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Molybdenum Hexacarbonyl Promoted Ring-Opening of Hydroxyimino Isoxazoles: Unexpected Pyrazole Formation

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Fused isoxazoles underwent reductive ring-opening in the presence of molybdenum hexacarbonyl to give the corresponding β-disubstituted compounds. 3,6,6-Trimethyl-6,7-dihydro-1,2-benzisoxazol-4(5*H*)-one oxime underwent reductive ring-opening in the presence of molybdenum hexacarbonyl to give 3,6,6-trimethyl-6,7-dihydro-1*H*-indazol-4(5*H*)-one. A mechanism is proposed.

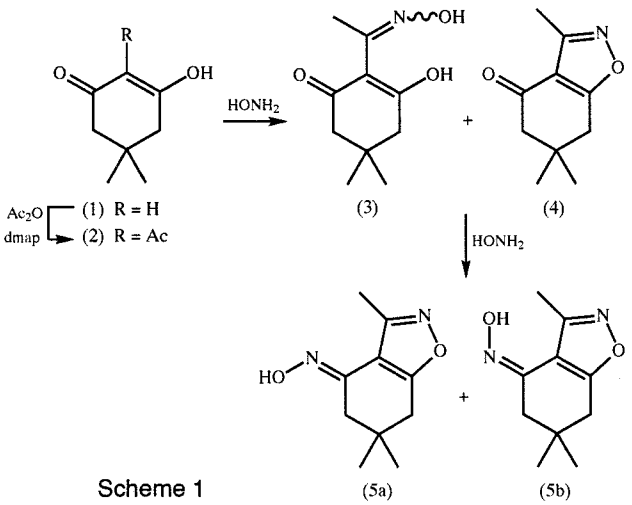
Introduction

Isoxazoles and isoxazolines are readily available by 1,3-dipolar cycloaddition of nitrile oxides[1] or by oximation of β-dicarbonyl compounds.[2] Much of the interest in isoxazoles stems from their use in the synthesis of other compounds. The reductive nitrogen–oxygen bond cleavage of isoxazoles is an important method for the construction of β-diketones, β-keto imines and β-keto esters, and their derivatives. We have taken advantage of this procedure to prepare bipyridine compounds[3] and were interested to extend this methodology to prepare 2-acetylcyclohexane-1,3-dione derivatives.[4]

Isoxazoles and isoxazolines have been cleaved in a variety of ways.[5] The most common of these are catalytic hydrogenolysis on Raney nickel in the presence of boric acids[6] and catalytic hydrogenolysis on platinum[7] or palladium.[8] Other methods of reductive ring-opening include treatment with iron pentacarbonyl[9] or molybdenum hexacarbonyl[10] in the presence of water, samarium diiodide,[11] sodium and t-butyl alcohol in liquid ammonia,[12] and yeast.[13] We herein describe the reductive ring-opening of a hydroxyimino isoxazole (5) using molybdenum hexacarbonyl, followed by an unexpected condensation to give the corresponding fused pyrazole (7).

Discussion

Dimedone (1) was converted into 2-acetyldimedone (2) by treatment with acetic anhydride and triethylamine in the presence of 4-(dimethylamino)-pyridine (dmap). Treatment (Scheme 1) of 2-acetyldimedone (2) with hydroxylamine under various conditions gave mixtures of 2-[1-(hydroxyimino)ethyl]-dimedone (3), 3,6,6-trimethyl-6,7-dihydro-1,2-benzisoxazol-4(5*H*)-one (4), (*E*)-(3,6,6-trimethyl-6,7-dihydro-1,2-benzisoxazol-4(5*H*)-one oxime) (5a) and (*Z*)-(3,6,6-trimethyl-6,7-dihydro-1,2-benzisoxazol-4(5*H*)-one oxime) (5b). Under carefully controlled conditions the 1,2-benzisoxazol-4(5*H*)-one (4) could be formed and isolated as the predominant product. Under forcing conditions a mixture of *E* oxime (5a) and *Z* oxime (5b) could be produced, and the major isomer (5a) was isolated. The *E* and *Z* oximes were assigned on the basis of the chemical shifts of the adjacent protons on the six-membered ring.[14]



Scheme 1

An approximately equimolar mixture of isomers (5a,b) was dissolved in acetonitrile and treated (Scheme 2) with molybdenum hexacarbonyl in the presence of water. In addition to a trace of starting material, two main products were isolated. These were identified as 2-acetyl-3-amino-5,5-dimethylcyclohex-2-enone (6) and 3,6,6-trimethyl-6,7-dihydro-1*H*-indazol-4(5*H*)-one (7). Both of these products were unexpected. They were identified by comparison with authentic samples of

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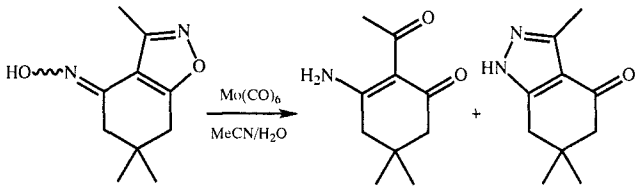
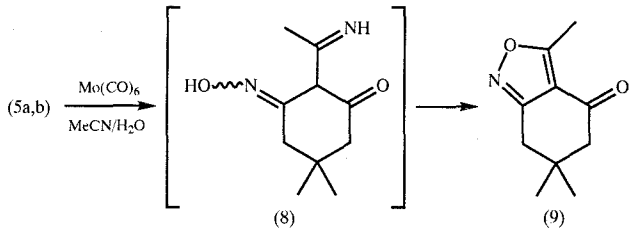
(6)[15] and (7)[16] which were prepared following literature procedures.



