Synthesis of Zwitterionic Salts of Pyridinium-Meldrum Acid and Barbiturate through Unique Four-component Reactions

Qi-Fang Wang, Li Hui, Hong Hou, and Chao-Guo Yan*

College of Chemistry & Chemical Engineering, Yangzhou University, Yangzhou 225002, China

Received October 14, 2009

An efficient synthetic procedure for the preparation of the unusual charge-separated pyridinium-Meldrum acid and *N,N*-dimethylbarbiturate acid zwitterionic salts was developed though a unique one-pot four-component reaction involving pyridine, aromatic aldehyde, Meldrum acid or *N,N*-dimethylbarbituric acid, and *p*-nitrobenzyl bromide in acetonitrile. By varying combinations of four components involving nitrogen-containing heterocycles, we conveniently established reactive α-halomethylene compounds, aldehydes and *β*-dicarbonyl compounds a library of zwitterionic salts.

Introduction

As one kind of heterocyclic ammonium salts, the special nature of pyridinium salts allows them to be used in a great variety of synthetic reactions.[1,2] Because of the aromatic character of the pyridine heterocycle, its basicity, and the electron-attracting influence of the nitrogen atom, pyridinium cations in combination with strongly electron-withdrawing substituent like carbonyl, cyano, or nitro groups increase the activity and, hence, the synthetic utility of methylene groups.[3] Pyridinium salts derived from α-halogenocarbonyl compounds are easily deprotonated to give pyridium ylide, which are prone to be high potential synthons and undergo versatile reactions.[4,5] The most known reaction is Michael addition of active methylene groups in pyridinium salts onto suitable acceptor compounds to give polysubstituted pyridines and terpyridines, in which the pyridyl unit is split off.[6,7] The second widely used reaction is 1,3-dipolar cycloaddition of pyridinium salt with acetylene and activated alkenes to give indolizine derivatives, in which the pyridyl unit is remained.[8–11] The third kind of reaction is tandem reaction of pyridinium salts with alkenes bearing with electron-withdrawing groups to give the corresponding cyclopropanes[12] and 2,3-dihydrofurans.[13] Recently, we realized that the versatile reactivity and very easily in situ formation of pyridinium salts can be used to develop multicomponent reactions and found some interesting results. Polysubstituted pyridines,[14] cyclopropanes,[15] dihydrofuranes,[16] and pyrido[1,2-*a*]benzimidazole derivatives[17] could be produced efficiently from one-pot multicomponent cyclization reaction involving pyridinium salts in situ. In continuation of our efforts to investigate new one-pot multicomponent reactions, we develop this kind of reaction to other reactive methylene compounds. Here we wish to report the formation of the unusual charge-separated pyridinium-Meldrum acid and *N,N*-dimethylbarbituric acid zwitterionic salts via new four-component reactions which involves pyridine, *p*-nitrobenzyl bromide, aromatic aldehydes and Meldrum acid or barbituric acid.

Results and Discussion

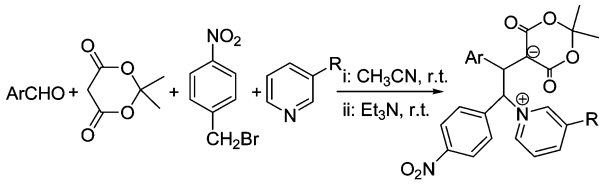
The first α-halomethyl substrate we examined was *p*-nitrobenzyl bromide. When a mixture of benzaldehyde, Meldrum acid, *p*-nitrobenzyl bromide, and an excess of pyridine in acetonitrile was stirred at room temperature for two hours, TLC analysis clearly showed that *p*-nitrobenzylpyridinium salt was formed in situ from the substitution reaction of *p*-nitrobenzyl bromide to pyridine, and benzylidene Meldrum acid was also formed in situ by Knoevenagel condensation of aromatic aldehyde with Meldrum acid catalyzed by pyridine. But the reaction could not go further even the mixture was stirred for additional two days. We thought that the basicity of pyridine might too weak to deprotonate the pyridinium salt to form pyridium ylide. One stronger base triethylamine was added to the system. After the mixture was stirred overnight, a lot of yellow precipitates were formed. After carefully analysis it is found that an unexpected zwitterionic salt **1a** was produced in 78% yield. **1a** has high polarity and high melting point, in which the positive charge is on the pyridium nitrogen atom and the negative charge is on methylene carbon atom, which is further delocalized onto the two carbonyl groups of Meldrum acid. This pyridinium-Meldrum acid zwitterion obviously results from the reaction of *N*-*p*-nitrobenzylpyridium bromide with arylidene Meldrum Acid which are both formed in situ. Similarly, various aromatic aldehydes were tested under the same conditions and the corresponding pyridinium-Meldrum acid zwitterions **1b**−**1k** were obtained in high yields (Table 1). This result demonstrated that aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents showed similar reactivity and reacted efficiently to yield the final products. As shown in Table 1, other pyridine derivatives such as 3-picoline also gave the corresponding zwitterionic salts **2a**−**2f** in very high yields (72−91%).

The structures of zwitterionic salts were fully characterized by ^{1}H and ^{13}C NMR, MS, and IR spectra and elemental

* To whom correspondence should be addressed. E-mail: cgyan@yzu.edu.cn.

