ORGANIC LETTERS

2005
Vol. 7, No. 12
2297−2300

Two Unprecedented Multicomponent Reactions Involving N-Heterocyclic Carbenes, Activated Acetylenes, and Aldehydes†

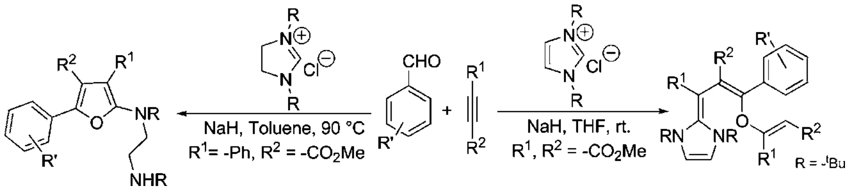
Vijay Nair,*,‡ V. Sreekumar,‡ S. Bindu,‡ and Eringathodi Suresh§

Organic Chemistry Division, Regional Research Laboratory (CSIR),
Trivandrum, India, and Central Salt and Marine Chemicals Research Institute (CSIR),
Bhavnagar 364 002, India

vijaynair_2001@yahoo.com

Received February 10, 2005 *(Revised Manuscript Received April 9, 2005)*

ABSTRACT

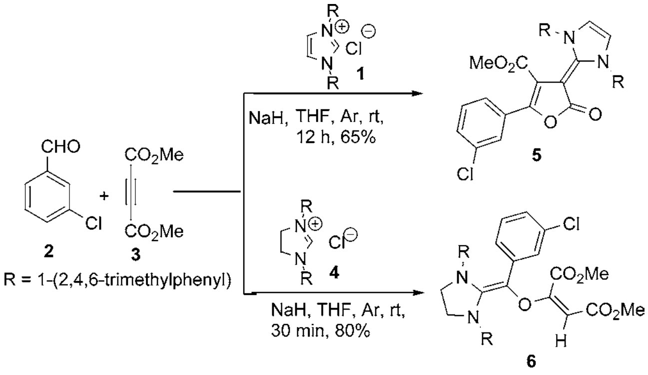


Two unprecedented multicomponent reactions of N-heterocyclic carbenes involving activated acetylenes and aldehydes are described.

Ever since Breslow's original demonstration of the remarkable catalytic properties of N-heterocyclic carbenes (NHCs),[1] the bold but unsuccessful attempt to synthesize an NHC by Wanzlick,[2] and the more recent isolation of stable NHCs by Arduengo,[3] these species have attracted considerable attention from organic chemists. Their role as excellent ligands for transition metals[4] and their ability to efficiently catalyze a number of organic reactions, most notably benzoin condensation,[1] transesterification,[5] aldol reaction, and Michael−Stetter reaction,[6,7] has contributed significantly to the enormous interest in NHCs. There is also a growing awareness of their potential application as reagents[8] in organic reactions as illustrated by their participation in 1,3-dipolar cycloadditions[9] and [4 + 1] cycloaddition reactions.[10]

In the context of our interest in multicomponent reactions (MCRs)[11] triggered by nucleophilic carbenes and related species, we envisioned the possibility of initiating MCRs by NHCs, and our effort in this area led to the first application of these species in MCRs (Scheme 1).[12]

Scheme 1



While the implications of the results are not fully apparent, they clearly warranted further research. Thus, we began to investigate the influence of the N-substituents on the reactiv-

---

† This paper is dedicated with best wishes to Professor Dr. Henning Hopf on the occasion of his 65th birthday.

‡ Regional Research Laboratory (CSIR).

§ Central Salt and Marine Chemicals Research Institute.

(1) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719.

(2) Wanzlick, H.-W. *Angew. Chem. Int. Ed.* **1962**, *1*, 75.

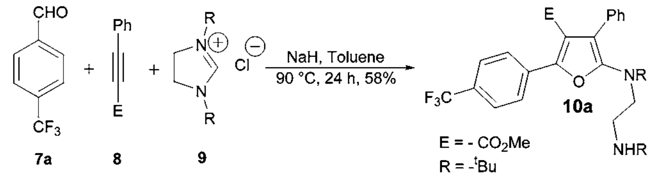
(3) Arduengo, A. J., III; Harlow, R. L.; Kline, M. K. *J. Am. Chem. Soc.* **1991**, *113*, 361.

