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Mesoionic 1,3-Oxazinium Olates. Rearrangement to Acylketenes and 3-Azabicyclo[3.1.1]heptanetriones

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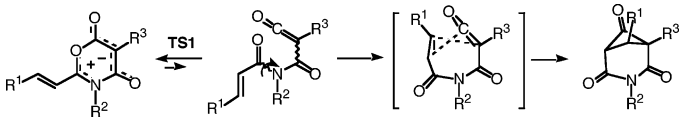
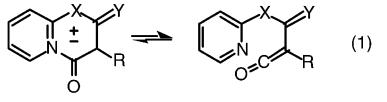


Metastable but isolable mesoionic 1,3-oxazinium 4-olates **9d**−**f** undergo ring opening to acylketenes **10** at or near room temperature. The ketenes undergo intramolecular criss-cross [2 + 2] cycloaddition to afford 3-azabicyclo[3.1.1]heptanetriones **12**. The structure of **12d** was established by X-ray crystallography.

Introduction

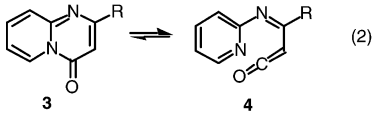
We have recently reported the reversible valence isomerization of mesoionic pyridopyrimidinium olates to the corresponding amidinoylketenes, e.g., **1** → **2**, which takes place in solution at or slightly above room temperature (eq 1).[2] Although the transient ketenes **2** could not



(1)

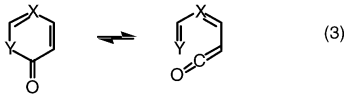
1 **2**

X and Y = NR or O



(2)

3 **4**



(3)

5 **6**

a X = CH, Y = O
b X = N, Y = O
c X = CH, Y = NR
d X = CH, Y = CH_2

be observed directly, the calculated activation barrier for the ring opening, **1** → **2**, was as low as 20 kcal/mol in one case.[2a] The formally nonmesoionic pyridopyrimidinones **3** undergo reversible ring opening to imidoylketenes **4** under conditions of flash vacuum thermolysis (FVT) (eq 2).[2,3] In addition, five-membered heterocyclic mesoionic compounds can undergo valence isomerization to the ring-opened ketenes, albeit sometimes with more difficulty, e.g., pyrrolopyridinium olates **5** to ketenes **6**[4] and sydnones to *N*-nitrosaminoketenes.[5,6] These ring-opening reactions are of considerable interest as likely examples of pseudopericyclic reactions,[7] taking place via a planar or nearly planar transition state and with very low activation barriers from the ketenes to the cyclized products.[8]

We now report the synthesis of 2-vinyl-1,3-oxazinium olates **9**, their facile ring opening to ketenes **10**, and recyclization to 3-azabicyclo[3.1.1]heptanetriones **12** in an intramolecular [2 + 2] criss-cross cycloaddition reaction.

Results and Discussion

The oxazinium olates **9d**−**f** (see Scheme 1 for key) were obtained as highly colored (red-orange) solids by reac-

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(2) (a) Andersen, H. G.; Mitschke, U.; Wentrup, C. *J. Chem. Soc., Perkin Trans. 2* **2001**, 602−607. (b) Fiksdahl, A.; Plüg, C.; Wentrup, C. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1841−1845.

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(6) Photochemical ring opening of sydnones to *N*-nitrosaminoketenes: Veedu, R. N.; Wentrup, C. Unpublished results, The University of Queensland, 2004.

(7) (a) Birney, D. M.; Wagenseller, P. E. *J. Am. Chem. Soc.* **1994**, *116*, 6262−6270. (b) Birney, D. M. *J. Org. Chem.* **1996**, *61*, 243−251.

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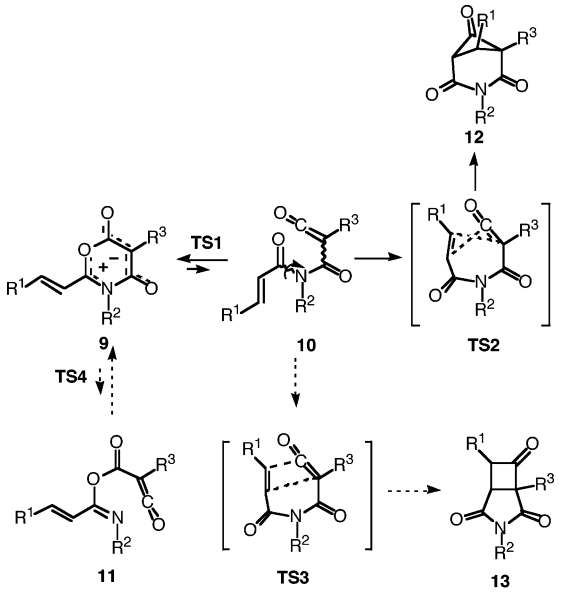
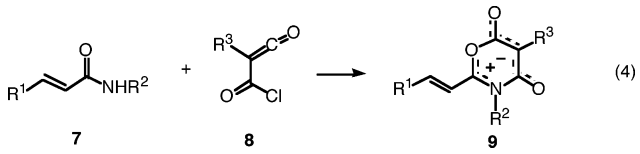
SCHEME 1