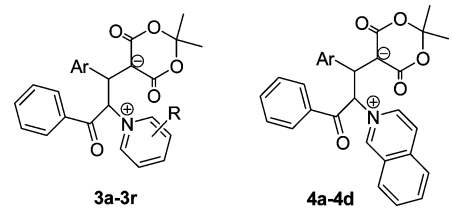
10.1021/cc900161z
Published on Web 01/21/2010

Table 1. Zwitterionic Salts of Pyridinium-Meldrum Acid from Reaction of *p*-Nitrobenzyl Bromide



entry	compd	Ar	R	yield (%)
1	**1a**	Ph	H	78
2	**1b**	*p*-$CH_3C_6H_4$	H	74
3	**1c**	*p*-$CH_3OC_6H_4$	H	72
4	**1d**	*p*-ClC_6H_4	H	78
5	**1e**	*p*-BrC_6H_4	H	75
6	**1f**	*p*-EtC_6H_4	H	72
7	**1g**	*p*-i-PrC_6H_4	H	80
8	**1h**	*m*-$PhOC_6H_4$	H	64
9	**1i**	*m*-$CH_3C_6H_4$	H	69
10	**1j**	*m*-ClC_6H_4	H	82
11	**1k**	*m*-$NO_2C_6H_4$	H	67
12	**2a**	Ph	CH_3	83
13	**2b**	*p*-$CH_3C_6H_4$	CH_3	82
14	**2c**	*p*-$CH_3OC_6H_4$	CH_3	73
15	**2d**	*p*-ClC_6H_4	CH_3	91
16	**2e**	*p*-$NO_2C_6H_4$	CH_3	72
17	**2f**	*m*-ClC_6H_4	CH_3	89

Table 2. Zwitterionic Salts of Pyridinium-Meldrum Acid from α-Phenacyl Bromide



entry	compd	Ar	R	yield (%)
1	**3a**	Ph	H	91
2	**3b**	*p*-$CH_3C_6H_4$	H	85
3	**3c**	*p*-$CH_3OC_6H_4$	H	71
4	**3d**	*p*-ClC_6H_4	H	94
5	**3e**	*p*-BrC_6H_4	H	88
6	**3f**	p-EtC_6H_4	H	83
7	**3g**	*p*-i-PrC_6H_4	H	78
8	**3h**	*m*-$PhOC_6H_4$	H	85
9	**3i**	*m*-ClC_6H_4	H	91
10	**3j**	*m*-$NO_2C_6H_4$	H	82
11	**3k**	Ph	3-CH_3	89
12	**3l**	*p*-$CH_3C_6H_4$	3-CH_3	95
13	**3m**	*p*-$CH_3OC_6H_4$	3-CH_3	84
14	**3n**	*p*-ClC_6H_4	3-CH_3	94
15	**3o**	*p*-$NO_2C_6H_4$	3-CH_3	83
16	**3p**	*m*-ClC_6H_4	3-CH_3	88
17	**3q**	Ph	4-CH_3	73
18	**3r**	*p*-$CH_3OC_6H_4$	4-CH_3	70
19	**4a**	Ph		88
20	**4b**	*p*-$CH_3C_6H_4$		86
21	**4c**	*p*-BrC_6H_4		94
22	**4d**	*m*-$NO_2C_6H_4$		96

analysis. This unprecedented result is of value to us not only because we are interested in the design of the new multicomonent reaction, but also because we are unable to find examples of other methods allowing for such convenient synthesis in related literature. Pyridinium zwitterions are usually very reactive species, which should be kept at low temperature and in an inert atmosphere. The majority of these zwitterions are synthesized by first preparing the pyridinium salt, followed by the elimination of an acid in the reaction with a base.[18] A literarure survey reveals that very early the addition product from benzylpyridinium bromide and chalcone can be isolated sometimes as cyclimonium chloride or perchlorate.[19a] Recently a similar charge-separated pyridinium barbiturate zwitterion was successfully prepared from 1,3-dimethylbarbituric acid and 2-pyridinecarbaldehyde in methanol.[19b] Some other stable pyridinium zwitterions have also been synthesized from pyridine participated multicomponent reactions.[20,21] The addition of nucleophiles such as triphenyl phosphine, pyridine, tertiary amine, dimethyl sulfoxide to activated alkynes like dimethyl acetylenedicarboxylate has been known to generate zwitterionic species. These reactive intermediates can be captured by suitable substrates to give versatile compounds.[22] Very recently the synthesis of stable charge-separated pyridinium-tetronic acid zwitterions from the three-component reaction of pyridine, isoquinoline, quinoline, or *N*-methylimidazole with dialkyl acetylenedicarboxylates and 3-chlorotetronic acid was described.[23] Here the stable pyridinium-Meldrum acid zwitterions can be successfully separated as the main products, which might the result of the negative charge on the carbon atom is greatly delocalized onto two carbonyl group.[24]

To evaluate the scope of this four-component reaction further, other reactive α-halomethyl compounds such as α-phenacyl bromide were also tested under the standard reaction conditions, and the results are summarized in Table 2. When pyridine was used in the reaction we are satisfied to find that analogy pyridinium-Meldrum acid zwitterions with benzoyl group (**3a**−**3j**) were obtained in very good yields (71−94%). When 3-picoline and 4-picoline was used in the reaction the zwitterionic salts (**3k**−**3r**) were also produced. However 4-picoline gave the zwitterionic salts in little lower yields (Entry 17, 18). When isoquinoline was used in the reaction the zwitterionic salts (**4a**−**4d**) were also produced in high yields (Entry 19−22). The structures of the products were fully characterized by ^1H and ^{13}C NMR, MS, and IR spectra and were further confirmed by single X-ray diffraction study performed for an representative compound **3a** (Figure 1). From the figure it is clearly seen that the formed zwitterionic salt came from all four components of the reaction. The pyridyl group and Meldrum acid unit exist in the same side of molecule, which cause the positive charge and negative charge in the shortest distance. The methylene carbon atom in Meldrum acid unit adopts a sp^2 hybrid and the negative charge is delocalized to two carbonyl groups.

