JOC*Note*

New Rearrangement of 4-Isoxazoline System: Conversion of Ketones into α,β-Unsaturated Amides

Ugo Chiacchio,*,† Antonio Rescifina,† Maria Assunta Chiacchio,† Giovanni Romeo,*,‡ and Roberto Romeo‡

Dipartimento di Scienze Chimiche, Università di Catania, Viale Andrea Doria 6, 95125 Catania, Italy

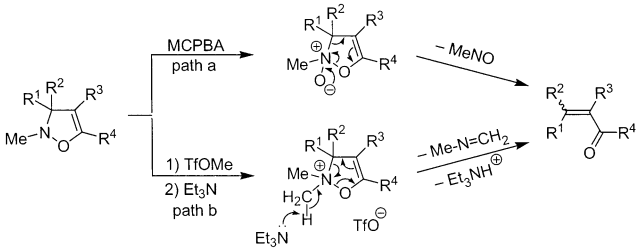
uchiacchio@dipchi.unict.it

Received January 30, 2003

Abstract: A new rearrangement pattern of the 4-isoxazoline system is reported. The reaction, starting from 3,3-disubstituted derivatives and leading to α,β-unsaturated amides, proceeds through the quaternarization of the nitrogen atom and involves the heterolytic cleavage of C_3-N bond, assisted by the formation of a relatively stable intermediate. The overall process represents a useful conversion of ketones into α,β-unsaturated amides.

The readiness of 4-isoxazolines to undergo rearrangement reactions is well-known.[1] The reactivity of this ring system, the so-called *N,O*-vinyl functionality,[2] is identifiable with the relatively low thermochemical stability of the N,O-bond, connected to a π-system. The most general feature is the thermal isomerization to 2-acylaziridines,[3] following the migration of nitrogen atom from position 1 to 4. The subsequent conversion to azomethyne ylides proceeds via conrotatory ring opening: the resulting dipoles can then give rise to ring closure to oxazolines,[4] or undergo a proton shift followed by cyclization to a pyrrole nucleus.[5] However, a number of additional chemical transformations have been reported that involve the C−C and C−H bonds at position 3, together with some N−O bond cleavages induced by prototropic processes, when a hydrogen atom is present at position 3 of the isoxazoline ring.[6]

SCHEME 1



Furthermore, the activation of the system, through N-oxidation or quaternization of the nitrogen atom, discloses new alternatives for the chemical conversion of the primary N,O-cycloadducts. In fact, treatment of 3,3-disubstituted 4-isoxazolines with *m*-chloroperbenzoic acid[7] (Scheme 1, path a) or methyl triflate and triethylamine[8] (Scheme 1, path b) afforded α,β-enones in excellent yields: the rearrangement process has been interpreted according to the cheletropic extrusion of nitrosomethane from the corresponding *N*-oxide or to the removal of the acid hydrogen atom at the *N*-methyl group in the isoxazolinium cation, respectively.

Further, the presence of an abstractable hydrogen at position 3 in the isoxazoline ring opens a different and competitive reaction route with formation of enamino derivatives:[9] all these processes originated from the N−O bond cleavage in the isoxazoline ring.

However, we have envisaged that the quaternarization of the nitrogen atom in the 4-isoxazoline system could lead, according to suitable substitution patterns and experimental conditions, to an increased chemical lability also of the C_3-N bond, besides the N−O bond, so as to induce the population of novel and alternative rearrangement pathways. Accordingly, in this paper we have examined the behavior of suitable 3,3-disubstituted 4-isoxazolines, by treatment with MeI, and we report a new rearrangement pattern of the isoxazoline nucleus that derives from the cleavage of C_3-N bond, assisted by the formation of a relatively stable intermediate.

Isoxazolines **1** and **2** have been prepared, starting from the corresponding ketones, as previously reported,[8] according to the well-known 1,3-dipolar cycloaddition of nitrones to ethyl propiolate (Scheme 2). The subsequent treatment of **1** and **2** with MeI in THF at reflux temperature leads to the exclusive formation of α,β-enones **3** and **4**, respectively (Scheme 2).[8]

This result has been rationalized on the basis of two competing reaction routes starting from the intermediate, not the isolated isoxazolinium salt, and involving the N,O-bond cleavage. In fact, it has been reported that, with I^-, a single electron-transfer (SET) mechanism is operating,[10] together with the ionic one, both leading to the expected α,β-enones[9] (Scheme 3).