a: $R^1 = R^2 = R^3 = H$
b: $R^1 = H$, $R^2 = R^3 = CH_3$
c: $R^1 = H$; $R^2 = R^3 = Ph$
d: $R^1 = R^2 = R^3 = Ph$
e: $R^1 = R^3 = Ph$; $R^2 = PhCH_2$
f: $R^1 = R^2 = Ph$; $R^3 = PhCH_2$

tion of amides **7** with chlorocarbonylketenes **8** (eq 4).[9] Compounds **9a**−**d** are the subject of a theoretical



(4)

investigation.[10] Olates **9d**−**f** are unstable but nonetheless isolable at room temperature. The colors rapidly fade by refluxing a toluene solution, or even by stirring at room temperature. This is due to a rearrangement to the bicycloheptanetriones **12d**−**f** (Scheme 1) which were obtained in good yields. The structure of **12d** was determined by X-ray crystallography (see Figure S1 in the Supporting Information document). The formation of **12** corresponds to ring opening of the oxazinium olates **9** to acylketenes **10** by breaking the O−CO bond. There was no evidence for the alternative ring opening to oxoketenes **11** (Scheme 1), which would have afforded isomeric products. Energy calculations[10] indicate that both **11** and the transition state for its formation (**TS4**) are significantly higher than those of **10** and the TS for its formation (**TS1**). The formation of the bicyclic product **12** corresponds to a criss-cross [2 + 2] cycloaddition of the vinyl substituent to the ketene C=C bond. The alternative [2 + 2] cycloaddition to give bicyclo[3.2.0]-heptanetrione **13** via **TS3** was not observed. Energy calculations[10] indicate that the criss-cross cycloaddition is favored because of steric constraints in the TS resulting from the vinyl substituent when R^1 = Ph.

X-ray structure determinations as well as calculations demonstrate that pyridinium olates (e.g., **1**)[5] and oxazinium olates[10] have structures with long C−N or C−O single bonds in the rings (1.44−1.49 Å) and acute NCO (OCO) angles (110−116°). In other words, these cyclic structures are distorted toward the transition states for their ring opening to ketenes. This can be seen as a manifestation of the Bürgi−Dunitz structure-correlation principle,[11] whereby the structures of stable compounds can tend toward the TSs for their formation or destruction, especially when the energy difference between the stable compound and the TS is small. The ring-opening reactions to ketenes **10** considered here are expected to be pseudopericyclic[7] in nature and, accordingly, to have planar or nearly planar TSs and modest activation barriers in keeping with the observation that they take place already at room temperature. More detailed information on the structures and energies of the oxazinium olates, oxazines, end products, ketene intermediates, and transition states are provided by theoretical calculations.[10]

Conclusion

Mesoionic 1,3-oxazinium olates **9d**−**f** have been synthesized as metastable but isolable compounds. They undergo facile ring opening to transient amidylketenes **10d**−**f**, even at room temperature. The amidylketenes **10d**−**f** recyclize to 3-aza-bicyclo[3.1.1]heptanetriones **12d**−**f** in good yields.

Experimental Section

Chlorocarbonylketenes **8** were prepared according to a literature procedure.[12] The phenyl and benzyl cinnamyl amides **7** were known and prepared according to a general procedure.[13] Benzene, toluene, hexane, diethyl ether, and THF were dried over sodium and distilled prior to use.

The oxazinium olates **9d**, **9e**, and **9f** are almost insoluble in $CDCl_3$ and acetone-d_6 and slightly soluble in CD_2Cl_2. A very fast color change takes place in DMSO and DMF (probably due to reaction with small amounts of water). The samples for NMR analysis were prepared by dissolving 20 mg of the oxazinium olate in 1 mL of CD_2Cl_2. Due to their thermal instability, it was not possible to recrystallize the oxazinium olates, and fully satisfactory microanalytical data were not always obtainable. The evidence for purity of the oxazinium olates (up to 90%) is based on the yields of the fully analyzed derived bicycloheptanetrione products **12**.