To continue the investigation, the behavior of another active methylene compound, *N,N*-dimethylbarbituric acid, which has very similar structure and reactivity with that of Meldrum acid, was envisaged in this four-component reaction. When four-component reactions of aromatic aldehyde, *N,N*-dimethylbarbituric acid, *p*-nitrobenzyl bromide or α-phenacyl bromide and pyridine in acetonitrile were carried out at the standard conditions, the pyridinium-*N,N*-dimethylbarbiturate zwitterionic salts **5a**−**5h** were formed in moderate yields (43−81%, Table 3). This result clearly demonstrated that this four-component reaction has great generality and

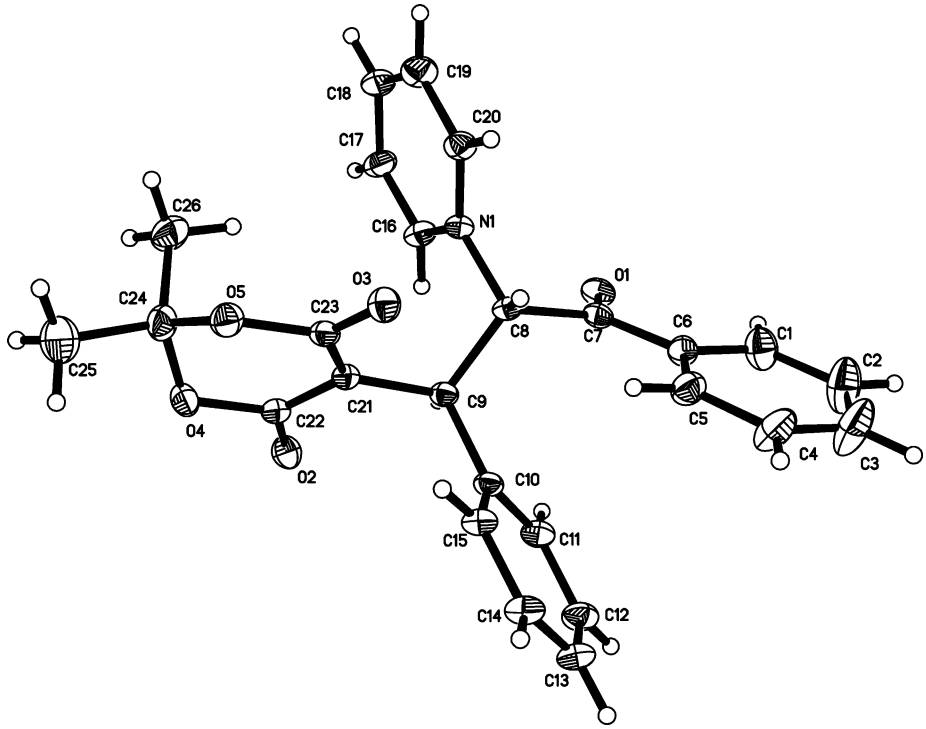
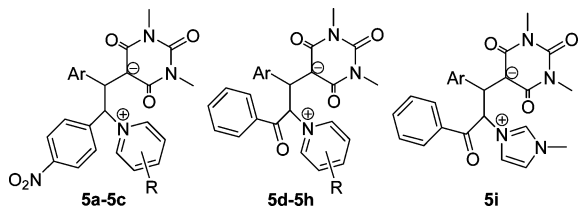


Figure 1. Molecular structure of zwitterionc salt **3a**.

Table 3. Zwitterionic Salts of Pyridinium and Imidazolium *N,N*-Dimethylbarbituric Acid

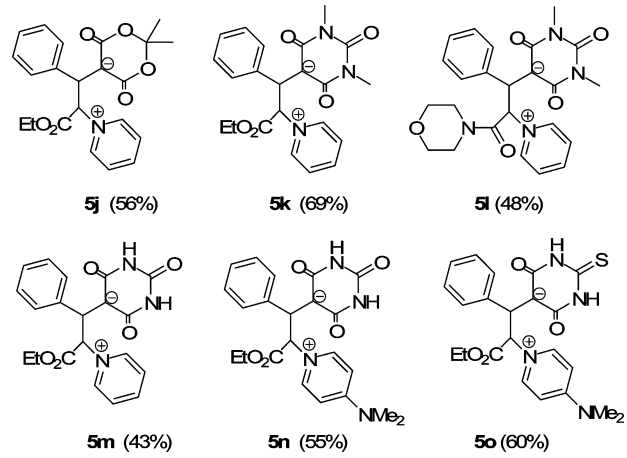


entry	compd	Ar	R	yield (%)
1	**5a**	Ph	H	66
2	**5b**	*p*-$CH_3C_6H_4$	H	68
3	**5c**	Ph	3-CH_3	43
4	**5d**	Ph	H	69
5	**5e**	*p*-$CH_3C_6H_4$	H	79
6	**5f**	Ph	2-CH_3	65
7	**5g**	Ph	3-CH_3	81
8	**5h**	*p*-$CH_3C_6H_4$	4-CH_3	43
9	**5i**	Ph		43

