Metal-Catalyzed, Intramolecular Reactions of α-Diazo Ketones with Isoxazoles

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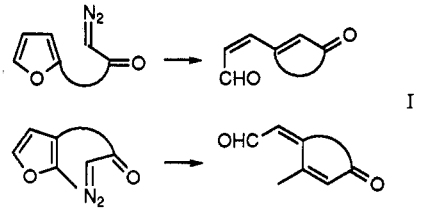
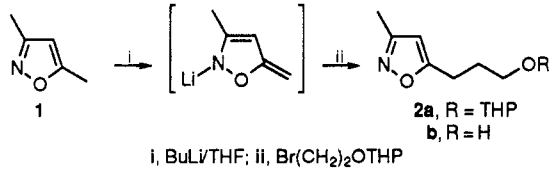
Recently it has been shown that the dirhodium tetraacetate-catalyzed decomposition of α-diazo carbonyl compounds in the presence of furans leads mostly to the unraveling of the heterocycles with the production of 1,4-diacyl-1,3-butadienes.[1] The intramolecular version of this reaction has yielded cycloalkenones β-substituted by acrolein side chains (or their ketone equivalents) (eqs I).[2] It now became of interest to investigate the latter reaction in the case of diazoacylisoxazoles.



I

The starting carboxylic acids, the precursors of the diazomethyl ketones, were prepared in the following manner. Treatment of 3,5-dimethylisoxazole (1) with *n*-butyllithium[3a] and thereafter with β-bromoethyl tetrahydropyranyl ether afforded isoxazole **2a** in 73% yield, whose exposure to methanolic acid furnished alcohol **2b** in 94% yield. Jones oxidation of the latter yielded (85%) acid **3a**. The regiochemistry of the **1** → **2a** transformation is in agreement with precedent[3] and the NMR spectra of the product fit those for a 5-methyl-substituted compound.[4]



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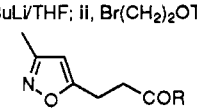
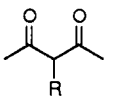
2a, R = THP
b, R = H

i, BuLi/THF; ii, $Br(CH_2)_2OTHP$

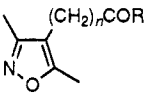


3a, R = OH
b, R = CHN_2

Alkylation of acetylacetone (**4a**) with methyl β-bromopropionate and potassium *tert*-butoxide gave diketone **4b** (85%), whose interaction with hydroxylamine led to isoxazole **5a** (91%). Alkaline hydrolysis of the later produced acid **5b** (83%). Alkylation of diketone **4a** with ethyl γ-bromobutyrate and potassium *tert*-butoxide yielded diketone **4c** (80%), whose treatment with methanolic hydroxylamine hydrochloride furnished isoxazole **5c** (99%). Base-induced hydrolysis of the latter afforded acid **5d** (94%).



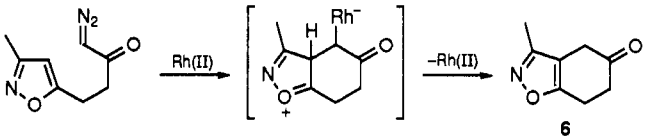
4a, R = H
b, R = $(CH_2)_2CO_2Me$
c, R = $(CH_2)_3CO_2Et$



5a, *n* = 2, R = OMe
b, *n* = 2, R = OH
c, *n* = 3, R = OMe
d, *n* = 3, R = OH
e, *n* = 2, R = CHN_2
f, *n* = 3, R = CHN_2

Exposure of acids **3a**, **5b**, and **5d** to oxalyl chloride, vacuum removal of the excess reagent, and slow addition of ether solutions of the remaining acid chlorides to an ethereal diazomethane solution led to diazo ketones **3b** (67%), **5e** (67%), and **5f** (63%), respectively. Decomposition of each of the diazo ketones was carried out over dirhodium tetraacetate in methylene chloride solution.

Diazo ketone **3b** produced bicyclic ketone **6** (61%), indicative of the following reaction mode.



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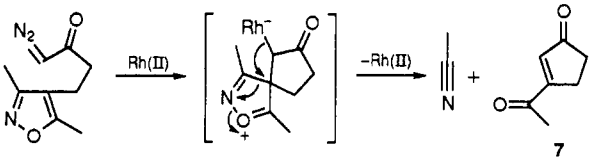
Diazo ketone **5e**, surprisingly, afforded diketone **7**[5] (67%), also indicative of side-chain interaction with the isoxazole β-carbon site, however with acetonitrile extrusion.