(8) See also related isomerization of oxovinylketenes to α-pyrones and analogous hetero-1,2,4,6-heptatetraene cyclizations: (a) Rodriguez-Otero, J.; Cabaleiro-Lago, E. M. *Chem. Eur. J.* **2003**, *9*, 1837−1843. (b) Zora, M. *J. Org. Chem.* **2004**, *69*, 1940−1947. (c) Thermal ring opening of α-pyrones and coumarins to ketenes: Wentrup, C.; Heilmeyer, W.; Kollenz, G. *Synthesis* **1994**, 1219−1248. (d) Matrix photochemical ring opening of α-pyrones to ketenes: Breda, S.; Reva, I.; Lapinski, L.; Fausto, R. *Phys. Chem. Chem. Phys.* **2004**, *6*, 929−937. Breda, S.; Reva, I.; Lapinski, L.; Fausto, R. *Photochem. Photobiol.* **2004**, *162*, 139−151. (e) *N*-acylimidoylketene to 1,3-oxazin-6-one: Alajarin, M.; Sanchez-Andrada, P.; Cossio, F. P.; Arrieta, A. *J. Org. Chem.* **2001**, *66*, 8370−8477. (f) *N*-acylvinylketenimine cyclizations: Alajarín, M.; Sánchez-Andrada, P.; Vidal, A.; Tovar, F. *J. Org. Chem.* **2005**, *70*, 1340−1349.

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(11) Bürgi, H. B.; Dunitz, J. D. *Acc. Chem. Res.* **1983**, *16*, 153−161.

(12) Nakanishi, S.; Butler, K. *Org. Prep. Proced. Int.* **1975**, *7*, 155.

(13) Vogel, A. I. *Textbook of Practical Organic Chemistry*, 4th ed.; Longmans: London, 1962; Vol. 21 (Aromatic Carboxylic Acids), pp 1204−1205.

3,5-Diphenyl-2-styryl-6*H*-6-oxo-1,3-oxazin-3-ium-4-olate (9d). A solution of chlorocarbonylphenylketene **8** (361 mg, 2 mmol) in anhydrous THF (10 mL) was added to a stirred solution of amide **7** ($R^1 = R^2 =$ Ph) (446 mg, 2 mmol) in 10 mL of anhydrous THF under N_2. The mixture was stirred at room temperature for 1 h. The precipitate was collected by filtration and washed with 30 mL of anhydrous THF to afford the desired **9d** as a red solid (550 mg, 75%): mp 210−211 °C; IR (KBr) ν_{max} 3033, 1754, 1675, 1617, 1574, 1424, 1355, 1132, 979, 767, 696, 631, 628 cm^{-1}; MS *m/z* (relative intensity) 367 (M^+, 26.66), 220 (24.65), 179 (29), 131 (100), 119 (15.08), 103 (30.45), 118 (18.27), 103 (30.45), 77 (19.14). 44 (15.08); ^1H NMR (500 MHz, CD_2Cl_2) δ 8.295 (d, $J = 15$ Hz, 1H), 7.77−7.18 (m, 15H), 6.295 (d, $J = 15$ Hz, 1H). Anal. Calcd for $C_{24}H_{17}NO_3$: C, 78.47; H, 4.63; N, 3.81. Found: C, 77.99; H, 4.54; N, 3.65.

1,3,7-Triphenyl-3-azabicyclo[3.1.1]heptane-2,4,6-trione (12d). Method A. Compound **9d** (367 mg, 1 mmol) in 30 mL of anhydrous toluene was refluxed for 4 h. After cooling, the separated solid was collected and recrystallized from ethyl acetate−hexane forming white prisms (264 mg; 72%).

