

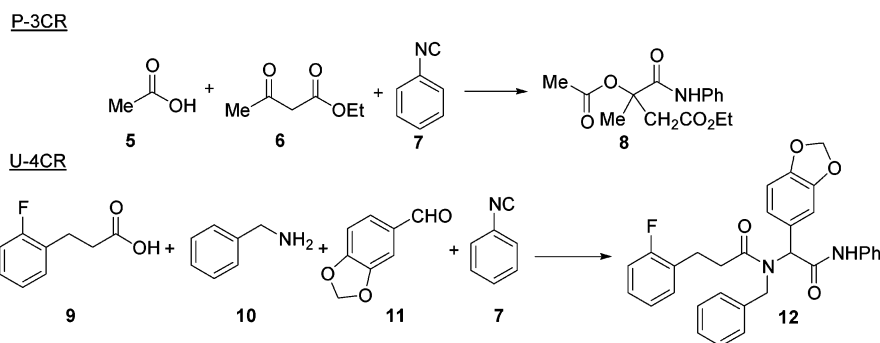
S. Bindu obtained her M.Sc in chemistry from Mahatma Gandhi University. She completed her Ph.D thesis (2003) under the supervision of Dr. Vijay Nair. She will soon start her post-doctoral fellowship with Professor Robert Coates at the University of Illinois in Urbana–Champaign.

A. R. Sreekanth obtained his M.Sc in chemistry from Mahatma Gandhi University. Subsequently he completed his Ph.D thesis (2002) under the supervision of Dr. Vijay Nair. At the present time he is engaged in postdoctoral work with Professor Christoph Schneider at the University of Göttingen in Germany.

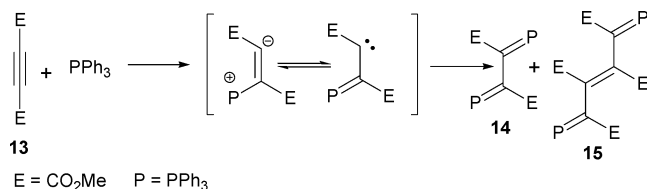
Joseph Swaroop Mathen obtained his M.Sc in chemistry from the University of Kerala. His doctoral research was carried out under the supervision of Dr. Vijay Nair, and he obtained his Ph.D (2001) from the University of Kerala. He is currently a Senior Research Associate with Albany Molecular Research, Inc., in Syracuse, NY.

Lakshmi Balagopal obtained her M.Sc in chemistry from Calicut University. She conducted her doctoral research under the supervision of Dr. Vijay Nair and obtained her Ph.D (2002) from Kerala University. She is currently a postdoctoral fellow at the Curie Institute (University of Paris, Sud) with Professor David Grierson. Shortly she will join the group of Professor Günter Helmchen at the University of Heidelberg as an Alexander von Humboldt Fellow.

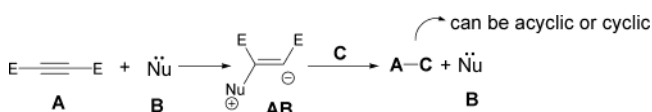
Scheme 2



Scheme 3



butions of Huisgen.<sup>7</sup> Consequent to the success of these reactions, the concept of generating and trapping a variety of zwitterionic species leading to heterocycles appeared attractive. Zwitterionic species often result from the addition of nucleophiles to activated alkynes like dimethyl acetylenedicarboxylate (DMAD).<sup>8</sup> A variety of nucleophiles such as triphenyl phosphine (PPh<sub>3</sub>),<sup>9</sup> pyridine,<sup>10</sup> tertiary amine,<sup>11</sup> dimethyl sulfoxide,<sup>12</sup> etc. has been known to generate zwitterionic species by this pathway. These reactive intermediates can be captured by suitable substrates, and, after a series of transformations, the nucleophile gets eliminated from the system. Thus, the effective role played by the nucleophile is to “conduct” a reaction involving two components (Figure 1).



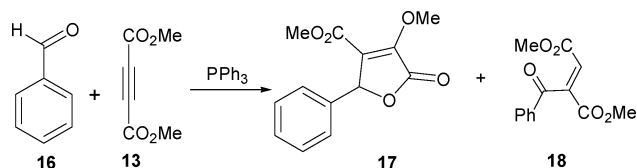
**FIGURE 1.** Formation and reaction pathway of zwitterionic intermediates.

In this type of two-component reactions catalyzed by nucleophiles, triphenyl phosphine (PPh<sub>3</sub>) has been the most studied nucleophilic species. As early as 1961, Tebby observed that addition of PPh<sub>3</sub> to various activated alkynes like DMAD, dicyanoacetylene, and dibenzoylacetylene generates zwitterionic intermediates.<sup>9</sup> The chemistry of these intermediates has been studied in detail (Scheme 3).

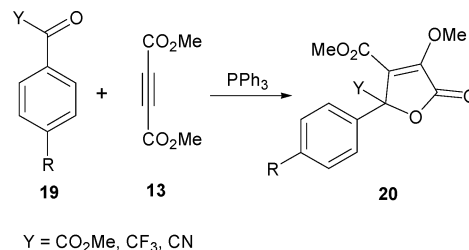
The trapping of this zwitterionic species with benzaldehyde, resulting in a low yield of the  $\gamma$ -lactone, has been reported by Winterfeldt (Scheme 4).<sup>8</sup>

Subsequently, Nozaki modified the Winterfeldt protocol by employing activated carbonyl compounds, obtaining reasonably good yields of the adducts (Scheme 5).<sup>13</sup>