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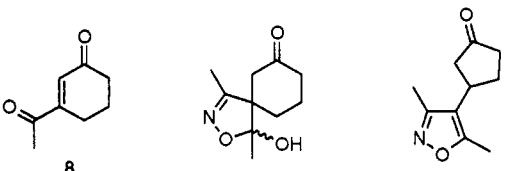
Finally, diazo ketone **5f** gave a mixture of products, diketone **8**[6] (27%) (reminiscent of structure **7**), ketone **9** (16%) (the product of β-cyclization without extrusion of acetonitrile, but with hydration on workup), and cyclopentanone **10** (14%) (the product of trivial carbon–hydrogen insertion[7]).[8]



8 **9** **10**

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It is noteworthy that in contrast to the behavior of diazoacylfurans, i.e. side-chain interaction at the heterocycle's α-carbon site (eqs I), the diazoacylisoxazoles form bonds at the heterocycle's β-carbon site.

Experimental Section

Melting points are uncorrected. Infrared spectra were taken on $CHCl_3$ solutions. Column chromatography was executed on 70–230-mesh Merck silica gel. All reactions were carried out under nitrogen and all extracts dried over Na_2SO_4.

3-(3-Methyl-5-isoxazolyl)propyl 2-Tetrahydropyranyl Ether (2a). A 2.5 M hexane solution of *n*-butyllithium (4 mL) was added dropwise to a stirring solution of 1.00 g (10 mmol) of commercially available 3,5-dimethylisoxazole in 40 mL of dry THF at −78 °C, and the mixture was then stirred at −20 °C for 2 h. A solution of 2.40 g (11 mmol) of 2-bromoethyl 2-tetrahydropyranyl ether in 10 mL of dry THF was added dropwise at −78 °C. The mixture then was allowed to warm to room temperature and was stirred for 4 h. The addition of a 5% hydrochloric acid solution brought the pH to 2 and the mixture was extracted with ether. The extract was washed with water, dried, and evaporated. Chromatography of the residue on neutral alumina (activity IV) and elution with chloroform yielded 1.67 g (73%) of colorless, liquid ether **2a**: IR (CH_2Cl_2) isoxazole 1595 (m) cm^{-1}.

Anal. Calcd for $C_{12}H_{19}O_3N$: C, 63.98; H, 8.50; N, 6.22. Found: C, 63.87; H, 8.61; N, 6.28.

3-(3-Methyl-5-isoxazolyl)-1-propanol (2b). A solution of 1.67 g (7.4 mmol) of ether **2a** and 120 mg of *p*-toluenesulfonic acid in 40 mL of methanol was stirred at room temperature for 3 h and then evaporated to dryness. Chromatography of the residue and elution with chloroform afforded 985 mg (94%) of colorless, liquid alcohol **2b**: IR OH 3520 (w), isoxazole 1560 (m) cm^{-1}.

Anal. Calcd for $C_7H_{11}O_2N$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.65; H, 7.77; N, 9.86.

β-(3-Methyl-5-isoxazolyl)propionic Acid (3a). Jones reagent was added dropwise to a stirring solution of 985 mg (7 mmol) of alcohol **2b** in 50 mL of acetone at 0 °C until the solution remained yellow. The mixture was stirred at room temperature for 15 min and then enough saturated $NaHSO_3$ solution was added to discharge the color of the mixture. The latter was evaporated and the residue diluted with water and extracted with chloroform. The extract was washed with water, dried, and evaporated. The residue was 920 mg (85%) of colorless, crystalline acid **3a**: mp 85–86 °C (benzene): IR (CH_2Cl_2) OH 3500 (br, w), C=O 1715 (s), isoxazole 1608 (m) cm^{-1}.

Anal. Calcd for $C_7H_9O_3N$: C, 54.19; H, 5.85; N, 9.03. Found: C, 54.28; H, 5.78; N, 9.12.

Methyl 4-Acetyl-5-oxohexanoate (4b). A solution of 3.37 g (20 mmol) of methyl β-bromopropionate in 2 mL of *tert*-butyl alcohol was added dropwise to a solution of 1.00 g (10 mmol) of acetylacetone (**4a**) and potassium *tert*-butoxide (from 590 mg, 15 mmol, of potassium) in 52 mL of *tert*-butyl alcohol, and the suspension was stirred at room temperature for 20 h. It then was brought to pH 2 by the addition of 5% hydrochloric acid. The solution was evaporated and the residue dissolved in chloroform and water. The aqueous layer was extracted with chloroform and the combined organic solutions were washed with water, dried, and evaporated. Chromatography of the residue and elution with chloroform furnished 1.57 g (85%) of colorless, liquid ester **4b**: IR C=O 1725 (s), 1691 (s) cm^{-1}.

Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.25; H, 7.42.

Ethyl 5-Acetyl-6-oxoheptanoate (4c). The same procedure and workup were used for the interaction of a solution of 11.7 g (60 mmol) of ethyl γ-bromobutyrate in 6 mL of *tert*-butyl alcohol with a solution of 3.00 g (30 mmol) of acetylacetone (**4a**) and potassium *tert*-butoxide (from 1.80 g, 45 mmol, of potassium) in 156 mL of *tert*-butyl alcohol. The product was 5.1 g (80%) of colorless, liquid ester **4c**: IR (neat) C=O 1725 (s), 1700 (s) cm^{-1}.

Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.52; H, 8.57.

Methyl β-(3,5-Dimethyl-4-isoxazolyl)propionate (5a). A solution of 510 mg (7.5 mmol) of hydroxylamine hydrochloride in 2 mL of water was added to a stirring solution of 1.40 g (7.5 mmol) of ester **4b** in 15 mL of methanol and the mixture refluxed for 12 h. The solution was filtered through an alumina pad and evaporated, yielding 1.25 g (91%) of colorless, liquid ester **5a**: IR C=O 1730 (s), isoxazole 1641 (m) cm^{-1}.

Anal. Calcd for $C_9H_{13}O_3N$: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.15; H, 7.08; N, 7.71.

Methyl γ-(3,5-Dimethyl-4-isoxazolyl)butyrate (5c). The same procedure and workup were used for interaction of a solution of 324 mg (4.6 mmol) of hydroxylamine hydrochloride in 1.5 mL of water with a solution of 1.00 g (4.6 mmol) of ester **4c** in 10 mL of methanol. The product was 910 mg (99%) of colorless, liquid ester **5c**: IR C=O 1730 (s), isoxazole 1630 (m) cm^{-1}.

Anal. Calcd for $C_{10}H_{15}O_3N$: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.78; H, 7.75; N, 7.15.

β-(3,5-Dimethyl-4-isoxazolyl)propionic Acid (5b). Ester **5a** (550 mg, 3 mmol) was stirred in 15 mL of a 5% methanolic potassium hydroxide solution, and the mixture was refluxed for 3 h. The cooled solution was concentrated to 5 mL under reduced pressure and poured into 15 mL of water. It then was brought to pH 2 with 5% hydrochloric acid solution and extracted with ethyl acetate. The extract was washed with water, dried, and evaporated. Crystallization of the solid residue from benzene gave 420 mg (83%) of colorless, crystalline needles of acid **5b**: mp 73–75 °C; IR: OH 3500 (br, w), C=O 1715 (s), isoxazole 1632 (m), cm^{-1}.

Anal. Calcd for $C_8H_{11}O_3N$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.92; H, 6.47; N, 8.24.

γ-(3,5-Dimethyl-4-isoxazolyl)butyric Acid (5d). The same procedure and workup were used for the interaction of 1.60 g (8.1 mmol) of ester **5c** with 40 mL of 5% methanolic potassium hydroxide solution. The product was 1.40 g (94%) of colorless, crystalline acid **5d**: mp 90–93 °C; IR OH 3510 (br, w), C=O 1710 (s), isoxazole 1634 (m) cm^{-1}.

Anal. Calcd for $C_9H_{13}O_3N$: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.12; H, 7.09; N, 7.69.

General Procedure. Preparation of Diazo Ketones. A mixture of 1 mmol of acid **3a**, **5b**, or **5d** and 10 mmol of oxalyl chloride was stirred at room temperature for 2 h and then the excess of oxalyl chloride removed under vacuum. A solution of the residue in 2 mL of dry ether was added dropwise to an ethereal solution (25 mL) of diazomethane and triethylamine (0.2 mL), and the mixture was stirred at room temperature for 12 h. It then was filtered and the filtrate concentrated under vacuum. Chromatography of the residual solution on neutral alumina (activity III) and elution with chloroform yielded yellow, liquid diazo ketone.