* Corresponding author. Phone: +39 095 7385014. Fax: +39 06 233208980.

† Università di Catania.

‡ Dipartimento Farmaco-Chimico, Università di Messina, Viale SS. Annunziata, 98168 Messina, Italy.

(1) (a) Huisgen, R.; Giera, H.; Polborn, K. *Liebigs Ann. Recl* **1997**, *8*, 1691. (b) Freeman, J. P. *Chem. Rev*. **1983**, *83*, 241.

(2) (a) Parpani, P.; Zecchi, G. *J. Org. Chem*. **1987**, *52*, 1417. (b) Padwa, A.; Wong, G. S. K. *J. Org. Chem*. **1986**, *51*, 3125. (c) Freeman, J. P.; Duchamp, D. J.; Chidester, C. G.; Slomp, G.; Szmuszkovicz, J.; Raban, M. *J. Am. Chem. Soc*. **1982**, *104*, 1380.

(3) (a) Ishikawa, T.; Kudoh, T.; Yoshida, J.; Yasuhara, A.; Manabe, S.; Saito, S. *Org. Lett*. **2002**, *4*, 1907. (b) Padwa, A.; Meske, M.; Ni, Z. *Tetrahedron*, **1995**, *51*, 89. (c) Padwa, A.; Dean, D. C. *J. Org. Chem*. **1990**, *95*, 405. (d) Mullen, G. B.; Bennett, G. A.; Georgiev, V. S. *Liebigs Ann. Chem*. **1990**, *1*, 109.

(4) (a) Liguori, A.; Ottanà, R.; Romeo, G.; Sindona, G.; Uccella, N. *Tetrahedron* **1988**, *44*, 1247 and 1255.

(5) (a) Zhao, B.-X.; Yu, Y.; Eguchi, S. *Tetrahedron* **1996**, *52*, 12049. (b) Yang, Y.; Ohno, M.; Eguchi, S. *Tetrahedron* **1993**, *49*, 823.

(6) (a) Jones, R. F.; Martin, J. N.; Smith, P.; Gelbrich, T.; Light, M. E.; Hursthouse, M. B. *J. Chem. Soc., Chem. Commun*. **2000**, 1949. (b) Zhao, B.-X.; Eguchi, S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2973. (c) Hendrickson, J. B.; Pearson, D. H. *Tetrahedron Lett*. **1983**, *24*, 4657.

(7) (a) Padwa, A.; Chiacchio, U.; Kline, D. N.; Perumattan, J. *J. Org. Chem*. **1988**, *53*, 2238.

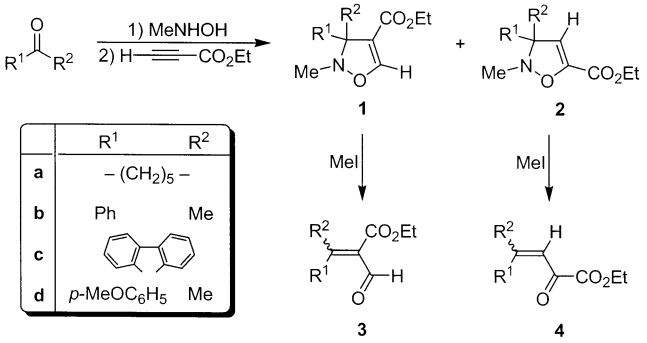
(8) (a) Chiacchio, U.; Liguori, A.; Rescifina, A.; Romeo, G.; Rossano, F.; Sindona, G.; Uccella, N. *Tetrahedron* **1992**, *48*, 123.

(9) Chiacchio, U.; Casuscelli, F.; Liguori, A.; Rescifina, A.; Romeo, G.; Sindona, G.; Uccella, N. *Heterocycles* **1993**, *36*, 585.

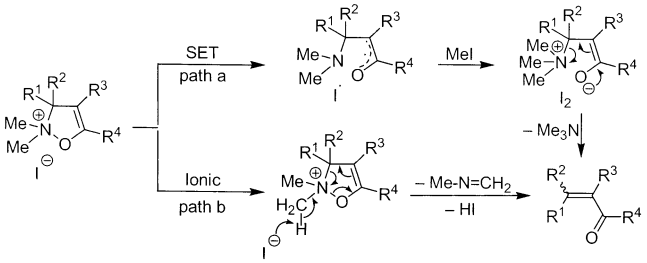
(10) (a) Eberson, L. *Adv. Phys. Org. Chem*. **1982**, *18*, 79. (b) Pros, A. *Acc. Chem. Res*. **1985**, *18*, 212.

