ORGANIC LETTERS

2006
Vol. 8, No. 14
3133−3136

Novel Annulation Reactions of Aryl Methyl Ketenes with Zwitterions Derived from Dimethyl Acetylenedicarboxylate and *N*-Alkylimidazoles

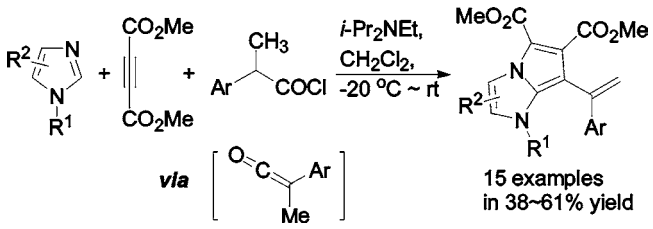
Cheng Ma,* Hanfeng Ding, and Yanguang Wang

Department of Chemistry, Zhejiang University, Hangzhou 310027, China

mcorg@zju.edu.cn

Received May 8, 2006

ABSTRACT

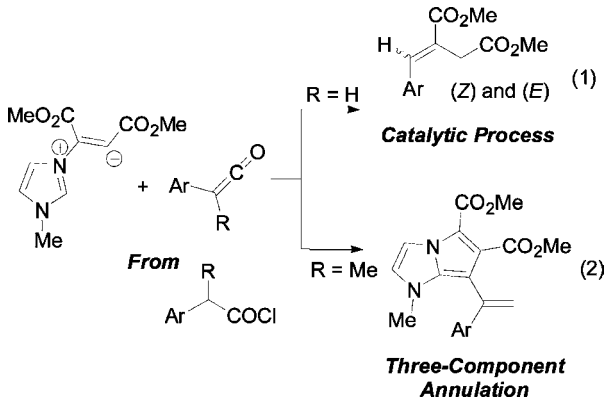


A novel three-component annulation reaction involving *N*-alkylimidazoles, dimethyl acetylenedicarboxylate, and in situ generated aryl methyl ketenes leading to the synthesis of 6-vinyl-1,3*a*-diazapentalene derivatives is reported.

Since their first preparation in 1905,[1] the cyclization reactions of ketenes have attracted enormous attention from organic chemists not only for the interest of theoretic research but also for the practical application.[2] Although the adducts of ketenes with pyridine or quinoline were observed almost 100 years ago,[3] which were subsequently proved to result from the cycloaddition of transient ketene zwitterions with another ketene,[4] the annulation strategy via the attacking of zwitterions to ketenes, which could be a multicomponent reaction, has received little attention until now.

The reaction of nucleophiles with activated acetylenes for C−C bond formation is of great significance in organic synthesis.[5] We have recently described a two-component reaction of dimethyl acetylenedicarboxylate (DMAD) with in situ generated arylketenes catalyzed by *N*-methylimidazole.[6] This reaction was proposed to proceed via a formal [2+2] cycloaddition of zwitterions from DMAD and *N*-methylimidazole with the C=C bond of ketenes (Scheme 1, eq 1).[7] Herein, we report a unique three-component reaction

Scheme 1. Reactions of the Zwitterion Derived from DMAD and *N*-Methylimidazole with Arylketene and Aryl Methyl Ketene



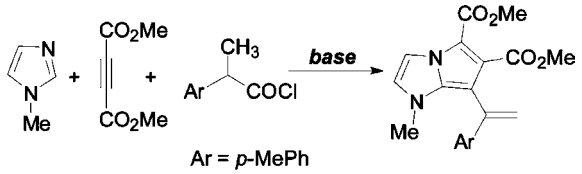
(1) Staudinger, H. *Chem. Ber.* **1905**, *38*, 1735.
(2) For reviews, see: (a) Tidwell, T. T. *Eur. J. Org. Chem.* **2006**, 563. (b) Tidwell, T. T. *Ketenes*; John Wiley & Sons: New York, 1995. (c) Hyatt, J.; Raynolds, R. W. *Org. React.* **1994**, *45*, 159. (d) Snider, B. E. *Chem. Rev.* **1988**, *88*, 793.
(3) Staudinger, H.; Klever, H. W.; Kober, P. *Liebigs Ann. Chem.* **1910**, *1*, 374.
(4) (a) Wollenberg, O. *Chem. Ber.* **1934**, *67*, 1675. (b) Berson, J. A.; Jones, W. M. *J. Am. Chem. Soc.* **1956**, *78*, 1625.