10.1021/ol0502782 CCC: $30.25

ity of imidazolin-2-ylidene and imidazol-2-ylidene toward activated acetylenes and aldehydes. The resulting novel multicomponent reactions are the subject of this communication.

Our studies commenced with exposure of *tert*-butyl-substituted imidazolin-2-ylidene, generated by the deprotonation of corresponding imidazolinium salt[13] **9** using NaH in dry toluene, with methyl phenylpropiolate and 4-trifluoromethyl benzaldehyde at 90 °C. The reaction afforded the aminofuran derivative **10a** in good yield (Scheme 2).[14]

Scheme 2



The structure of the product **10a** was established by spectroscopic and X-ray analysis (Figure 1).[15] The carbomethoxy protons resonated as a singlet at δ 3.63 while the methylene protons displayed two separate sets of triplets, centered at δ 3.12 ($J = 6.5$ Hz) and δ 2.37 ($J = 6.5$ Hz), in the ^{1}H NMR spectrum. The ester carbonyl group displayed a ^{13}C resonance signal at δ 165.1 supporting the IR absorption at 1723 cm^{-1}.

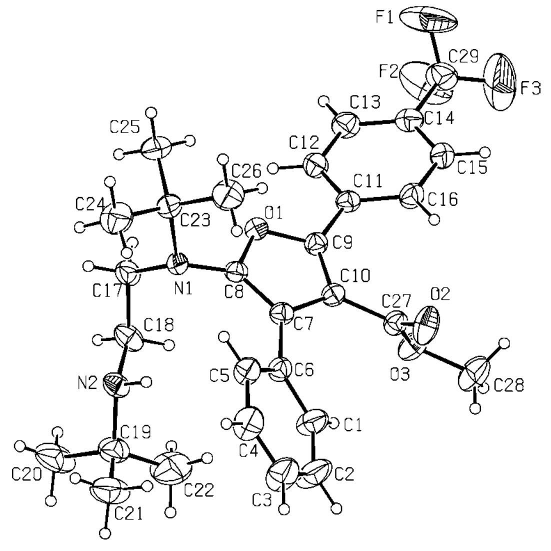
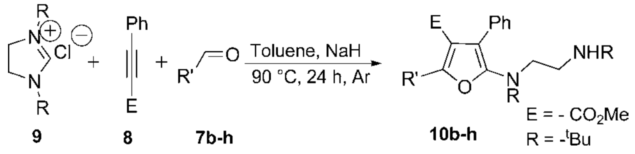


Figure 1. Single-crystal X-ray structure of compound **10a**.

A variety of aromatic aldehydes were found to be suitable candidates for aminofuran synthesis, and methyl phenylpropiolate was found to be a suitable acetylenic component. The results are summarized in Table 1.

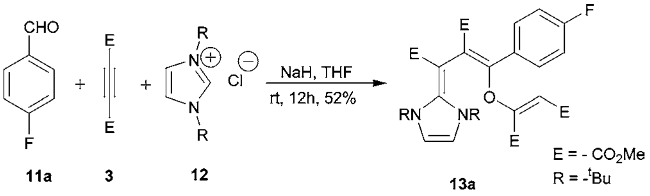
Table 1.



entry	aldehyde	product	yield (%)
1	R′ = 3,4-dichlorophenyl, **7b**	**10b**	53
2	R′= 4-chlorophenyl, **7c**	**10c**	55
3	R′ = 4-bromophenyl, **7d**	**10d**	65
4	R′ = phenyl, **7e**	**10e**	47
5	R′ = 4-methylphenyl, **7f**	**10f**	40
6	R′ = 4-fluorophenyl, **7g**	**10g**	54
7	R′ = 2-thienyl, **7h**	**10h**	55

Encouraged by the results obtained with *tert*-butyl-substituted imidazolin-2-ylidene, we turned our attention to 1,3-di-*tert*-butylimidazol-2-ylidene. To our surprise, the carbene formed in situ failed to react with methyl phenylpropiolate and aldehydes. However, the reaction of the carbene with dimethyl acetylenedicarboxylate (DMAD) and 4-fluorobenzaldehyde proceeded smoothly to deliver an acyclic four-component adduct **13a** in 52% yield (Scheme 3).[16]

Scheme 3



The structure of the product **13a** was established by spectroscopic analysis. Four methoxycarbonyl groups reso-

---

(4) (a) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290. (b) Herrmann, W. A.; Köcher, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2162. (c) Weskamp, T.; Schattenmann, W. C.; Spiegler, M.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2490. (d) Nolan, S. P.; Kelly, R. A., III; Navarro, O. *J. Am. Chem. Soc.* **2003**, *125*, 16194.