can be developed to other active methylene compounds. This kind of pyridinium-*N,N*-dimethylbarbiturate zwitterionic salt has very similar structure with the zwitterion prepared by Jursic's group.[19b] It is interesting to find that *N*-methylimidazole can take part in the reaction to yield the zwitterionic salt **5i** in moderate yield (entry 9). In zwitterionic salts **5a**−**5i**, the positive charge is on the nitrogen atom of pyridine or imidazole. The negative charge is on the methylene carbon of barbituric acid and is also delocalized onto the two electron-withdrawing carbonyl groups, which improves the stability of the zwitterionic salts.

Finally, to further explore the potential of this protocol for synthesis versatile zwitterionic salts, we investigated the reactions involving ethyl α-bromoacetate and *N*-chloroacetylmorphiline. The four-component reaction also proceeds very smoothly and more zwitterionic salts **5j**−**5o** were obtained in satisfied yields (Scheme 1). It can be seen that

Scheme 1. Molecular Structures of Zwitterionic Salts **5j**−**5o**



more component combinations involving 4-(dimethylamino)pyridine and barbiturate or thiobarbiturate have been used in the reaction, which demonstrated that this four-component reaction has very potential generality. The single crystal structure of **5k** was also determined by X-ray diffraction (Figure 2). The pyridinium group and *N,N*-dimethylbarbiturate unit also exist in the same side of molecule, which cause the positive charge and negative charge are in the shortest distance.

Encouraged by these results, we turned our attention to attempt to study the reactivity of the obtained zwitterionic salts. When four-component reactions of aromatic aldehyde, *N,N*-dimethylbarbituric acid, *p*-benzyl bromide and pyridine in acetonitrile were carried out at refluxed condition for 24 h, it is very interesting to find that a mixture of cyclopropanes **6a**−**6c** and 2,3-dihydrofuran **7a**−**7d** were formed in lower yields which were successfully separated by the TLC (Table. 4). The structures of cyclopropanes and 2,3-dihydrofurans were characterized with spectroscopy. ^{1}H NMR analysis

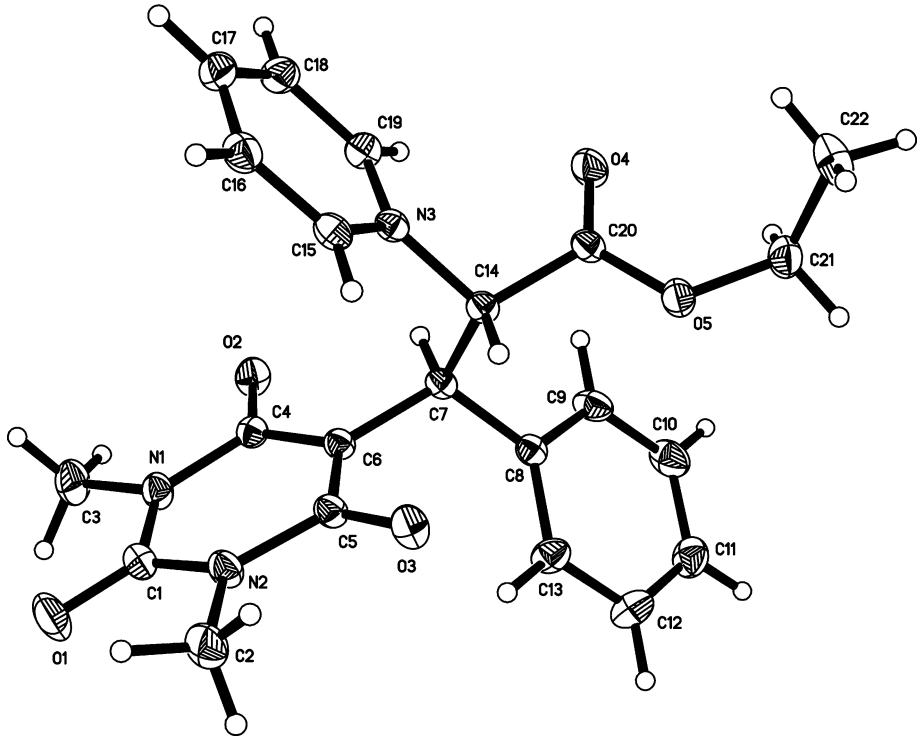
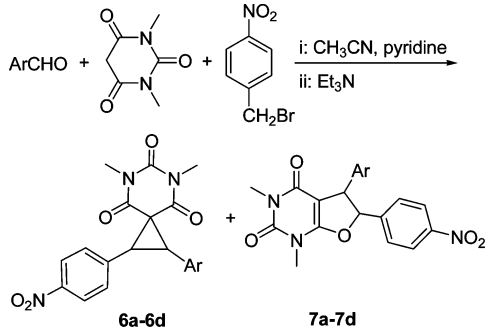


Figure 2. Molecular structure of zwitterionc salt **5k**.