10.1021/ol061126p CCC: $33.50
Published on Web 06/08/2006

involving *N*-alkylimidazoles, DMAD, and in situ generated aryl methyl ketenes leading to 6-vinyl-1,3*a*-diazapentalene derivatives as the products (Scheme 1, eq 2).[8]

We started our investigations by the reaction of *N*-methylimidazole (**1a**), DMAD, and *p*-tolyl methyl ketene, in situ generated from α-methyl *p*-methylphenylacetyl chloride (**2a**) in the presence of *i*-Pr_2NEt, in CH_2Cl_2 under a nitrogen atmosphere (Table 1). Surprisingly, an annulation

Table 1. Effect of Reaction Conditions on the Three-Component Annulation Reaction for the Synthesis of **3a**[a]



1a **2a** **3a**

entry	base	solvent	temp (°C)	time[b]	yield (%)[c]
1	*i*-Pr_2NEt	CH_2Cl_2	−20 ∼ 20	3	58
2	*i*-Pr_2NEt	CH_2Cl_2	−20 ∼ 40	3	56
3	*i*-Pr_2NEt	CH_2Cl_2	−78 ∼ 0	4	<5
4	*i*-Pr_2NEt	THF	−20 ∼ 20	5	<5
5	*i*-Pr_2NEt	CH_3CN	−20 ∼ 20	5	18
6	*i*-Pr_2NEt	toluene	−20 ∼ 20	10	0
7	*i*-Pr_2NEt	DMSO	20	10	0
8	Et_3N	CH_2Cl_2	−20 ∼ 20	5	16
9	DBU	CH_2Cl_2	−20 ∼ 20	10	0

[a] Reaction conditions: **1a** (1 mmol), DMAD (1 mmol), **2a** (1 mmol), and base (1.5 mmol). [b] Reaction time for consuming all of the starting materials. [c] Yields of isolated product.

reaction occurred with the 1,3*a*-diazapentalene derivative **3a** as the product. The structural elucidation of **3a** rested upon NMR analysis and was unambiguously confirmed by single-crystal X-ray diffraction (Figure 1).

As ketenes typically add substrates across one of their cumulated double bonds, the C═C or C═O bond, to yield a cyclic compound,[9] it is noteworthy that *p*-tolyl methyl ketene acted as a one-carbon component in the annulation reaction to form a five-membered ring. Moreover, precedent for trapping 1,4-zwitterions by unsaturated compounds (such as

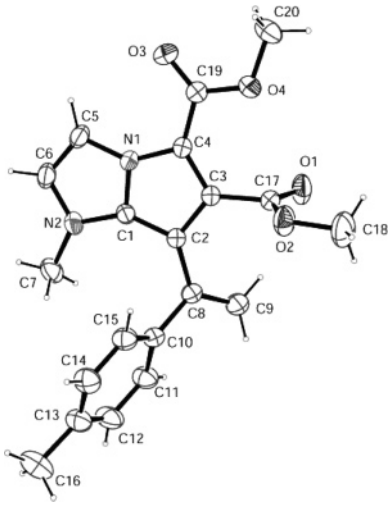


Figure 1. X-ray structure of compound **3a**.

carbon dioxide, isocyanates, and imines) resulted in six-membered rings exclusively.[7,10]

An initial survey of solvents demonstrated that CH_2Cl_2 is the solvent of choice (Table 1, entries 1 and 2). It was shown that the reaction temperature has a dramatic effect on the yield of **3a**, and the best yield was obtained when the reaction was carried out by dropping a mixture of acetyl chloride **2a** and DMAD to the solution of *N*-methylimidazole and *i*-Pr_2NEt in CH_2Cl_2 at −20 °C and raising it to room temperature for an additional 3 h. In contrast, the reaction was quite sluggish at lower temperature, and only trace product **3a** (entry 3) was found if the reaction temperature was kept below 0 °C. Moreover, among the bases we examined, *i*-Pr_2NEt was proved to be the optimum base, and the yield of product decreased significantly when another base such as NEt_3 or DBU was used (entries 8 and 9).

As disclosed in Table 2, the reaction was found to be applicable to a variety of α-methyl arylacetyl chlorides (**2**) resulting in 6-vinyl-1,3*a*-diazapentalene derivatives **3a**−**m** in moderate to good yields, even when the aromatic group of the acetyl chloride was bulky (entries 6−9, 11, and 12), electron-rich (entries 1, 2, and 7), or electron-poor (entries 4−6 and 8−10). However, the acetyl chlorides with an electron-rich aromatic group performed better than their electron-poor counterparts. Moreover, the size of the substituted group on the nitrogen atom of imidazole was demonstrated to have some negative effects on the reaction, and longer reaction times were required when **1b** and **1c** were used to carry out the reaction, possibly because of the steric hindrance in the cyclization step (entries 11−13). However, α-methyl 4-nitrophenylacetyl chloride only afforded trace product and some unidentified byproducts under these conditions (entry 14).