Method B. Compound **9d** (367 mg, 1 mmol) was dissolved in dry CH_2Cl_2 (50 mL). The red solution was stirred for 3 days at room temperature under N_2. The solvent was removed, and the residue was triturated with hexane and then filtered and recrystallized from ethyl acetate−hexane to afford white crystals (301 mg, 85%): mp 218 °C; IR (KBr) 3023, 1792, 1740, 1693, 1346, 1237, 1157, 757, 694, 524 cm^{-1}; MS *m/z* (relative intensity) 367 (M^+, 24), 339 (9,2), 223 (5.1), 220 (22.1), 207 (23.2), 206 (8.6), 192 (8.9), 191 (10.2), 180 (6.9), 179 (22.8), 178 (8.3), 132 (9.2), 131 (100.0), 119 (6.9), 118 (22.5), 103 (28.0), 92 (6.9), 91 (14.5), 89 (8.9), 77 (19.5) 44 (5.6); ^1H NMR (500 MHz, DMSO) δ 7.52−7.15 (m, 15H), 5.10 (s, 1H), 4.72 (s, 1H); ^{13}C NMR (125 MHz, DMSO) δ 188.2, 169.0, 167.7, 135.4, 133.9, 130.9, 128.8, 128.7, 128.6, 128.5, 128.3, 128.1, 127.9, 127.7, 127.6, 84.4, 71.0, 45.3. Anal. Calad for $C_{24}H_{17}NO_3$: C, 78.47; H, 4.63; N, 3.81. Found: C, 78.31; H, 4.71; N, 3.94.

3-Benzyl-5-phenyl-2-styryl-6*H*-6-oxo-1,3-oxazin-3-ium-4-olate (9e). A solution of chlorocarbonylphenylketene **8** (361 mg, 2 mmol) in dry diethyl ether (15 mL) was added to stirred solution of amide 7 ($R^1 =$ Ph; $R^2 = PhCH_2$) (474 mg, 2 mmol) in 10 mL of dry diethyl ether under nitrogen atmosphere. A precipitate was formed instantly. The reaction mixture was filtered and washed with 30 mL of dry ether to afford the desired **9e** as a brown solid (701 mg, 92%): mp 118−119 °C; IR (KBr) ν_{max} 3033, 2963, 1754, 1676, 1614, 1498, 1452, 1425, 1355, 1132 979, 767, 695, 632 cm^{-1}; MS *m/z* (relative intensity) 381 (M^+, 33.45), 220 (56.71), 192 (12.24), 132 (15.09), 131 (79.15), 118 (100), 106 (14.68), 105 (32.23), 91 (53.44), 89 (12.64), 77 (30.6), 44 (19.17); ^1H NMR (500 MHz, CD_2Cl_2) δ 8.265 (d, $J = 15$ Hz, 1H), 7.76−7.08 (m, 15H), 6.915 (d, $J = 15$ Hz, 1H), 5.47 (s, 2H). Anal. Calcd for $C_{25}H_{19}NO_3$: C, 78.74; H, 4.98; N, 3.67. Found: C, 78.42;, H, 4.89; N, 3.63.

3-Benzyl-1,7-diphenyl-3-azabicyclo[3.1.1]heptane-2,4,6-trione (12e). Compound **9e** (381 mg, 1 mmol) dissolved in 15 mL of anhydrous THF was refluxed for 30 min. The solvent was removed and the precipitate was recrystallized from ethyl acetate−hexane to afford white crystals (343 mg, 90%): mp 180 °C; IR (KBr) 3004, 2956, 1796, 1740, 1691, 1498, 1457, 1351, 1331, 1216, 1153, 928, 773, 694, 525, 516 cm^{-1}; MS *m/z* (relative intensity) 381 (M^+, 33.1), 353 (11.9), 221 (10.5), 220 (59.7), 192 (15.0), 191 (15.9), 189 (5.2), 179 (10.8), 178 (9.1), 132 (6.5), 131 (51.9), 119 (9.3), 118 (100), 115 (5.2), 106 (5.5), 105 (21.6), 103 (21.3), 91 (34.1), 89 (8.1), 77 (15.1), 65 (6.0); ^1H NMR (500 MHz, $CDCl_3$) δ 7.44−7.07 (m, 15H), 5.00 (AB quartet, $J \approx 10$ Hz, 2 H, N-CH_2), 4.39 (1H, CH), 4.06 (1H, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.87 (Cq), 169.73 (Cq), 167.90 (Cq), 135.94 (Cq), 134.75 (Cq), 130.15 (Cq), 128.87 (CH), 128.85 (CH), 128.72 (CH), 128.46 (CH), 128.29 (CH), 128.24 (CH), 128.12 (CH), 128.06 (CH), 127.73 (CH), 84.74 (Cq), 72.13 (CH), 47.37 (CH), 44.38 (CH_2); spectral assignments were confirmed by ^{13}C DEPT 135 and HMQC $^1H-^{13}C$ correlations. Anal. Calcd for $C_{25}H_{19}NO_3$: C, 78.74; H, 4.98; N, 3.67. Found: C, 78.86; H, 4.88; N, 3.46.