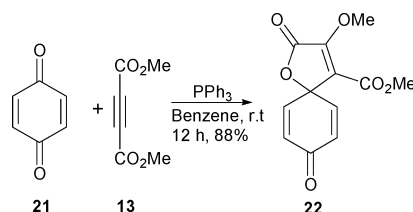
Scheme 4



Scheme 5



Scheme 6



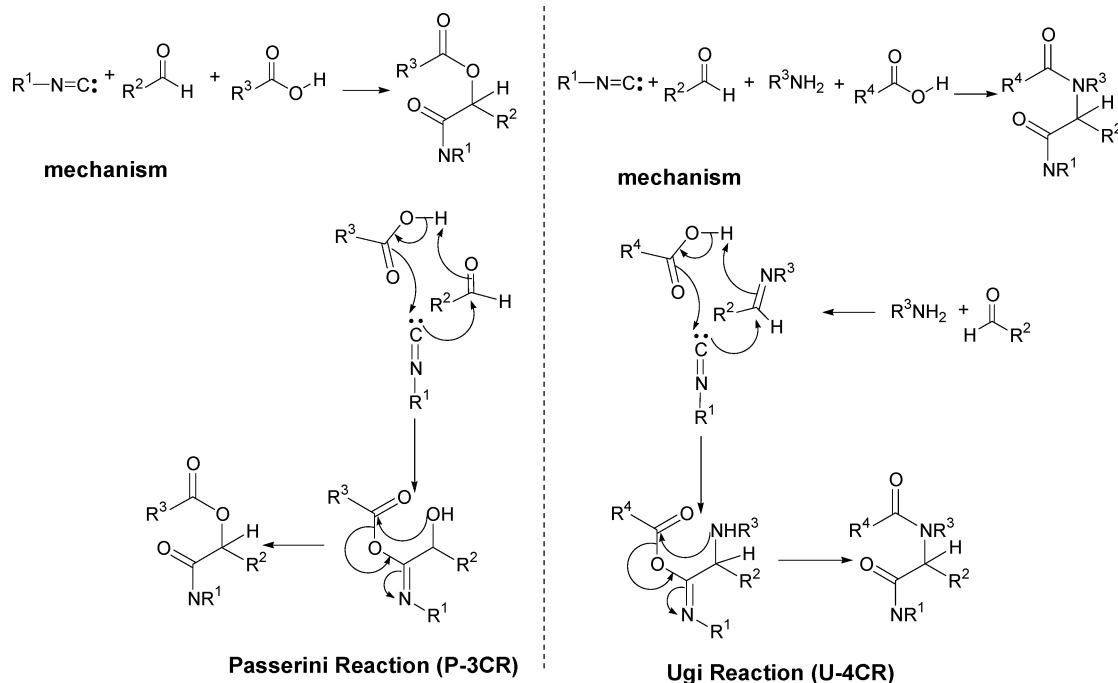
We observed that the activated carbonyl of benzoquinones can successfully take part in these reactions, affording spirofused heterocyclic compounds (Scheme 6).<sup>14</sup>

It is worth mentioning that Trost<sup>15</sup> and Lu<sup>16</sup> have independently developed the intra- and intermolecular two-component transformations of electron-deficient alkynes and allenes catalyzed by PPh<sub>3</sub>, and an account of this work has appeared recently.<sup>17</sup>

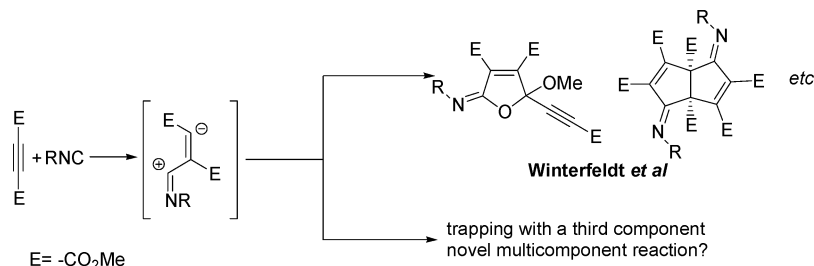
Similar zwitterionic species have been known to result from the addition of an isocyanide to DMAD. Isocyanides, however, differ in their reactivity profile due to the presence of the formal divalent carbon. In transformations involving these entities, this divalent carbon gets converted to a tetravalent state, which makes the addition irreversible. It may be recalled that this property of isocyanides has been crucial in the successful development of classical multicomponent reactions like P-3CR and U-4CR (Scheme 7).

Winterfeldt, in his pioneering work, had observed that isocyanides readily add to DMAD, affording several ad-

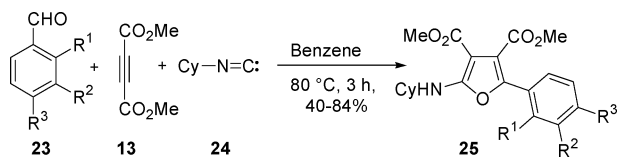
Scheme 7



Scheme 8

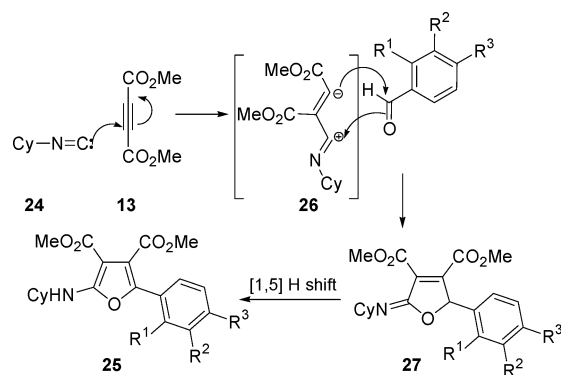


Scheme 9

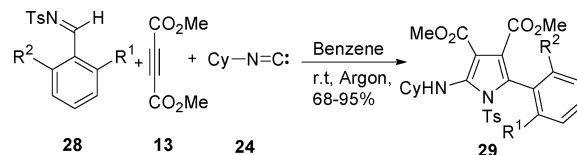


ducts,<sup>18</sup> all essentially involving isocyanide and DMAD in different proportions. Subsequently, George et al. have established the structure of the adducts by single-crystal X-ray analysis and also studied their thermal isomerizations.<sup>19</sup> We reasoned that the high nucleophilicity and the formal divalent nature of isocyanides augur well for the development of novel multicomponent reactions other than P-3CR and U-4CR. As a conceptual framework, this involves the capture of the zwitterionic species, generated by the addition of nucleophilic carbenes to DMAD, by a third component (Scheme 8). This simple theme was appealing in its promise of access to several heterocyclic compounds in high yields, in a convenient one-pot operation. One remarkable feature of the methodology is that, in principle, each of the three components can be varied, thus allowing the delivery of a large number of compounds, rendering the process particularly attractive for the construction of combinatorial sortiments.<sup>20</sup> Our

Scheme 10

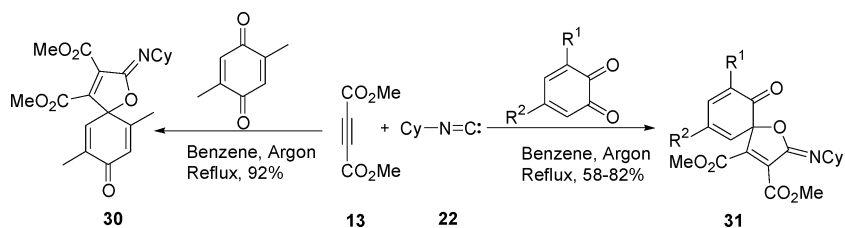


Scheme 11

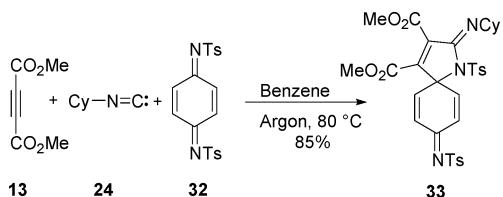


efforts in this direction, along with the seminal work by other groups in this area, is the major focus of the present Account.