(5) (a) Grasa, G. A.; Kissling, R. M.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 3583. (b) Grasa, G. A.; Güveli, T.; Singh, R.; Nolan, S. P. *J. Org. Chem.* **2003**, *7*, 2812. (c) Nyce, G. W.; Lamboy, J. A.; Connor, E. F.; Waymouth, J. L.; Hedrick, R. M. *Org. Lett.* **2002**, *4*, 3587. (d) Singh, R.; Kissling, R. M.; Letellier, M.-A.; Nolan, S. P. *J. Org. Chem.* **2004**, *69*, 209.

(6) (a) Teles, J. H.; Melder, J. P.; Ebel, K.; Schneider, R.; Gehrer, E.; Harder, W.; Brode, S.; Enders, D.; Breuer, K.; Rabbe, G. *Helv. Chim. Acta* **1996**, *79*, 1271. (b) Davis, J. H., Jr.; Forrester, K. *Tetrahedron Lett.* **1999**, *40*, 1621. (c) Enders, D.; Breuer, K.; Runsink, J.; Teles, J. H. *Helv. Chim. Acta* **1996**, *79*, 1899. (d) Enders, D.; Kallfass, U. *Angew. Chem., Int. Ed.* **2002**, *41*, 1743. (e) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298.

(7) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534 and references therein.

(8) Nair, V.; Bindu, S.; Sreekumar, V. *Angew. Chem., Int. Ed.* **2004**, *43*, 5130.

(9) Enders, D.; Breuer, K.; Raabe, J.; Runsink, J.; Teles, J. H. *Liebigs Ann.* **1996**, 2019.

(10) (a) Rigby, J. H.; Wang, Z. *Org. Lett.* **2002**, *4*, 4289. (b) Rigby, J. H.; Wang Z. *Org. Lett.* **2003**, *5*, 263.

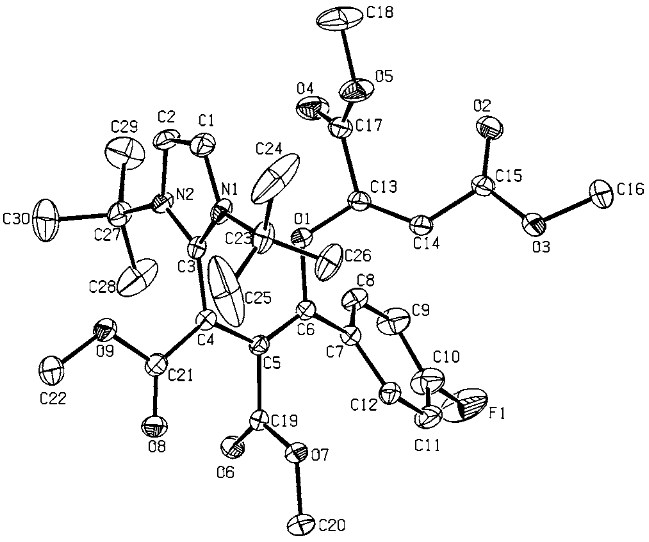
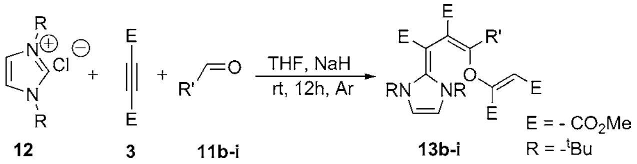


Figure 2. Single-crystal X-ray structure of compound **13a**.

nated at δ 3.78, 3.77, 3.52, and 3.42 in the ^{1}H NMR spectrum. The ester carbonyl groups displayed ^{13}C resonance signals at δ 169.3, 165.5, 163.9, and 163.1 supporting the IR absorption at 1742 cm^{-1}. The olefinic proton was discernible at δ 4.96. The final proof for the structure and stereochemistry was obtained from single-crystal X-ray analysis (Figure 2).