5-Benzyl-3-phenyl-2-styryl-6*H*-6-oxo-1,3-oxazin-3-ium-4-olate (9f). A solution of chlorocarbonylbenzylketene **8** (389 mg, 2 mmol) in dry diethyl ether (15 mL) was added to a stirred solution of amide **7** ($R^1 = R^2 =$ Ph) (446 mg, 2 mmol) in 5 mL of dry THF under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 2 h. After cooling, the orange product was filtered and washed with 30 mL of dry benzene to afford 495 mg (65%): mp 122−123 °C; IR (KBr) 3028, 2923, 1761, 1670, 1615, 1490, 1419, 1325, 1019, 765, 697 cm^{-1}; MS *m/z* (relative intensity) 381 (M^+, 7.2), 354 (5.6), 353 (27.1), 296 (8.5), 295 (39.5), 281 (11.0), 268 (5.7), 267 (19.5), 262 (8.1), 253 (17.8), 234 (9.2), 223 (6.8), 222 (5.9), 221 (16.3), 164 (7.2), 158 (6.5), 156 (5.4), 145 (8.5), 132 (12.4), 131 (100.0), 130 (9.8), 122 (6.1), 121 (22.7), 118 (9.6), 115 (9.1), 105 (9.1), 104 (30.4), 103 (31.1), 92 (6.0), 91 (69.7), 89 (9.5), 77 (26.7), 65 (6.3), 51 (6.0); ^1H NMR (500 MHz, CD_2Cl_2) δ 8.215 (d, $J = 15$ Hz, 1H), 7.63−7.16 (m, 15H), 6.255 (d, $J = 15$ Hz, 1H), 3.67 (s, 2H). Anal. Calcd for $C_{25}H_{19}NO_3$: C, 78.74; H, 4.98; N, 3.67. Found: C, 78.39; H, 4.83; N, 3.48.

1-Benzyl-3,7-diphenyl-3-azabicyclo[3.1.1]heptane-2,4,6-trione (12f). Method A. Compound **9f** (381 mg, 1 mmol) in 10 mL of anhydrous THF was refluxed for 2 h. The solvent was removed and the residue was triturated with hexane, then filtered and recrystallized from ethyl acetate−hexane to give 191 mg of white crystals (50%).

Method B. A solution of ketene **8b** (194.5 mg, 1 mmol) in dry THF (10 mL) was added to a stirred solution of amide **7a** (223 mg, 1 mmol) in 5 mL of dry THF under a nitrogen atmosphere. The mixture was refluxed for 2 h. The solvent was removed, and 10 mL of dry hexane was added. The resulting mixture was kept for 1 h at 0 °C. The precipitate was filtered and recrystallized from ethyl acetate−hexane to afford white crystals (228.6 mg, 60%): mp 181−182 °C; IR (KBr) ν_{max} 3020, 2911, 1789, 1738, 1698, 1496, 1353, 1147, 756, 738, 692 cm^{-1}; MS *m/z* (relative intensity) 381 (M^+, 9.3), 354 (10.9), 353 (39.6), 262 (6.9), 250 (6.0), 234 (9.9), 223 (7.7), 222 (6.6), 221 (24.2), 206 (5.2), 193 (5.1), 156 (7.7), 132 (10.1), 131 (100.0), 118 (8.2), 115 (16.0), 105 (5.1), 103 (26.7), 102 (5.6), 93 (6.9), 92 (5.5), 91 (58.3), 77 (17.9), 65 (6.0); ^1H NMR (500 MHz, DMSO) δ 7.50−7.00 (m, 15H), 4.79 (s, 1H), 4.72 (s, 1H), 2.91 (AB quartet, $J = 15$ Hz, 2H); ^{13}C NMR (125 MHz, DMSO) δ 188.81, 169.85, 168.00, 135.41, 134.60, 133.93, 129.53, 128.90, 128.83, 128.79, 128.39, 127.97, 127.64, 125.96, 81.57, 70.58, 44.68, 30.73 (one *p*-C in the aromatic region not accounted for due to overlapping signals). Anal. Calcd for $C_{25}H_{19}NO_3$: C, 78.74; H, 4.98; N, 3.67. Found: C, 78.83; H, 4.96; N, 3.68.

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Supporting Information Available: X-ray crystal data and ORTEP drawing (Figure S1) of the structure of compound **12d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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