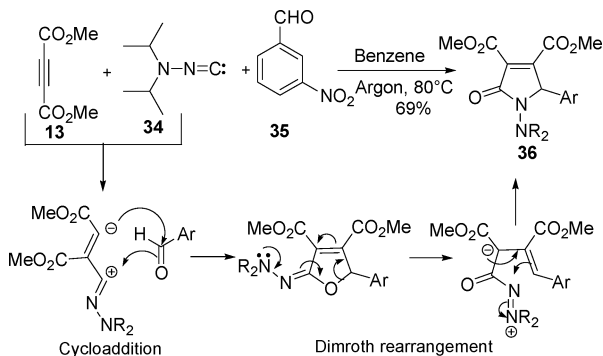
Scheme 12



Scheme 13



Scheme 14



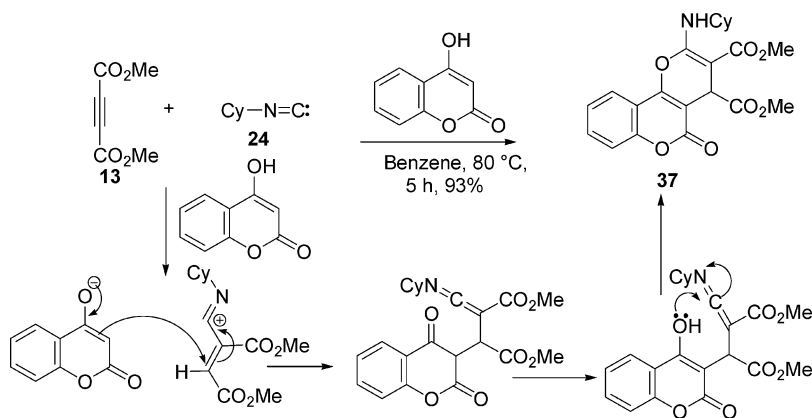
The subject matter of this Account is grouped under the following headings: 1. Trapping of the Zwitterionic Species Generated by the Addition of Isocyanides to DMAD; 2. Trapping of the Zwitterionic Species Generated by the Addition of Dimethoxycarbene to DMAD; 3. Trapping of the Zwitterionic Species Generated by the Addition of *N*-Heterocyclic Carbenes to DMAD; 4. Studies with Isoquinoline as the Nucleophile; and 5. Concluding Remarks.

## 1. Trapping of the Zwitterionic Species Generated by the Addition of Isocyanides to DMAD

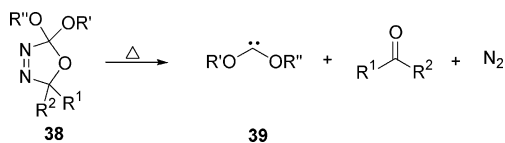
There have been attempts to trap the zwitterionic species generated by the addition of isocyanides to DMAD (Winterfeldt's zwitterion) by a third component,<sup>21</sup> but these were essentially unsuccessful. Undoubtedly, a successful reaction held the prospect of discovering novel multicomponent reactions. With the conviction of the soundness of the conceptual framework and with our experience in the related  $\text{PPh}_3$ -induced reactions (vide supra), we decided to explore this area. The correct choice of the third component was crucial; it should be inert toward both DMAD and isocyanide and at the same time should be more reactive toward the zwitterion than DMAD itself! After much careful experimentation, we broke through the problem: aldehydes satisfied both of these criteria. Thus, the reaction of DMAD, cyclohexyl isocyanide, and 3-nitrobenzaldehyde in refluxing benzene afforded the 2-aminofuran **25** in good yield (Scheme 9). The reaction was found to be general, with aldehydes **23** giving the analogous adducts in good yields.<sup>22</sup> It may be pointed out that the aminofurans generally are very good  $4\pi$ -components in cycloaddition reactions and can serve as the starting material in many natural product syntheses.<sup>23</sup>

A mechanistic rationale for this transformation is depicted in Scheme 10. The initial event involves the generation of the zwitterion **26** by the addition of isocyanide to DMAD. This zwitterionic species then annulates the aldehyde carbonyl, affording the primary adduct **27**, which eventually yields the final furan derivative **25** after a [1,5] H shift. The annulation step can be concerted or