Table 4. Synthesis of Cyclopropanes and 2,3-Dihydrofurans from Four Component Reactions



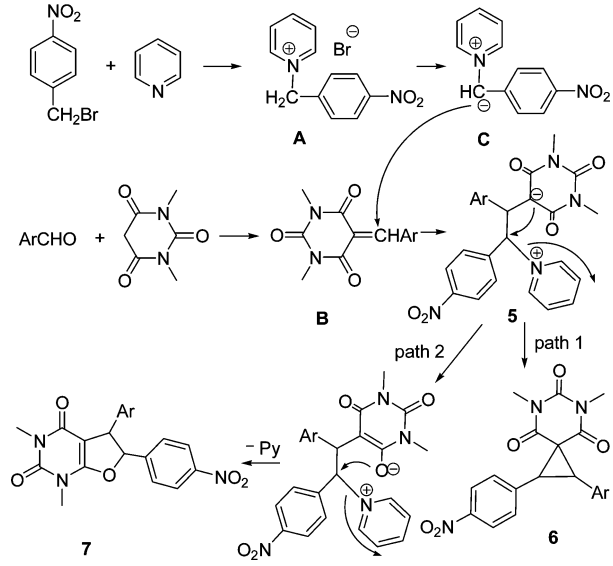
6a-6d 7a-7d

entry	Ar	6	yield (%)	7	yield (%, cis/trans)
1	Ph	**6a**	33	**7a**	36 (1:8)
2	*p*-$CH_3C_6H_4$			**7b**	31 (1:11)
3	*p*-ClC_6H_4	**6b**	30	**7c**	35 (2:5)
4	*p*-BrC_6H_4	**6c**	28	**7d**	33 (2:5)

revealed that the cyclopropanes **6a**−**6c** were found to be in the thermodynamically stable trans orientation on the basis of the comparison of the coupling constants of two protons on 2,3-position. On the other hand 2,3-dihydrofuranes **7a**−**7d** were found to have cis and trans isomers in different ratios also based on the ^{1}H NMR analysis. This preliminary result clearly indicates that the above prepared zwitterionic salts have potential application in organic synthesis.

To explain the mechanism of this one-pot multicomponent reaction, we propose a plausible reaction course, which is illustrated in Scheme 2. This mechanism is based on the our previously established for the synthesis of cyclopropanes and dihydrofurans via the tandem reaction of pyridinium salt.[15,16] The first step is the formation of the two reaction intermediates already identified by the experiments described in the preceding paragraph, namely the *N*-*p*-nitrobenzylpyridinium

Scheme 2. Proposed Mechanism of the Four Component Reaction



bromide (**A**) formed from the substitution of *p*-nitrobenzyl bromide to pyridine and the arylidene *N,N*-dimethylbarbituric acid (**B**) formed by the Knoevenagel condensation of aromatic aldehyde with *N,N*-dimethylbarbituric acid. The second step is a Michael addition of a pyridinium ylide (**C**) which is formed by deprotonation of the *N*-*p*-nitrobenzylpyridinium species (**A**) by triethylamine to (**B**) to afford the zwitterion salt **5**. On heating this zwitterion salt proceeds further according to two different paths to give different products. In the first path the intramolecular substitution of the carbanion replaces pyridine with formation of the cyclopropane **6**. In the second path the carbanion transfers to resonance-stabilized enolate through the keto−enol tautomerism, which in turn substitutes pyridine to give the 2,3-

dihydrofuran **7**. In this proposed reaction mechanism pyridine acts as a nucleophilic tertiary amine to form pyridinium cation and zwitterionic salt, as a base to catalyze Knoevenagel condensation and as a good leaving group to finish the intramolecular substitution reaction.

Conclusions

In conclusion, we described here an unexpected and interesting four-component reaction including pyridine, aromatic aldehyde, Meldrum acid or *N,N*-dimethylbarbituric acid and *p*-nitrobenzyl bromide. A series of unusual charge-separated pyridinium-Meldrum acid and barbituric acid zwitterionic salts are prepared in high yields in very convenient manner. Prominent among the advantages of this new method are novelty, operational simplicity, and good yields. The stability, reactivity and the formation mechanism of this kind of zwitterionic salts are also investigated. Further expansion of the reaction scope and synthetic applications of this methodology are in progress in our laboratory.