10.1021/jo034135+ CCC: $25.00
Published on Web 03/26/2003

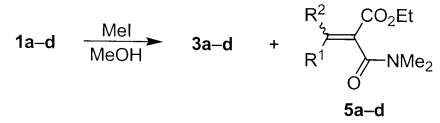
SCHEME 2



SCHEME 3



SCHEME 4



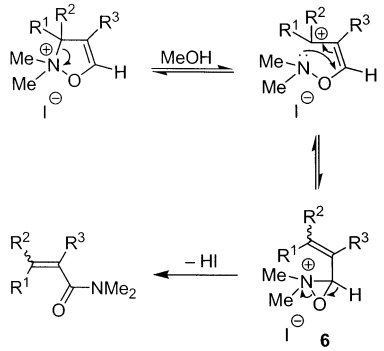
5a–d

However, when the same reaction was performed on compounds **1** in polar solvents such as methanol, *N*,*N*-dimethylformamide, or acetonitrile, besides the corresponding compounds **3**, the formation of α,*β*-unsaturated amides **5** as minor products was observed (Scheme 4).

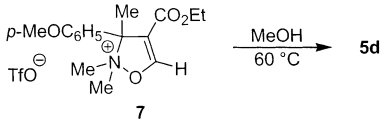
Structures of compounds **5** have been assigned on the basis of ^{1}H and ^{13}C NMR data and confirmed by MS measurements. The assignment of the *E*/*Z* configuration for amides **5b**,**d**, appears to be not reliable on the basis of (^{1}H−^{1}H) NOEDS experiments; however, a heteronuclear Overhauser effect has been successfully measured between C_1 and protons of methyl group at C_3, in (*E*)-compounds, by a classical one-dimensional (^{1}H−^{13}C) HOESY sequence.[11] Moreover, the stereochemical assignments have been supported by semiempirical PM3 calculations. In both cases, the (*E*)-isomer was more stable than the (*Z*)-isomer by 0.87 and 0.78 kcal/mol for **5b** and **5d**, respectively; these values reflect the *E*/*Z* ratio of 4.3:1 and 3.7:1, respectively, which is very near to the experimental one (5:1 and 4.5:1).

Two competing reaction routes are, then, operating: the pathway leading to enones, derived from the cleavage of the N−O bond, and the reaction channel leading to amides. In an apolar medium, the homolytic cleavage of the N−O bond leads, through a redox process, to α,*β*-enones.[8] The presence of a polar solvent such as methanol, on the contrary, promotes an alternative reaction scheme. In fact, the formation of α,*β*-unsaturated amides

SCHEME 5



SCHEME 6



7

5 can be rationalized on the basis of the heterolytic cleavage of the C_3−N bond of isoxazolines **1**, assisted by the solvent, which leads to the formation of an allylic tertiary carbocation. The subsequent migration of the nitrogen lone pair at the C_5 carbon atom affords an intermediate, not the isolated oxaziridinium cation **6**. In the presence of an easily abstractable proton, the equilibrium is shifted toward α,*β*-unsaturated amides **5** (Scheme 5); otherwise, as in the case of isoxazoline **2b**, devoid of a hydrogen atom at C_5, the equilibrium turns back toward the isoxazolinium salt and, then, through the reported single-electron transfer mechanism and/or the competitive basic attack of iodide ion to *N*-methyl hydrogen atoms, to the corresponding α,*β*-enone **4b**.

We have attempted to improve the alternative rearrangement process linked to the C_3−N bond cleavage by depressing the reaction route leading to α,*β*-enones. In this aim, isoxazolines **1** have been reacted with MeI in the presence of a stoichiometric amount of silver perchlorate in order to precipitate the iodide ion. The crude reaction mixture shows the exclusive formation of α,*β*-unsaturated amides **5** in a nearly quantitative yield.

The obtained results clearly indicate that the removal of iodide ion blocks the redox process leading to the formation of α,*β*-enones; at the same time, the perchlorate ion, released into the solution, is a base too weak to induce the removal of the proton at the *N*-methyl group. In this way, both routes leading to α,*β*-enones are prevented.