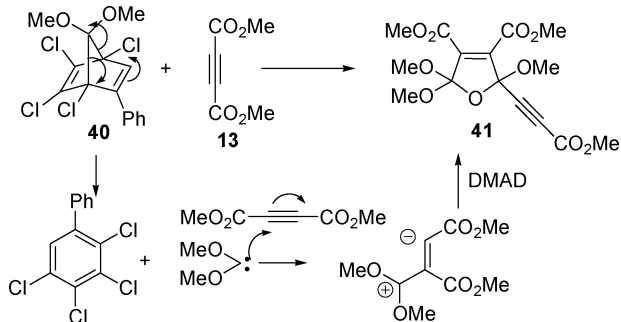
Scheme 15



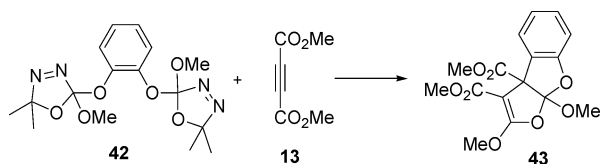
Scheme 16



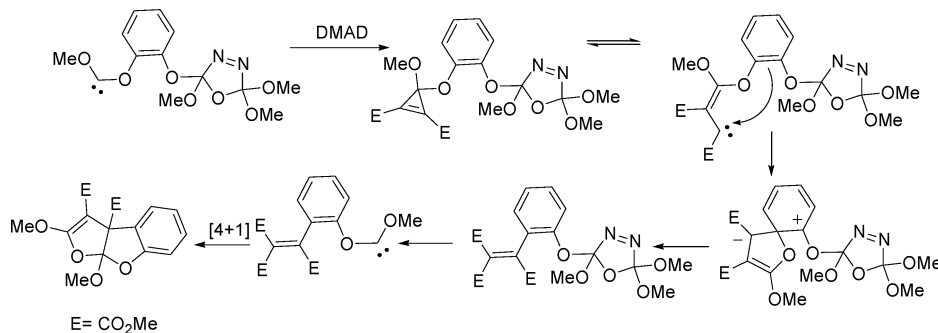
Scheme 17



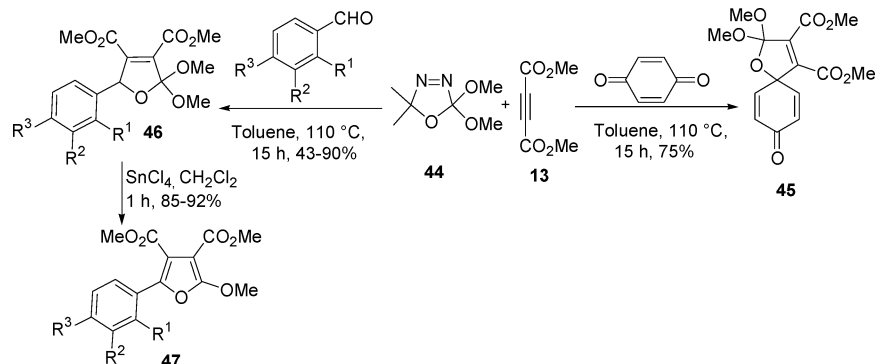
Scheme 18



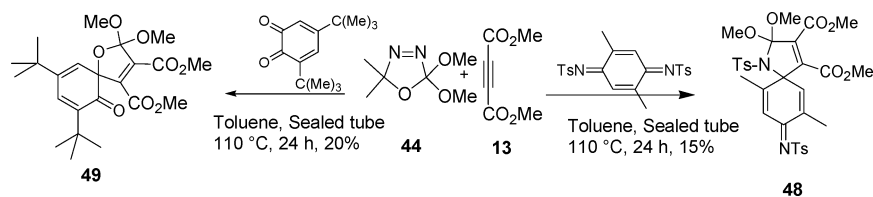
Scheme 19



Scheme 20



Scheme 21



stepwise; the present experience does not allow a distinction to be drawn.

Impressed by the success of the reaction, we turned our attention to trapping the zwitterion with imines, as this would furnish aminopyrrole derivatives if the reaction proceeded parallel to the case of aldehydes. In the event, the reaction followed the expected course, affording the aminopyrrole derivatives **29** in good yields (Scheme 11).<sup>24</sup>

In addition, we studied the reactivity of zwitterionic species toward quinone. This was particularly interesting, considering the fact that quinones offer multiple sites of potent reactivity. It was found that both *o*- and *p*-benzoquinones were annulated by the zwitterion at the C=O function, yielding spirofused heterocyclic structures (Scheme 12).<sup>25</sup>

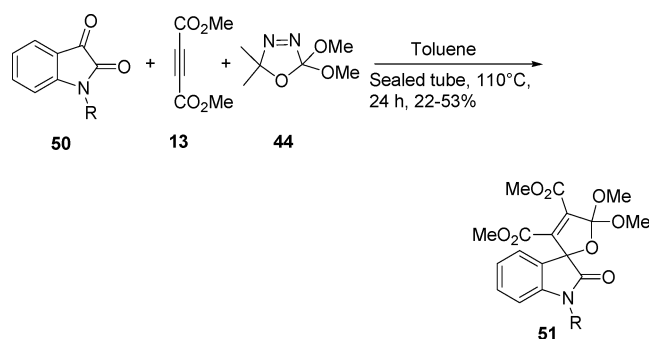
*p*-Quinoneimines also behaved analogously, affording the spirodihydropyrrole derivative **33** (Scheme 13).<sup>24</sup>

When we employed *N*-isocyanides in the reaction with aldehydes, the pyrrolinone **36** resulted from the domino cycloaddition–Dimroth rearrangement sequence (Scheme 14).<sup>26</sup>

During our studies, it was also established that the zwitterionic intermediate can be efficiently intercepted by heterocyclic C–H acids. The trapping of the zwitter-



Scheme 22



terion by 4-hydroxycoumarin to afford a pyranocoumarin derivative is a typical example. Other acids of similar nature also afforded the analogous adducts (Scheme 15).<sup>27</sup>

## 2. Trapping of the Zwitterionic Species Generated by the Addition of Dimethoxycarbene to DMAD

With the reasonable expectation that nucleophilic carbenes would play the key role in analogous reactions, we decided to explore this area. The overwhelming success of the reactions involving isocyanides, which can be regarded as nucleophilic carbenes, provided an optimistic scenario, and the easy availability of nucleophilic carbenes such as dimethoxycarbene by the Warkentin protocol provided the additional impetus. Parenthetically, it may be added that, although dimethoxy and other nucleophilic carbenes have been known in the literature for some time,<sup>28</sup> the past few years have witnessed renewed interest in the chemistry of these species, thanks mainly to the efforts of Warkentin. Thermolysis of suitably substituted oxadiazolines readily afforded alkoxy- and alkylthio-substituted carbenes (Scheme 16).<sup>29</sup>

Earlier studies by Hoffmann had shown that dimethoxycarbene underwent addition to DMAD, affording a 1:2 adduct **41** in low yield (Scheme 17).<sup>30</sup>

The unique reactivity of nucleophilic carbenes offers vast potential in natural product synthesis, as illustrated by the recent synthesis of the azepinoindole substructure, which is present in a number of stemona alkaloids, by Rigby.<sup>31</sup> In this Account, however, the focus is on some novel multicomponent reactions based on these species. To put things in perspective, the reaction of dimethoxycarbene with DMAD is briefly mentioned.

In a mechanistically intriguing reaction, the thermolysis of bis(oxadiazoline) **42** in the presence of DMAD resulted in the formation of the fused, three-ring heterocyclic system **43** (Scheme 18).<sup>32</sup>

A mechanistic rationale for the reaction à la Warkentin can be represented as shown in Scheme 19.<sup>32</sup>

To the best of our knowledge, there has not been any successful attempt to trap the initially formed 1:1 zwitterionic species of dimethoxycarbene and DMAD with a third component. We reasoned that the intermediate could be trapped, since the reactivity of dimethoxycarbene is comparable to that of isocyanides. The validity of this assumption was attested by the successful interception of the zwitterionic species with aldehydes and quinones (Scheme 20).<sup>33</sup>

The attempted interception of the zwitterion with *o*-quinones and quinoneimides also gave the corresponding products, albeit in low yields. This may be due to the reduction of the quinonoid moieties by electron transfer during the course of the reaction (Scheme 21).