Experimental Section

Typical Procedure for the Preparation Pyridinium-Meldrum Acid Zwitterionic Salt from Reaction of *p*-Nitrobenzyl Bromide (Entry 1 in Table 1). A mixture of benzaldehyde (2.0 mmol), Meldrum acid (2.0 mmol), *p*-nitrobenzyl bromide (2.0 mmol), and an excess of pyridine (4.0 mmol) in acetonitrile was stirred at room temperature for two hours; then triethylamine (2.0 mmol) was added to the system. After the mixture was stirred over night, the yellow precipitates formed and were collected by filtration and washed with ethanol and petroleum ether to give the pure product **1a**. Yield: 78.4%. mp: 216−218 °C. IR (KBr): 3432(w), 3061(w), 1581(vs), 1523(m), 1491(w), 1389(m), 1350(m), 1259(w), 1205(w), 1106(w), 1047(vw), 926(vw), 740(w) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ(ppm): 9.05 (d, $J = 6.0$ Hz, 2H, PyH), 8.38 (t, $J = 7.8$ Hz, 1H, PyH), 8.13 (d, $J = 8.4$ Hz, 2H, *p*-$NO_2C_6H_4$), 7.93 (t, $J = 7.8$ Hz, 2H, PyH), 7.54 (d, $J = 8.4$ Hz, 2H, *p*-$NO_2C_6H_4$), 7.46−7.43 (m, 3H, C_6H_5, CH), 7.17−7.11 (m, 3H, C_6H_5), 5.19 (d, $J = 12.0$ Hz, 1H, CH), 1.44 (s, 3H, CH_3), 1.42 (s, 3H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ(ppm): 142.6, 129.3, 128.6, 128.4, 127.4, 124.5, 109.4, 65.9, 58.5, 45.9, 18.5, 15.3. MS(ESI−): $m/z = 445.98$. Anal. Calcd for $C_{25}H_{22}N_2O_6$: C 67.26, H 4.97, N 6.27; found C 67.35, H 5.20, N 5.97.

Typical Procedure for the Preparation Pyridinium-Meldrum Acid Zwitterionic Salt from Reaction of α-Phenacyl Bromide (Entry 1 in Table 2). A mixture of benzaldehyde (2.0 mmol), Meldrum acid (2.0 mmol), α-phenacyl bromide (2.0 mmol), and an excess of pyridine (4.0 mmol) in acetonitrile was stirred at room temperature for two hours; then triethylamine (2.0 mmol) was added to the system. After the mixture was stirred overnight, the yellow precipitates were collected by filtration and washed with ethanol and petroleum ether to give the pure product **3a**. Yield: 83.2%. mp: 204−206 °C. IR (KBr): 3437(w), 3035(w), 1579(vs), 1523(m), 1387(m), 1349(m), 1260(w), 1205(w), 1108(w), 1049(vw), 868(vw), 800(vw), 730(w), 704(w) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ(ppm): 8.94 (d, $J = 6.0$ Hz, 1H, PyH), 8.84 (s, 1H, PyH), 8.12 (d, $J = 7.8$ Hz, 1H, PyH), 8.10 (d, $J = 8.4$ Hz, 2H, *p*-$NO_2C_6H_4$), 7.98 (t, $J = 7.2$ Hz, 1H, PyH), 7.54 (d, $J = 8.4$ Hz, 2H, *p*-$NO_2C_6H_4$), 7.45 (d, $J = 7.2$ Hz, 2H, C_6H_5), 7.41 (d, $J = 12.6$ Hz, 1H, CH), 7.14 (t, $J = 7.2$ Hz, 2H, C_6H_5), 7.09 (t, $J = 7.2$ Hz, 1H, C_6H_5), 5.18 (d, $J = 12.0$ Hz, 1H, CH), 2.57 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.42 (s, 3H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ(ppm): 148.3, 145.8, 144.1, 143.2, 141.7, 140.5, 139.1, 129.3, 128.5, 126.8, 126.7, 124.4, 101.5, 74.0, 45.9, 27.7, 23.8, 18.9. MS(ESI−): $m/z = 459.63$. Anal. Calcd for $C_{26}H_{24}N_2O_6$: C 67.82, H 5.25, N 6.08; found C 67.69, H 5.56, N 5.70.

Typical Procedure for the Preparation Pyridinium-*N,N*-dimethylbarbituric Acid Zwitterionic Salt (Entry 1 in Table 3). A mixture of benzaldehyde (2.0 mmol), *N,N*-dimethylbarbituric acid (2.0 mmol), *p*-nitrobenzyl bromide (2.0 mmol), and an excess of pyridine (4.0 mmol) in acetonitrile was stirred at room temperature for two hours, then triethylamine (2.0 mmol) was added to the system. After the mixture was stirred overnight, the yellow precipitates were formed, which were collected by filtration and washed with ethanol and petroleum ether to give the pure product **5a**. Yield: 65.6%. mp: 156−158 °C. IR (KBr): 3425(s), 1661(s), 1571(vs), 1525(s), 1430(s), 1384(m), 1351(s), 1264(w), 1148(w), 1039(w), 840(vw), 816(w), 775(m), 703(m), 671(m) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ(ppm): 9.03 (d, $J = 6.0$ Hz, 2H, PyH), 8.35 (t, $J = 7.8$ Hz, 1H, PyH), 8.14 (d, $J = 8.4$ Hz, 2H, *p*-$NO_2C_6H_4$), 7.88 (t, $J = 7.2$ Hz, 2H, PyH), 7.67 (d, $J = 6.6$ Hz, 1H, CH), 7.62 (d, $J = 9.0$ Hz, 2H, *p*-$NO_2C_6H_4$), 7.57 (d, $J = 7.8$ Hz, 2H, C_6H_5), 7.16 (t, $J = 7.8$ Hz, 2H, C_6H_5), 7.10 (t, $J = 7.2$ Hz, 1H, C_6H_5), 5.46 (d, $J = 12.6$ Hz, 1H, CH), 3.20 (s, 3H, CH_3), 3.10 (s, 3H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ(ppm): 163.9, 153.3, 148.4, 145.3, 144.4, 142.9, 140.0, 129.3, 128.8, 128.4, 127.3, 127.0, 124.6, 84.9, 45.9, 27.8, 27.1. MS(ESI−): $m/z = 457.65$. Anal. Calcd for $C_{25}H_{22}N_4O_5$: C 65.49, H 4.84, N 12.22; found C 65.27, H 5.20, N 11.85.