The obtainment of N,N-disubstituted amides appears to be an indirect confirmation of the formation in the described process of an isoxazolinium salt as a precursor of the rearrangement pathway. However, further support for the suggested mechanism has been achieved by the isolation of the isoxazolinium salt **7**, obtained by treatment of isoxazoline **1d** with methyl triflate in CCl_4 at room temperature for 10 h (Scheme 6). Further heating in methanol solution afforded, in quantitative yield, the amide **5d**, thus confirming that only the ionic pathway, leading to enamides, is operating in the absence of the iodide ion.

In conclusion, the described procedure constitutes a convenient conversion of ketones to α,*β*-unsaturated

(11) (a) Ancian, B.; Canet, D.; Mutzenhardt, P. *Chem. Phys. Lett.* **2001**, *336*, 410. (b) Stott, K. and Keeler, J. *Magn. Reson. Chem.* **1996**, *34*, 554.

amides. The complete reaction scheme proceeds through the formation of intermediate 4-isoxazolines, easily accessible by 1,3-dipolar cycloaddition reaction, followed by treatment with methyl triflate and rearrangement of intermediate isoxazolinium salt by heating in methanol solution. The clear advantages of the process are linked to the good global yields (67−85%) obtained and the mild reaction conditions utilized.

Experimental Section

Rearrangement of 4-Isoxazolines 1 in Methanol Solution. A solution of 4-isoxazoline **1** (1.80 mmol) and iodomethane (1.70 mL, 27.3 mmol) in methanol (10 mL) was heated at 80 °C in an oil bath, under magnetic stirring, for 12 h. After this time, removal of the solvent, at reduced pressure, and column flash chromatography on silica gel (ethyl ether/cyclohexane 9:1) afforded, besides the expected α,β-enones **3** (80−88% yield), α,β-unsaturated amides **5** as minor products (8−12% yield).

Synthesis of Amides 5. *General Procedure.* To a solution of 4-isoxazoline **1** (0.72 mmol) in anhydrous CH_2Cl_2 (20 mL) was added methyl trifluoromethanesulfonate (85 μL, 0.75 mmol), and the mixture, magnetically stirred, was allowed to react for 2 h at room temperature. Evaporation of the solvent under reduced pressure gave the crude salt **7,** which was dissolved in methanol (5 mL) and heated at reflux. After 1 h, the solvent was evaporated at reduced pressure and the residue purified by column flash chromatography on silica gel (ethyl ether/cyclohexane 9:1).

Ethyl 2-Cyclohexylidene-3-(dimethylamino)-3-oxopropanoate (5a): 204.5 mg, 95%, light yellow oil; IR (neat) 1730, 1625 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.38 (t, 3H, J = 7.1 Hz), 1.31−2.88 (m, 10H), 2.65 (s, 3H, *N*-Me), 2.83 (s, 3H, *N*-Me), 4.33 (q, 2H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.9, 22.0, 23.3, 24.9, 28.3, 34.00, 34.1, 36.5, 60.6, 159.4, 161.8; HRMS (EI) calcd for $[M^+]$ $C_{13}H_{21}NO_3$ 239.1521, found 239.1524. Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.25; H, 8.84; N, 5.85. Found: C, 65.48; H, 8,82; N, 5.84.

Ethyl (2*E*/*Z*)-2-[(Dimethylamino)carbonyl]-3-phenylbut-2-enoate (5b). First eluted product ((*E*)-isomer): 188.6 mg, 80.2%, light yellow oil; IR (neat) 1735, 1650, 1150 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.95 (t, 3H, J = 7.0 Hz), 2.11 (s, 3H), 3.01 (s, 3H, *N*-Me), 3.09 (s, 3H, *N*-Me), 3.96 (q, 2H, J = 7.0 Hz), 7.11−7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.1, 22.8, 34.0, 37.2, 60.0, 126.0, 127.0, 127.9, 140.7, 149.1, 163.9, 166.8; HRMS (EI) calcd for $[M^+]$ $C_{15}H_{19}NO_3$ 261.1365, found 261.1363. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.81; H, 7,30; N, 5.37.

Further eluted product ((*Z*)-isomer): 37.5 mg, 16.0%, light yellow oil; IR (neat) 1735, 1650, 1150 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.30 (t, 3H, J = 7.0 Hz), 2.38 (s, 3H), 2.41 (s, 3H, *N*-Me), 2.68 (s, 3H, *N*-Me), 4.26 (q, 2H, J = 7.0 Hz), 7.12−7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.7, 21.3, 33.6, 37.1, 60.2, 126.6, 127.5, 127.9, 140.7, 150.4, 164.3, 167.0. HRMS (EI) calcd for $[M^+]$ $C_{15}H_{19}NO_3$ 261.1365, found 261.1362. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.79; H, 7,34; N, 5.34.