When applied to isatins, a class of biologically important molecules, the reaction furnished the spiro dihydrofuran derivatives in moderate yields (Scheme 22).

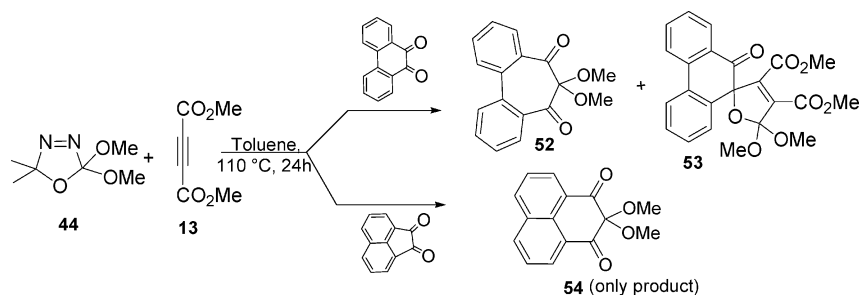
A different kind of reactivity pattern was observed with other 1,2 diones like phenanthrene quinone and acenaphthene quinone under similar conditions; both inserted and intercepted products were obtained<sup>34</sup> (Scheme 23)

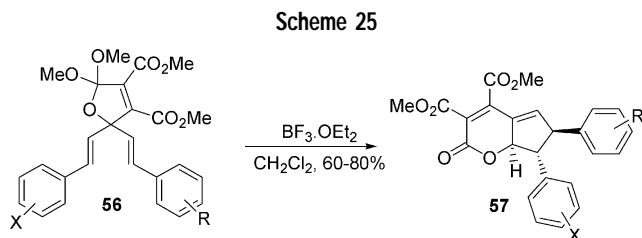
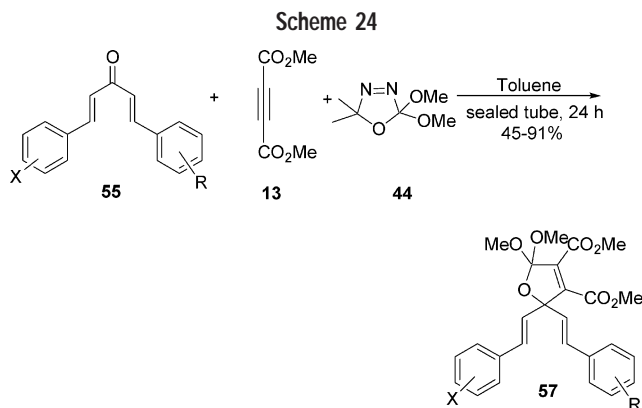
1,4-Dienones are a group of interesting organic compounds whose participation in many organic reactions has been studied in detail; the most important one is the cationic electrocyclization reaction termed the Nazarov reaction.<sup>35</sup> The multicomponent reaction of 1,4-dienones, DMAD, and dimethoxycarbene afforded the distyrenyl dihydrofurans in good yields (Scheme 24).

When the distyrenyl dihydrofurans were exposed to a Lewis acid, they underwent an interrupted Nazarov reaction, yielding bicyclic lactones as shown in Scheme 25.<sup>36</sup>

A mechanistic rationale for this reaction is given in Scheme 26. Initial coordination of the Lewis acid to the dihydrofuran derivative **56** yields the diallyl cation which undergoes a facile  $4\pi$  electrocyclic ring closure resulting in a new C–C bond, two new stereocenters and an allyl cation. This allyl cation is trapped by the pendant ortho ester borate, establishing a new C–O bond and elimina-

Scheme 23





tion of methanol, ultimately leading to the bicyclic lactone **57**.

### 3. Trapping of the Zwitterionic Species Generated by the Addition of *N*-Heterocyclic Carbenes to DMAD

Ever since the isolation and characterization of a stable crystalline diaminocarbene by Arduengo in 1991, there has been growing interest in the exploration of the structure and chemical reactivities of *N*-heterocyclic carbenes.<sup>37</sup> By virtue of their strong  $\sigma$ -donating ability, *N*-heterocyclic carbenes have found impressive use as ligands in the preparation of catalysts in organometallic chemistry.<sup>38</sup> Even though the coordination and catalytic properties of NHCs have been studied in detail, much of the fundamental chemistry of these species remains unexplored. In this context, we decided to exploit the nucleophilic properties of these carbenes in MCRs with DMAD and electrophiles such as aldehydes. Our studies commenced by exposing 3-chlorobenzaldehyde to DMAD and 1,3-dimesitylimidazol-2-ylidene, generated in situ by the reaction of 1,3-dimesitylimidazolium chloride with sodium

hydride in THF under an argon atmosphere. A facile reaction leading to the formation of the furanone derivative **60** occurred (Scheme 27).<sup>39</sup>

Similar reactions were observed with other substituted aldehydes, and furanone derivatives were obtained in moderate to excellent yields.

A mechanistic rationale for this reaction is given in Scheme 28.

It is conceivable that the addition is initiated by the formation of the zwitterion **61** from the carbene and DMAD, which adds to the aldehyde to form another zwitterionic species **62**. This ion, presumably for steric reasons, adds to the ester carbonyl of DMAD in preference to the iminium ion to afford **63**, which subsequently eliminates a proton to furnish the furanone derivative **60**.