A variety of aldehydes were found to be suitable partners in the reaction, and the results are summarized in Table 2.

Table 2.

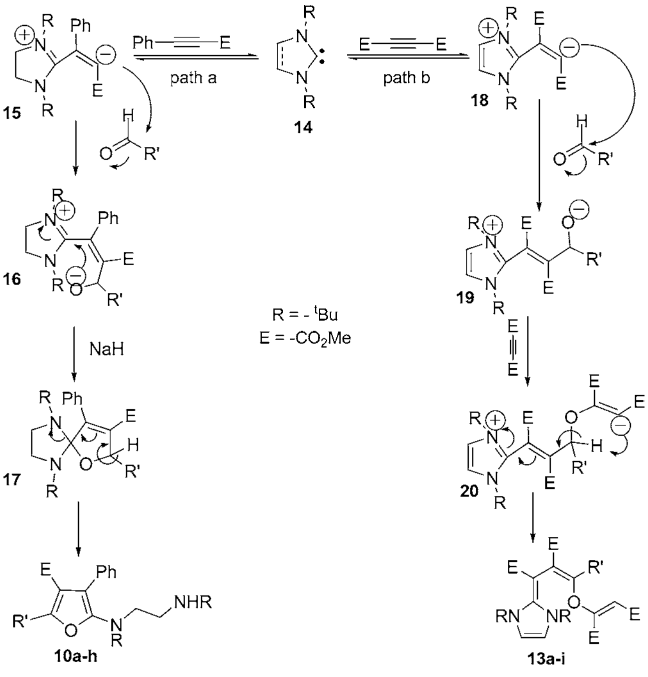


entry	aldehyde	product	yield (%)
1	R′ = 3,4-dichlorophenyl, **11b**	**13b**	56
2	R′= 3-chlorophenyl, **11c**	**13c**	52
3	R′ = 4-bromophenyl, **11d**	**13d**	51
4	R′ = 4-trifluoro methylphenyl, **11e**	**13e**	65
5	R′ = 4-nitrophenyl, **11f**	**13f**	45
6	R′ = 1-naphthyl, **11g**	**13g**	51
7	R′ = 4-methylphenyl, **11h**	**13h**	20
8	R′ = 2-thienyl, **11i**	**13i**	30

It is especially noteworthy that both olefinic bonds created in the reaction are formed with complete stereoselectivity.

The two reactions described here may be rationalized by considering the stereoelectronic features of the carbene and the dipolar intermediates generated during the course of the reactions (Scheme 4). The imidazolin-2-ylidene adds first to activated acetylene to form a dipole **15**. The latter then undergoes a dipolar cycloaddition/cyclization with aldehyde to form the intermediate **17**, which in turn opens to form aminofuran derivatives **10a−h**. The dipolar intermediate **18**

Scheme 4



---

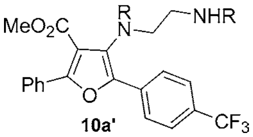
(11) (a) Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekanth, A. R.; Balagopal, L. *Acc. Chem. Res.* **2003**, *36*, 899. (b) Nair, V.; Bindu, S.; Sreekumar, V.; Balagopal, L. *Synthesis* **2003**, 1446.

(12) Nair, V.; Bindu, S.; Sreekumar, V.; Rath, N. P. *Org. Lett.* **2003**, *5*, 665.

(13) Arduengo, A. J., III; Krafczyk, R.; Schmutzler, R. *Tetrahedron* **1999**, 55, 14523.