Acknowledgment. This work was financially supported by the National Natural Science Foundation of China (Grant No. 20672091 and 20972132).

Supporting Information Available. Experimental details and characterization data including IR, MS, ^1H, and ^{13}C NMR spectra, as well as X-ray crystallographic data for new compounds. This information is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Kröhnke, F. *Angew. Chem., Int. Ed.* **1963**, *2*, 225. (b) Kröhnke, F.; Zecher, W. *Angew. Chem., Int. Ed.* **1962**, *1*, 626.
(2) (a) Kojima, S.; Hiroikea, K.; Ohkata, K. *Tetrahedron Lett.* **2004**, *45*, 3565. (b) Kojima, S.; Fujitomo, K.; Shinohara, Y.; Shimizu, M.; Ohkata, K. *Tetrahedron Lett.* **2000**, *41*, 9847.
(3) (a) Yamada, S.; Yamamoto, J.; Ohta, E. *Tetrahedron Lett.* **2007**, *48*, 855. (b) Vo, N. N.; Eyermann, C. J.; Hodge, C. N. *Tetrahedron Lett.* **1997**, *38*, 7951. (c) Tsuge, O.; Kanemasa, S.; Takenaka, S. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3137.
(4) (a) Neve, F.; Crispini, A.; Campagna, S. *Inorg. Chem.* **1997**, *36*, 6150. (b) MacGillivray, L. R.; Diamente, P. R.; Reid, J. L.; Ripmeester, J. A. *Chem. Commun.* **2000**, 359.
(5) Barrio, M. C. G.; Barrio, J. R.; Walker, G.; Novelli, A.; Leonard, N. J. *J. Am. Chem. Soc.* **1973**, *95*, 4891.

(6) (a) Kröhnke, F. *Synthesis* **1976**, 1. (b) Ulrich, G.; Ziessel, R. *J. Org. Chem.* **2004**, *69*, 2070. (c) Yam, V. W. W.; Wong, K. M. C.; Zhu, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 1400. (d) Coppo, P.; Duati, M.; Kozhevnikov, V. N.; Hofstraat, J. W.; De Cola, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 1806. (e) Pabst, G. R.; Pfüller, O. C.; Sauer, J. *Tetrahedron* **1999**, *55*, 5047. (f) Hovinen, J.; Hakala, H. *Org. Lett.* **2001**, *3*, 2473. (g) Kozhevnikov, V. N.; Kozhevnikov, D. M.; Nikitina, T. V.; Rusinov, V. L.; Chupakhin, O. N.; Zabel, M.; König, B. *J. Org. Chem.* **2003**, *68*, 2882. (h) Lai, S. W.; Chan, M. C. W.; Cheung, K. K.; Che, C. M. *Inorg. Chem.* **1999**, *38*, 4262.

(7) (a) Eryazici, I.; Moorefield, C. N.; Durmus, S.; Newkone, G. R. *J. Org. Chem.* **2006**, *71*, 1009. (b) Tu, S. J.; Jia, R. H.; Jiang, B.; Zhang, J. Y.; Zhang, Y.; Yao, C. S.; Ji, S. J. *Tetrahedron* **2007**, *63*, 381. (c) Constable, E. C.; Edwards, A. J.; Martínez-Máñez, R.; Raithby, P. R. *J. Chem. Soc., Dalton Trans.* **1995**, 3253. (d) Constable, E. C.; Edwards, A. J.; Raithby, P. R.; Soto, J.; Tendero, M. J. L.; Martínez-Máñez, R. *Polyhedron* **1995**, *14* (20), 3061.

(8) (a) Bora, U.; Saikia, A.; Boruah, R. C. *Org. Lett.* **2003**, *5*, 435. (b) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123. (c) Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168. (d) Sasaki, T.; Kanematsu, K.; Yukimoto, Y.; Ochiai, S. *J. Org. Chem.* **1971**, *36*, 813. (e) Xia, Z. Q.; Przewloka, T.; Koya, K.; Ono, M.; Chen, S. J.; Sun, L. J. *Tetrahedron Lett.* **2006**, *47*, 8817.

(9) (a) Katritzky, A. R.; Grzeskowiak, N. E.; Alvarez-Buila, J. *J. Chem. Soc., Perkin Trans.* **1981**, 1180. (b) Druta, I. I.; Dinica, R. M.; Bacu, E.; Humelnicu, I. *Tetrahedron* **1998**, *54*, 10811. (c) Dinica, R. M.; Druta, I. I.; Pettinari, C. *Synlett* **2000**, *7*, 1013. (d) Druta, I. I.; Andrei, M. A.; Ganj, C. I.; Aburel, P. S. *Tetrahedron* **1999**, *55* (45), 13063. (e) Furdui, B.; Dinica, R.; Druta, I. I.; Demeunynck, M. *Synthesis* **2006**, *16*, 2640.

(10) (a) Peng, W. M.; Zhu, S. Z. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3204. (b) Zhu, S. Z.; Qin, C. Y.; Wang, Y. L.; Chu, Q. L. *J. Fluorine Chem.* **1999**, *99* (2), 183. (c) Zhang, X. C.; Huang, W. Y. *Synthesis* **1999**, *1*, 51. (d) Wu, K.; Chen, Q. Y. *Synthesis* **2003**, 35.