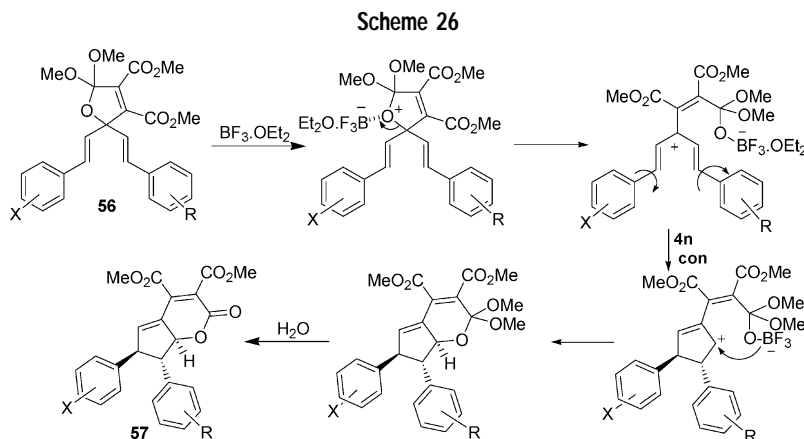
### 4. Studies with Isoquinoline as the Nucleophile

In related investigations, we have found that the zwitterion from isoquinoline and DMAD can be trapped by aldehydes and quinones in a manner akin to the trapping of the zwitterion from isocyanide or dimethoxycarbene and DMAD. Illustrative examples are given in Scheme 29.<sup>40</sup>

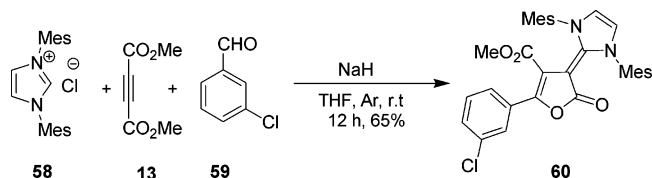
Analogous three-component condensation of isoquinoline, DMAD, and *N*-tosylimine resulted in the diastereoselective synthesis of 2*H*-pyrimido[2,1-*a*]isoquinoline derivatives in good yields (Scheme 30).<sup>41</sup>

### 5. Concluding Remarks

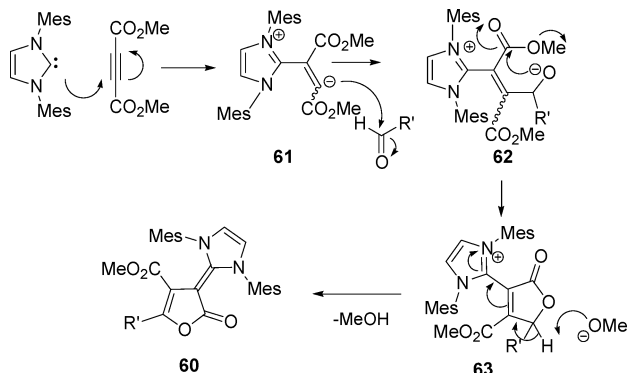
Novel multicomponent reactions based on isocyanides and nucleophilic carbenes such as dimethoxycarbene and 1,3-dimesitylimidazol-2-ylidene offer a convenient entry into several interesting heterocyclic structures. The three components involved in the reaction are nucleophilic carbenes, an activated acetylene, and an intercepting molecule. As far as the third component is concerned, it has the maximum range, spanning from aldehydes to quinonoids. This list includes a large number of electrophilic species, and consequently the reaction can give rise to a variety of heterocyclic structures. As for the first component, isocyanides and nucleophilic carbenes such



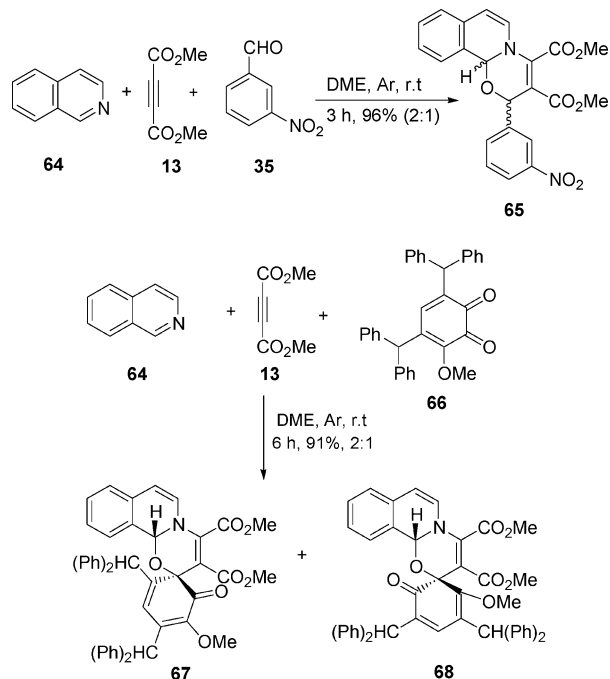
Scheme 27



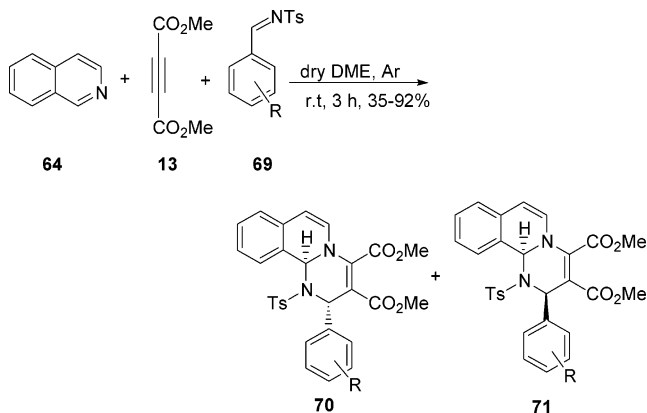
Scheme 28



Scheme 29



Scheme 30



The authors thank Council of Scientific and Industrial research, New Delhi, for providing financial assistance.