1-Diazo-4-(3-methyl-5-isoxazolyl)-2-butanone (3b): 67%; IR C=N_2 2102 (s), C=O 1633 (s), isoxazole 1594 (w) cm^{-1}.

1-Diazo-4-(3,5-dimethyl-4-isoxazolyl)-2-butanone (5e): 67%; IR C=N_2 2103 (s), C=O 1635 (s), isoxazole 1600 (w) cm^{-1}.

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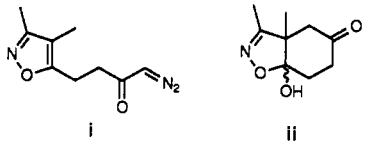
(8) When diazo ketone **i** [IR (CH_2Cl_2) C=N_2 2103 (s), C=O 1635 (s), isoxazole 1603 (w) cm^{-1}; ^1H NMR δ 1.89 (s, 3, 4-Me), 2.18 (s, 3, 3-Me), 2.6–2.8 (m, 2, benzyl Hs), 2.9–3.1 (m, 2, $COCH_2$), 5.26 (s, 1, CHN_2)], prepared from 3,4,5-trimethylisoxazole[9] by way of the route to **3b**, was decomposed in methylene chloride solution over dirhodium tetraacetate (followed by aqueous workup), there was obtained ketone **ii** [IR (CH_2Cl_2) OH 3580 (m), C=O 1723 (s), C=N 1640 (w), 1610 (w) cm^{-1}; ^1H NMR δ 1.28 (s, 3, 3a-Me), 1.88 (s, 3, 3-Me), 2.3–2.6 (m, 6, methylenes); ^{13}C NMR δ 9.8 (3-Me), 18.0 (3a-Me), 30.8 (C-7), 35.3 (C-6), 47.0 (C-4), 55.5 (C-3a), 106.5 (C-7a), 161.5 (C-3), 209.0 (C-5)] (10%).



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1-Diazo-5-(3,5-dimethyl-4-isoxazolyl)-2-pentanone (5f): 63%; IR C=N_2 2102 (s), C=O 1635 (s), isoxazole 1590 (w) cm^{-1}.

General Procedure. Diazo Ketone Decompositions. A solution of 1 mmol of diazo ketone in 80 mL of methylene chloride was added dropwise over a 12-h period to a suspension of 20 mg of dirhodium tetraacetate in 15 mL of methylene chloride. The mixture was evaporated under vacuum and the residue chromatographed.

3-Methyl-6,7-dihydro-5(4*H*)-benzisoxazolone (6) (eluted with 20:1 benzene/ethyl acetate): colorless liquid (61%); IR (CH_2Cl_2) C=O 1711 (s), isoxazole 1600 (w) cm^{-1}.

Anal. Calcd for $C_8H_7O_2N$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.49; H, 4.70; N, 9.31.

3-Acetyl-2-cyclopentenone[5] (7) (eluted with chloroform): colorless liquid (67%); IR and ^1H NMR spectrally identical with reported data.[5]

Anal. Calcd for $C_7H_8O_2$: C, 67.73; H, 6.50. Found: C, 67.69; H, 6.61.

3-Acetyl-2-cyclohexenone[6] (8) (eluted with 9:1 hexane/ethyl acetate): colorless liquid (27%, first eluent); IR spectrally identical with reported data.[6a]

4,5-Dihydro-5-hydroxy-3,5-dimethyl-4,4-(β-oxopentamethylene)isoxazole (9): colorless liquid (16%, third eluent); IR OH 3560 (m), C=O 1712 (s), isoxazole 1600 (w) cm^{-1}.

Anal. Calcd for $C_{10}H_{15}O_3N$: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.82; H, 7.74; N, 7.15.

3-(3,5-Dimethyl-4-isoxazolyl)cyclopentanone (10): colorless liquid (14%, second eluent); IR (CH_2Cl_2) C=O 1739 (s), isoxazole 1625 (w) cm^{-1}.

Anal. Calcd for $C_{10}H_{13}O_2N$: C, 61.53; H, 6.71; N, 7.17. Found: C, 61.45; H, 6.81; N, 7.21.

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Supplementary Material Available: ^1H NMR spectral data of **2a, 2b, 3a, 3b, 4b, 4c, 5a, 5b, 5c, 5d, 5e, 5f, 6, 8, 9,** and **10** and ^{13}C NMR spectral data of **2a, 2b, 3a, 4b, 4c, 5a, 5b, 5c, 5d, 6, 7, 8, 9,** and **10** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.