(11) (a) Zhang, X. D.; Hu, Y. F.; Hu, H. W. *J. Chem. Soc., Perkin Trans. 1* **1993**, *20*, 2487. (b) Wang, B. X.; Zhang, X. C.; Li, J.; Jiang, X.; Hu, Y. F.; Hu, H. W. *J. Chem. Soc., Perkin Trans.* **1999**, 1571. (c) Hu, J. X.; Jiang, X.; He, T.; Zhou, J.; Hu, Y. F.; Hu, H. W. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1820.

(12) (a) Shestopalov, A. M.; Litvinov, V. P.; Rodinovskaya, L. A.; Sharanin, Y. A. *Zh. Org. Khim.* **1991**, 146. (b) Vo, N. H.; Eyermann, C. J.; Hodge, C. N. *Tetrahedron Lett.* **1997**, *38*, 7951. (c) Kojima, S.; Suzuki, M.; Watanabe, A.; Ohkata, K. *Tetrahedron Lett.* **2006**, *47*, 9061. (d) Kojima, S.; Hiroike, K.; Ohkata, K. *Tetrahedron Lett.* **2004**, *45*, 3565. (e) Kojima, S.; Fujitomo, K.; Shinohara, Y.; Shimizu, M.; Ohkata, K. *Tetrahedron Lett.* **2000**, *41*, 9847. (f) Yamada, S.; Yamamoto, J.; Ohta, E. *Tetrahedron Lett.* **2007**, *48*, 855.

(13) Chuang, C. P.; Tsai, A. I. *Synthesis* **2006**, *4*, 675.

(14) (a) Yan, C. G.; Cai, X. M.; Wang, Q. F.; Wang, T. Y.; Zheng, M. *Org. Biomol. Chem.* **2007**, *5*, 945. (b) Yan, C. G.; Song, X. K.; Wang, Q. F.; Sun, J.; Siemeling, U.; Bruhn, C. *Chem. Commun.* **2008**, 1440.

(15) Wang, Q. F.; Song, X. K.; J, Chen.; Yan, C. G. *J. Comb. Chem.* **2009**, *11*, 1007.

(16) Wang, Q. F.; Hou, H.; Hui, L.; Yan, C. G. *J. Org. Chem.* **2009**, *74*, 7403.

(17) Yan, C. G.; Wang, Q. F.; Song, X. K.; Sun, J. *J. Org. Chem.* **2009**, *74* (2), 710.

(18) (a) Visser, P.; Zuhse, R.; Wong, M. W.; Wentrup, C. *J. Am. Chem. Soc.* **1996**, *118*, 12598. (b) Kuhn, A.; Pluüg, C.; Wentrup, C. *J. Am. Chem. Soc.* **2000**, *122*, 1945. (c) Zia-Ebrahimi, M.; Reutzel, S. M.; Dorman, D. E.; Spangle, L. A.; Deeter, J. B. *Chem. Mater.* **1994**, *6*, 822–826. (d) Wenkert, E.; Michelotti, E. L.; St. Pyrek, J. *J. Org. Chem.* **1984**, *49* (10), 1832.

(19) (a) Curtz, J.; Dach, R.; Duchardt, K. H.; Kröhnke, F. *Chem. Ber.* **1979**, *112* (6), 2199. (b) Jursic, B. S.; Neumann, D. M.; Moore, Z.; Stevens, E. D. *J. Org. Chem.* **2002**, *67*, 2372.

(20) (a) Varga, L.; Nagy, T.; Dormán, G.; Kálmán, F.; Urge, L.; Darvas, F. *J. Comb. Chem.* **2006**, *8*, 338. (b) Wamhoff, H.; Schmidt, A. *J. Org. Chem.* **1993**, *58*, 6976.

(21) (a) Jursic, B. S.; Neumann, D. M.; Martin, K. L.; Stevens, E. D. *Org. Lett.* **2002**, *4*, 811. (b) Sosnovskikh, V. Y.; Usachev, B. I.; Sizov, A. Y.; Vorontsov, I. I.; Shklyaev, Y. V. *Org. Lett.* **2003**, *5*, 3123. (c) Zhang, S. L.; Huang, Z. S.; An, L. K.; Bu, X. Z.; Ma, L.; Li, Y. M.; Chan, A. S. C.; Gu, L. Q. *Org. Lett.* **2004**, *6*, 4853. (d) Foye, W.; Jones, R. W.; Ghoshal, P. K.; Almassian, B. *J. Med. Chem.* **1987**, *30*, 57.

(22) (a) Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekanth, A. R.; Mathen, J. S.; Balagopal, L. *Acc. Chem. Res.* **2003**, *36*, 899. (b) Nair, V.; MENON, R. S.; Sreekanth, A. R.; Abhilash, N.; Biju, A. T. *Acc. Chem. Res.* **2006**, *39*, 520.

(23) Shaabani, A.; Rezayan, A. H.; Sarvary, A.; Heidary, M.; Ng, S. W. *Tetrahedron* **2009**, *65*, 6063.

(24) Bernasconi, C. F.; Murray, C. J. *J. Am. Chem. Soc.* **1986**, *108*, 5257.

CC900161Z