## References

- Dömling, A.; Ugi, I. Multicomponent Reactions with Isocyanides. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210.
- Laurent, A.; Gerhardt, C. F. Ueber einige Stickstoffverbindungen des Benzoyls. *Liebigs Ann. Chem.* **1838**, *28*, 265.
- Robinson, R. Synthesis of Tropinone. *J. Chem. Soc.* **1917**, *111*, 762–768.
- (a) Passerini, M. Sopra gli isonitrili(I). Composto del p-isonitril-azobenzolo con acetone ed acido acetico. *Gazz. Chim. Ital.* **1921**, *51* (II), 126–129. (b) Passerini, M. Sopra gli isonitrili(I). Sopra gli isonitrili(II). Composti con aldeidi o con chetoni ed acidi organici monobasici. *Gazz. Chim. Ital.* **1921**, *51* (II), 181–188.
- Ugi, I.; Meyr, R.; Fitzer, U.; Steinbrücker, C. Versuche mit Isonitrilen. *Angew. Chem.* **1959**, *71*, 386.
- Nair, V. The reaction of Meldrum's Acid with Aldehydes and Phloroglucinol: A Synthesis of Dihydrocoumarins. *Synth. Commun.* **1987**, *17*, 723–727.
- Huisgen, R. Centenary Lecture 1,3-Dipolar Cycloadditions. *Proc. Chem. Soc.* **1961**, 357–369.
- Winterfeldt, E. Additions to the Activated CC Triple Bond. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 423–434.
- (a) Johnson, A. W.; Tebby, J. C. The Adducts from Triphenylphosphine and Dimethyl Acetylenedicarboxylate. *J. Chem. Soc.* **1961**, 2126–2130. (b) Tebby, J. C.; Wilson, I. F.; Griffiths, D. V. Reactions of Phosphines with Acetylenes. Part 18. The Mechanism of formation of 1,2-Alkylidene Phosphoranes. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2133–2135.
- (a) Diels, O.; Alder, K. Synthesen in der hydroaromatischen Reihe. *Liebigs Ann. Chem.* **1932**, *498*, 16–49. (b) Acheson, R. M. Reactions of Acetylene carboxylic Acids and Their Esters with Nitrogen-Containing Heterocyclic Compounds. *Adv. Heterocycl. Chem.* **1963**, *1*, 125–165.
- Winterfeldt, E. Reaktionen des Propiolsäureesters mit tertiären Aminen. *Chem. Ber.* **1964**, *97*, 1952–1958.
- Winterfeldt, E. Additionen an die Dreifachbindung III Die Reaktion von Acetylenedicarbonsäure-dimethyl ester mit Dimethylsulfoxid. *Chem. Ber.* **1965**, *98*, 1581–1587.
- (a) Winterfeldt, E.; Dillinger, H. J. Additionen an die Dreifachbindung VI Heterocyclen aus Acetylenverbindungen. *Chem. Ber.* **1966**, *99*, 1558–1568. (b) Nozaki, K.; Sato, N.; Ikeda, K.; Takaya, H. Synthesis of Highly Functionalised  $\gamma$ -Butyrolactones from Activated Carbonyl Compounds and Dimethyl Acetylenedicarboxylate. *J. Org. Chem.* **1996**, *61*, 4516–4519.
- Nair, V.; Nair, J. S.; Vinod, A. U. Triphenyl Phosphine Catalysed Addition of Dimethyl Acetylenedicarboxylate to *o*- and *p*-Quinones: A Novel synthesis of Spirolactones. *J. Chem. Soc., Perkin Trans 1* **1998**, 3129–3130.
- Trost, B. M.; Schmidt, T. A. A Simple Synthesis of Dienones via Isomerization of Alkynes Effected by Palladium-Catalysts. *J. Am. Chem. Soc.* **1988**, *110*, 2301–2303.
- Ma, D.; Lin, Y.; Lu, X.; Yu, Y. A Novel Stereoselective Synthesis of Conjugated Dienones. *Tetrahedron Lett.* **1988**, *29*, 1045–1048.
- Lu, X.; Zhang, C.; Xu, Z. Reactions of Electron deficient Alkynes and Allenes under Phosphine Catalysis. *Acc. Chem. Res.* **2001**, *34*, 535–544.
- (a) Winterfeldt, E.; Schumann, D.; Dillinger, H. J. Additionen an die Dreifachbindung XI Struktur und Reaktionen des 2:1-Adduck-

as dimethoxycarbene and 1,3-dimesitylimidazol-2-ylidene have been successfully employed so far, and other nucleophilic carbenes are expected to follow suit. The successful use of isoquinoline as a nucleophile is expected to add another dimension to the MCRs. The major limitation of the process, at this time, is with regard to the activated acetylene component; so far it has been found that only DMAD gives consistently high yields of the product with different other components. It is reasonable to assume that, in due course, other acetylenes or related compounds that can find application in these reactions would emerge. It is expected that this class of reactions will attract the attention of synthetic organic chemists in the near future.