(14) Representative experimental procedure and spectral data: NaH (20 mg, 0.84 mmol) was added to a suspension of the carbene precursor **9** (122 mg, 0.56 mmol) in dry toluene under argon atmosphere. This was followed by the addition of methyl phenylpropiolate (68 mg, 0.42 mmol) and the aldehyde **7a** (50 mg, 0.28 mmol), and the resulting solution was stirred for 24 h at 90 °C. The reaction mixture was then passed through a short pad of Celite. After removal of the solvent, the residue was subjected to chromatography on a neutral alumina column using 80:20 hexanes−ethyl acetate solvent mixture to afford **10a** (84 mg, 58%) as a white crystalline solid. Mp: 105−106 °C. IR (KBr) $\nu_{\max}$: 2969, 1723, 1619, 1506, 1326, 1164, 1130, 1104, 1023, 864, 697 cm^{-1}. ^{1}H NMR δ: 7.89 (d, J = 9.0 Hz, 2H), 7.66 (d, J = 9.0 Hz, 2H) 7.39−7.25 (m, 6H), 3.63 (s, 3H), 3.12 (t, J = 6.5 Hz, 2H), 2.37 (t, J = 6.5 Hz, 2H), 1.21 (s, 9H), 0.89 (s, 9H). ^{13}C NMR δ: 165.1, 152.6, 148.6, 140.3, 133.3, 132.1, 130.0, 129.0, 127.8, 127.3, 127.0, 125.2, 120.2, 115.6, 109.3, 108.2, 56.9, 51.6, 50.3, 48.6, 41.4, 28.5, 28.3, 27.3. HRMS (EI): calcd for $C_{29}H_{35}F_3N_2O_3$ 516.2599, found 516.2600. CCDC file no. 266011.

(15) On the basis of spectroscopic data, we had originally suggested the structure **10a′** for this compound. One of the reviewers cast doubt on our structure assignment and suggested that we should get X-ray data on this compound. On the basis of the single-crystal X-ray data, we have now revised the structure to **10a**, which is an isomeric relationship to **10a′**. The mechanistic postulation has also been modified. It may be mentioned that the spectroscopic data cannot distinguish the two structures. The insightful suggestion of the reviewer prompting us to obtain single-crystal X-ray data, which led to the correct structure assignment, is gratefully acknowledged.



10a'

generated by the reaction of **14** and **3** adds to the aldehyde to form an alkoxide intermediate **19**. This alkoxide **19** undergoes nucleophilic addition to DMAD to form the zwitterionic intermediate **20**. The latter then stabilizes through an internal proton abstraction furnishing the products **13a**−**i**.

In conclusion, we have uncovered two new multicomponent reactions; the first one constitutes a facile synthesis of substituted aminofuran derivatives and the second reaction is a three-reagent, pseudo-four-component process leading to novel diene derivatives. The tunable reactivity of the carbene observed here may be useful for the synthesis of designer oligomers and heterocycles with interesting properties.

Acknowledgment. We thank the Council of Scientific and Industrial Research (CSIR), New Delhi, for financial assistance.

Supporting Information Available: Detailed synthetic procedures and spectroscopic characterization of compounds and single-crystal X-ray data of compound **10a** and **13a**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0502782

---

(16) **Representative Experimental Procedure and Spectral Data.** NaH (28 mg, 1.2 mmol) was added to a suspension of the carbene precursor **12** (172 mg, 0.80 mmol) in dry THF under argon atmosphere. This was followed by the addition of DMAD (114 mg, 0.80 mmol) and the aldehyde **11a** (50 mg, 0.40 mmol), and the resulting solution was stirred for 12 h. The reaction mixture was then passed through a short pad of Celite. After removal of the solvent, the residue was subjected to chromatography on a neutral alumina column using 30:70 hexanes−ethyl acetate solvent mixture to afford **13a** (93 mg, 52%) as a red crystalline solid. Mp: 234−235 °C. IR (KBr) $\nu_{\max}$: 2929, 1742, 1636, 1563, 1444, 1346, 1212, 1139, 1056, 906, 643 cm^{-1}. ^{1}H NMR δ: 7.29−7.17 (m, 4H), 6.95−6.90 (m, 2H), 4.96 (s, 1H), 3.73 (s, 3H), 3.69 (s, 3H), 3.54 (s, 3H), 3.46 (s, 3H), 1.70 (s, 18H). ^{13}C NMR δ: 169.3, 165.5, 163.9, 163.1, 162.6, 159.4, 149.4, 131.0, 130.9, 128.3, 128.2, 128.1, 117.3, 117.2, 115.3, 115.0, 99.5, 96.0, 63.2, 62.0, 52.3, 52.3, 52.0, 51.3, 48.9, 30.2. CCDC file no. 267780.