(5) (a) Dickstein, J. I.; Miller, S. I. *The Chemistry of Functional Groups. The Chemistry of Carbon−Carbon Triple Bond Part 2*; Patai, S., Ed.; Wiley: Chichester, 1978; Chapter 19, p 813. (b) Winterfeldt, E. *Chemistry of Acetylenes*; Vieche, H. G., Ed.; Dekker: New York, 1969; p 267. (c) Winterfeldt, E. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 423. (d) Acheson, R. M. *Adv. Heterocycl. Chem.* **1963**, *1*, 125.

(6) Ding, H.; Ma, C.; Yang, Y.; Wang, Y. *Org. Lett.* **2005**, *7*, 2125.

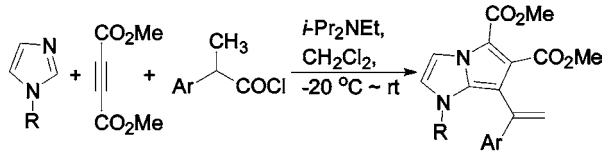
(7) For the reaction of zwitterions from 1-methylimidazole and DMAD with isocyanate, see: Adib, M.; Mollahosseini, M.; Yavari, H.; Sayahi, M. H.; Bijanzadeh, H. R. *Synlett* **2004**, 1086.

(8) For a previous synthesis of 1,3*a*-diazapentalene by a 1,3-dipolar cycloaddition reaction, see: (a) Boekelheide, V.; Fedoruk, N. A. *J. Am. Chem. Soc.* **1968**, *90*, 3830. (b) Oqura, H.; Kikuchi, K. *J. Org. Chem.* **1972**, *37*, 2679.

(9) For the cycloaddition of ketene through the C═O bond, see: (a) England, D. C.; Krespan, C. G. *J. Am. Chem. Soc.* **1965**, *87*, 4019. (b) DoMinh, T.; Strautz, O. P. *J. Am. Chem. Soc.* **1970**, *92*, 1766. (c) Yamabe, S.; Dai, T.; Minato, T.; Machiguchi, T.; Hasegawa, T. *J. Am. Chem. Soc.* **1996**, *118*, 6518. (d) Machiguchi, T.; Okamoto, J.; Morita, Y.; Hasegawa, T.; Yamabe, S.; Minato, T. *J. Am. Chem. Soc.* **2006**, *128*, 44.

(10) For the reaction of 1,4-zwitterions derived from Lewis base and DMAD, see: (a) Huisgen, R.; Morikawa, M.; Herbig, K.; Brunn, E. *Chem. Ber.* **1967**, *100*, 1094. (b) Acheson, R. M.; Plunkett, A. O. *J. Chem. Soc.* **1964**, 2676−2683. (c) Nair, V.; Sreekanth, A. R.; Abhilash, N.; Bhadbhade, M. M.; Gonnade, R. C. *Org. Lett.* **2002**, *4*, 3575.

Table 2. Annulation Reaction of *N*-Alkylmethylimidazole (**1**), DMAD, and Acetyl Chloride **2** for the Synthesis of Compound **3**[a]



1 **2** **3a-n**

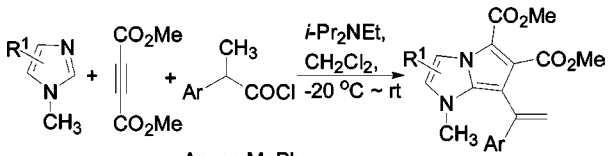
1a: R = Me
1b: R = Et
1c: R = *n*-Bu

entry	R	Ar	time (h)[b]	yield of **3** (%)[c]
1	Me	4-MeC_6H_4	3	**3a**, 58
2	Me	4-MeOC_6H_4	3	**3b**, 60
3	Me	Ph	3	**3c**, 55
4	Me	4-ClC_6H_4	3	**3d**, 50
5	Me	3-ClC_6H_4	3	**3e**, 52
6	Me	2-ClC_6H_4	3	**3f**, 47
7	Me	1-naphthyl	5	**3g**, 53
8	Me	2,4-dichlorophenyl	5	**3h**, 51
9	Me	2-BrC_6H_4	5	**3i**, 46
10	Me	4-BrC_6H_4	5	**3j**, 43
11	C_2H_5	2-ClC_6H_4	5	**3k**, 38
12	C_2H_5	2,4-dichlorophenyl	12	**3l**, 42
13	*n*-Bu	4-MeC_6H_4	10	**3m**, 49
14	Me	4-$NO_2C_6H_4$	10	**3n**, <5

[a] Reaction conditions: A mixture of **2** (1 mmol) and DMAD (1 mmol) was added dropwise to the solution of **1** (1 mmol) and *i*-Pr_2NEt (1.5 mmol) in CH_2Cl_2 at −20 °C, then to room temperature. [b] Reaction time for consuming all of the starting materials. [c] Yield of isolated product.