Ethyl 3-(Dimethylamino)-2-(9*H*-fluoren-9-ylidene)-3-oxopropanoate (5c): 289.2 mg, 100%, light yellow oil; IR (neat) 1725, 1645 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.40 (t, 3H, J = 7.0 Hz), 3.05 (s, 3H, *N*-Me), 3.15 (s, 3H, *N*-Me), 4.45 (q, 2H, J = 7.0 Hz), 6.97−8.15 (m, 8H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.1, 33.9, 37.2, 60.6, 117.2, 118.5, 118.9, 123.8, 126.1, 126.5, 127.1, 128.8, 130.2, 133.8, 138.3, 140.1, 142.3, 144.5; HRMS (EI) calcd for $[M^+]$ $C_{20}H_{19}NO_3$ 321.1365, found 321.1368. Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.91; H, 5.97; N, 4.33.

Ethyl (2*E*/*Z*)-2-[(Dimethylamino)carbonyl]-3(4-methoxyphenyl)but-2-enoate (5d). First eluted product ((*E*)-isomer): 212.4 mg, 81.0%, light yellow oil; IR (neat) 1700, 1625, 1170 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.03 (t, 3H, J = 7.1 Hz), 2.09 (s, 3H), 3.08 (s, 3H, *N*-Me), 3.09 (s, 3H, *N*-Me), 3.80 (s, 3H, *O*-Me), 4.01 (q, 2H, J = 7.1 Hz), 6.82−7.35 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.8, 23.3, 34.6, 37.8, 55.2, 60.6, 113.4, 127.1, 128.1, 133.1, 149.6, 159.4, 164.6, 167.6; HRMS (EI) calcd for $[M^+]$ $C_{16}H_{21}NO_4$ 291.1470, found 291.1468. Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 65.77; H, 7,28; N, 4.80.

Further eluted product ((*Z*)-isomer): 47.1 mg, 18.0%, light yellow oil; IR (neat) 1705, 1620, 1165 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.29 (t, 3H, J = 7.1 Hz), 2.46 (s, 3H), 2.66 (s, 3H, *N*-Me), 2.74 (s, 3H, *N*-Me), 3.80 (s, 3H, *O*-Me), 4.25 (q, 2H, J = 7.1 Hz), 6.83−7.38 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.2, 21.8, 34.5, 37.6, 55.3, 60.5, 113.3, 127.1, 128.3, 133.2, 150.2, 159.9, 165.5, 168.2; HRMS (EI) calcd for $[M^+]$ $C_{16}H_{21}NO_4$ 291.1470, found 291.1467. Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 65.69; H, 7,25; N, 4.82.

4-(Ethoxycarbonyl)-3-(4-methoxyphenyl)-2,2,3-trimethyl-2,3-dihydroisoxazol-2-ium Trifluoromethanesulfonate (7). To a solution of 4-isoxazoline **1d** (200 mg, 0.72 mmol) in anhydrous CCl_4 (20 mL) was added methyl trifluoromethanesulfonate (85 μL, 0.75 mmol), and the mixture, magnetically stirred, was allowed to react for 10 h at room temperature. Evaporation of solvent under reduced pressure gave the salt **7** (317.8 mg, 100%, sticky oil): ^1H NMR ($CDCl_3$, 500 MHz) δ 1.26 (t, 3H, J = 7.1 Hz), 2.42 (s, 3H), 3.06 (s, 3H), 3.83 (s, 6H), 4.23 (q, 2H, J = 7.1 Hz), 6.87−7.41 (m, 4H), 7.77 (s, 1H, H_5); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1, 18.3, 53.4, 53.5, 55.8, 60.4, 89.3, 112.7, (q, J = 315 Hz), 126.3, 117.2, 125.7, 131.5, 151.8, 156.3, 161.4; HRMS (FAB+) calcd for $[MH^+]$ $C_{17}H_{23}F_3NO_7S$ 442.1147, found 442.1143. Anal. Calcd for $C_{17}H_{22}F_3NO_7S$: C, 46.26; H, 5.02; N, 3.17; S, 7.26. Found: C, 46.09; H, 5.03; N, 3.16; S, 7.24.

Acknowledgment. We thank MIUR (FIRB) and CNR for their financial support.

JO034135+