- tes aus Acetylenedicarbonester und Isonitrilen. *Chem. Ber.* **1969**, *102*, 1656–1664. (b) Dillinger, H. J.; Fengler, G.; Schumann, D.; Winterfeldt, E. Additionen an die dreifachbindung-XXI: Das kinetisch kontrollierte addukt aus tert.butylisonitril und acetylenedicarbonester. *Tetrahedron* **1974**, *30*, 2553. (c) Dillinger, H. J.; Fengler, G.; Schumann, D.; Winterfeldt, E. Additionen an die dreifachbindung-XXII: Das thermodynamisch kontrollierte addukt aus tert.butylisonitril und acetylenedicarbonester. *Tetrahedron* **1974**, *30*, 2561–2564.
- (19) Junjappa, H.; Saxena, M. K.; Ramaiah, D.; Lohray, B. B.; Rath, N. P.; George, M. V. Structure and Thermal Isomerization of the Adducts Formed in the reaction of Cyclohexyl Isocyanide with Dimethyl Acetylenedicarboxylate. *J. Org. Chem.* **1998**, *63*, 9801–9805.
- (20) Professor Roald Hoffmann has categorically rejected the use of “library” to describe a collection of compounds. Instead he has recommended the word “sortiment”. and we subscribe to his view, see: Hoffmann, R. Not a Library. *Angew. Chem., Int. Ed.* **2001**, *40*, 3337–3340.
- (21) Krebs, A.; Guntner, A.; Versteylen, S.; Schulz, S. [1+2]-cycloadditionen von Isocyaniden an indiamine. *Tetrahedron Lett.* **1984**, *25*, 2333–2336.
- (22) Nair, V.; Vinod, A. U. The Reaction of Cyclohexyl Isocyanide with Dimethyl Acetylenedicarboxylate with Aldehydes: A Novel Synthesis of Aminofuran Derivatives. *Chem. Commun.* **2000**, 1019–1020.
- (23) Padwa, A.; Brodney, M. A.; Satake, K.; Straub, C. S. Cycloaddition–Rearrangement Sequence of 2-Amido Substituted Furans as a Method of Synthesizing Hexahydroindolinones. *J. Org. Chem.* **1999**, *64*, 4617–4626.
- (24) Nair, V.; Vinod, A. U. A Novel Synthesis of 2-Aminopyrroles Using a Three Component Reaction. *J. Org. Chem.* **2001**, *66*, 4427–4429.
- (25) Nair, V.; Vinod, A. U.; Nair, J. S.; Sreekanth, A. R.; Rath, N. P. The Reaction of Cyclohexyl Isocyanide and Dimethyl Acetylenedicarboxylate with o- and p-Quinones: A Novel Synthesis of Imino-lactones. *Tetrahedron Lett.* **2000**, *41*, 6675–6679.
- (26) Nair, V.; Mathen, J. S.; Vinod, A. U.; Varma, R. L. Aminoisocyanides in Multicomponent Reactions (MCRs): A Facile Synthesis of Substituted 3(5H)-Pyrrolin-2-ones via a Dimroth Type Rearrangement. *Chem. Lett.* **2001**, 738–739.
- (27) Nair, V.; Vinod, A. U.; Ramesh, R.; Menon, R. S.; Varma, R. L.; Mathew, S.; Chiaroni, A. An Efficient Multicomponent Reaction Involving the Interception of the Zwitterionic Intermediate between DMAD and Isocyanides with Some Active Methylene Compounds. *Heterocycles* **2002**, *58*, 147–151.
- (28) (a) Hoffmann, R. W. Generation of Carbenes by Thermal Cycloelimination. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 529–537. (b) Moss, R. A.; Wlostowski, M.; Terpinski, J.; Kmeick-Lawryniewicz, G.; Krogh-Jespersen, K. A Diazirine Precursor for a Dioxacarbene and Reactions of Methoxyphenoxy Carbene. *J. Am. Chem. Soc.* **1987**, *109*, 3811–3812.
- (29) (a) El-Saidi, M.; Kassam, K.; Pole, D. L.; Tadey, T.; Warkentin, J. 2,2-Dialkoxy- $\Delta^3$ -1,3,4-oxadiazolines: Convenient Thermal Sources of Dialkoxy-carbenes. *J. Am. Chem. Soc.* **1992**, *114*, 8751–8752. (b) Rigby, J. H.; Laurent, S.; Dong, W.; Danca, D. M. Bis (alkylthio) carbenes as Novel Reagents for Organic Synthesis. *Tetrahedron* **2000**, *56*, 10101–10111.
- (30) Hoffmann, R. W.; Lillienblum, W.; Dittrich, B. Addition von Dimethoxycarben an C–C Mehrfachbindungen. *Chem. Ber.* **1974**, *107*, 3395–3407.
- (31) Rigby, J. H.; Laurent, S.; Cavezza, A.; Heeg, M. J. Construction of the Azepinoindole Core Tricycle of the Stemonia Alkaloids. *J. Org. Chem.* **1998**, *63*, 5587–5591.
- (32) Lu, X.; Warkentin, J. Ipsi Aromatic Substitution from Reaction of a Carbene with DMAD. *Tetrahedron Lett.* **1999**, *40*, 1483–1486.
- (33) Nair, V.; Bindu, S.; Balagopal, L. A novel multicomponent reaction of dimethoxycarbene and DMAD with aldehydes and quinones: Facile synthesis of dihydrofuran derivatives. *Tetrahedron Lett.* **2001**, *42*, 2043–2044.
- (34) Nair, V.; Ani Deepthi; Balagopal, L.; Bindu, S., unpublished results.
- (35) Reviews: (a) Denmark, S. E. In *Comprehensive Organic Synthesis*, Vol. 5; Trost, B. M., Flemming, I., Eds.; Pergamon: Oxford, 1991; pp 751–784. (b) Habermas, K. L.; Denmark, S. E.; Jones, T. K. *Org. React. (N.Y.)* **1994**, *45*, 1.
- (36) (a) Bender, J. A.; Blize, A. E.; Browder, C. C.; Giese, S.; West, F. G. Highly Diastereoselective Cycloisomerization of Acyclic Trienones. The Interrupted Nazarov Reaction. *J. Org. Chem.* **1998**, *63*, 2430–2431. (b) Giese, S.; West, F. G. The Reductive Nazarov Cyclization. *Tetrahedron Lett.* **1998**, *39*, 8393–8396. (c) Wang, Y.; Arif, A. M.; West, F. G.; A Novel Cycloisomerization of Tetraenones: [4+3] Trapping of the Nazarov Oxyallyl Intermediate. *J. Am. Chem. Soc.* **1999**, *121*, 876–877. (d) Browder, C. C.; West, F. G. Formation of Hydrindanes and Tricyclo[4.3.0.0<sup>3,8</sup>]nonanes via 6-Endo Trapping of the Nazarov Oxyallyl Intermediate. *Synlett* **1999**, 1363–1366. (e) Bender, J. A.; Arif, A. M.; West, F. G. Nazarov-Initiated Diastereoselective Cascade Polycyclization of Aryltrieneones. *J. Am. Chem. Soc.* **1999**, *121*, 7443–7444. (f) Giese, S.; Kastrup, L.; Steins, D.; West, F. G. *Angew. Chem., Int. Ed.* **2000**, *39*, 1970–1973. (g) Browder, C. C.; Marmsäter, F. P.; West, F. G. Highly Efficient Trapping of the Nazarov Intermediate with Substituted Arenes. *Org. Lett.* **2001**, *3*, 3033–3035. (g) Nair, V.; Bindu, S.; Sreekanth, V.; Chiaroni, A. A novel approach to the synthesis of bicyclic lactones via an Interrupted Nazarov reaction of gem-divinyl dihydrofurans. *Org. Lett.* **2002**, *4*, 2821–2823.
- (37) Arduengo, A. J., III; Harlow, R. L.; Kline, M. A. A Stable Crystalline Carbene. *J. Am. Chem. Soc.* **1991**, *113*, 361–363.
- (38) (a) Hermann, W. A. N-Heterocyclic Carbenes: A New Concept in Organometallic Catalysis. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290–1309. (b) Hermann, W. A.; Köcher, C. N-Heterocyclic Carbenes. *Angew. Chem., Int. Ed.* **1997**, *36*, 2162–2187.
- (39) Nair, V.; Bindu, S.; Sreekanth, V.; Rath, N. P. Unprecedented Reactivity of N-Heterocyclic Carbenes toward DMAD and Aldehydes Leading to Novel Multicomponent Reactions. *Org. Lett.* **2003**, *5*, 665–667.
- (40) Nair, V.; Sreekanth, A. R.; Biju, A. T.; Rath, N. P.; The reaction of isoquinoline and dimethyl acetylenedicarboxylate with 1,2- and 1,4-benzoquinones: a novel synthesis of spiro[1,3]oxazino[2,3-a]isoquinolines. *Tetrahedron Lett.* **2003**, *44*, 729–732.
- (41) Nair, V.; Sreekanth, A. R.; Abhilash, N.; Bhadrachand, M. M.; Gonnade, R. C. A Novel Three Component Reaction for the Diastereoselective Synthesis of 2H-Pyrimido[2,1-a]isoquinolines via 1,4-Dipolar Cycloaddition. *Org. Lett.* **2002**, *4*, 3575–3577.

AR020258P