Further investigation on the structure of *N*-methylimidazole was conducted by using 1,4- and 1,5-dimethylimidazole (**1d** and **1e**) instead of **1a** in this reaction to afford corresponding products **3o** and **3p** in 57% and 61% yields, respectively (Scheme 2).

Scheme 2. Annulation Reaction of Compounds **1d** and **1e**



Ar = *p*-MePh

1d-e **2a** **3o-p**

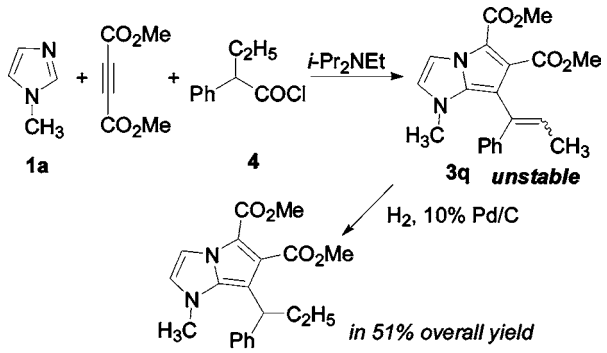
1d: R^1 = 4-Me
1e: R^1 = 5-Me

3o, 57%
3p, 61%

Moreover, aryl ethyl ketene (**4**) was also found to be applicable to this reaction. For example, phenyl ethyl ketene, generated in situ from the corresponding acetyl chloride, reacted smoothly with *N*-methylimidazole **1a** and DMAD to afford the unstable product **3q**, which could be further reduced to compound **5** in an overall yield of 51% (Scheme 3).

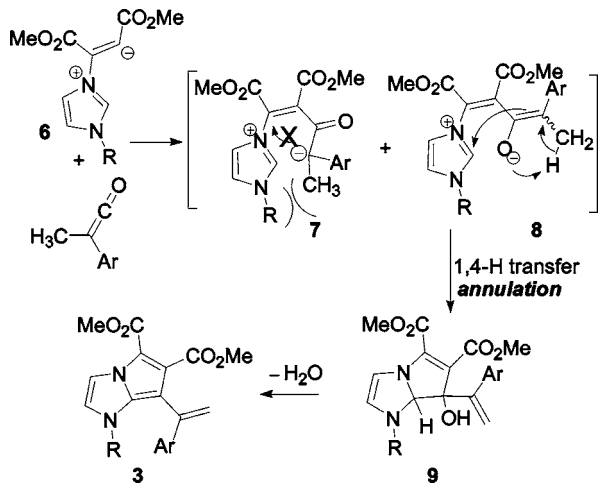
The mechanism of this novel annulation reaction has not been unequivocally established, but one reasonable possibility

Scheme 3. Annulation Reaction of α-Ethyl Phenylacetyl Chloride and **1a**, DMAD



is outlined in Scheme 4. Thus, the addition of the *N*-alkylimidazole to DMAD affords the zwitterion **6**, and the

Scheme 4. Proposed Mechanism for the Formation of 6-Vinyl-1,3*a*-diazapentalene Derivatives **3**



latter can further attack the in situ generated aryl methyl ketene leading to zwitterionic species **7** and **8**. Presumably, for steric reasons, the following cyclization of zwitterion **7** is forbidden. Instead, an intramolecular proton transfer from the α-methyl group to the oxygen anion of **8** proceeds to form intermediate **9** via an umpolung carbonyl anion[11] nucleophilic attack on the imidazolium ring. Finally, the elimination of water from **9** yields the 6-vinyl-1,3*a*-diazapentalene derivative **3**.

In conclusion, a novel, three-component cyclization involving *N*-alkylimidazole, DMAD, and in situ generated aryl methyl ketenes leading to the preparation of 6-vinyl-1,3*a*-diazapentalene derivatives has been reported. It is ascertained that the whole tandem reaction sequence pivots on the addition of a 1,4-zwitterion to ketenes, and the α-H of aryl methyl ketenes plays a decisive role in the cyclization step. Further studies will focus on the development of related transformations to exploit the unique structure and reactivity of ketene chemistry.

Acknowledgment. We thank Dr. J.-M. Gu (Department of Chemistry, Zhejiang University) for X-ray diffraction analysis.

Supporting Information Available: General experimental procedures and spectroscopic data for all compounds and crystallographic data for **3a** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

OL061126P

(11) For reviews, see: (a) Johnson, J. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1326. (b) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239. (c) Hase, T. A., Ed. *Umpoled Synthons*; Wiley: New York, 1987.