Scheme 2

The expected initial product of molybdenum hexacarbonyl promoted ring-opening of isoxazoles (5a,b) is the corresponding β-keto imine (8) or tautomer thereof. This compound has the potential (Scheme 3) to ring-close to form 3,6,6-trimethyl-6,7-dihydro-2,1-benzisoxazole-4(5*H*)-one (9). Although compound (9) could not be isolated, it was detected in the reaction mixture by v.p.c. and identified by co-injection of an authentic sample (see below). A subsequent molybdenum hexacarbonyl promoted *in situ* ring-opening of (9) would give the isolated product 2-acetyl-3-amino-5,5-dimethylcyclohex-2-enone (6).

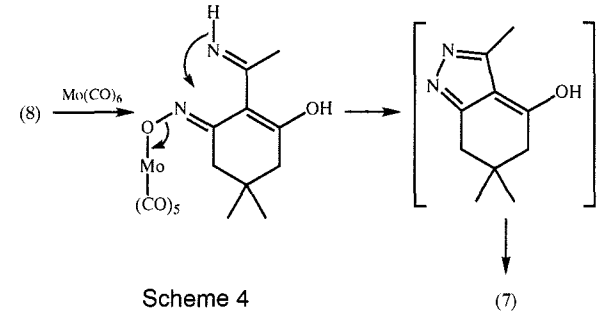


Scheme 3

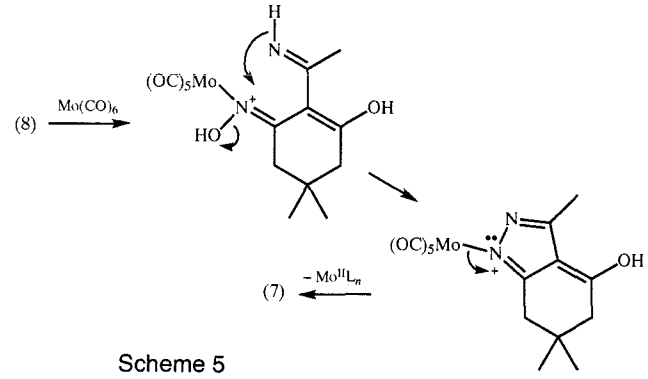
To support this postulation an authentic sample of 3,6,6-trimethyl-6,7-dihydro-2,1-benzisoxazole-4(5*H*)-one (9) was prepared by treating 2-acetyl-3-chloro-5,5-dimethylcyclohex-2-enone with sodium azide according to the method of Akhrem and Lakhvich.[15] Subsequent treatment of the isoxazole (9) with molybdenum hexacarbonyl and water gave 2-acetyl-3-amino-5,5-dimethylcyclohex-2-enone (6).

We speculate that the other unexpected product, 3,6,6-trimethyl-6,7-dihydro-1*H*-indazol-4(5*H*)-one (7), could also be formed from the intermediate (8). If the oxygen atom of the ring oxime is activated by molybdenum hexacarbonyl complexation, the imine (or enamine tautomer) nitrogen could attack the oxime nitrogen leading to a pyrazole product (Scheme 4).* A related mechanism has been postulated for the conversion of nitrosamines into secondary amines by a molybdenum hexacarbonyl assisted N–O bond cleavage.[17]

Metal carbonyl induced N–O bond cleavage of the oxime group has been previously reported, and the mechanism postulated involves an intermediate iminium ion stabilized by metal carbonyl complexation.[18]



Scheme 4



Scheme 5

To investigate the relative reactivity of (*E*)-(3,6,6-trimethyl-6,7-dihydro-1,2-benzisoxazol-4(5*H*)-one oxime) (5a) and its *Z* isomer (5b) in this reaction, a pure sample of the *E* oxime (5a) was reacted with molybdenum hexacarbonyl under identical conditions as the mixture of isomers. The product composition of this reaction was essentially the same as that obtained previously. This indicates that the molybdenum hexacarbonyl–oxime complex may facilitate epimerization of the *E* and *Z* oxime forms.

Experimental

General

For general details see ref. 4.

*2-[1-(Hydroxyimino)ethyl]-5,5-dimethylcyclohexane-1,3-dione (3) and 3,6,6-Trimethyl-6,7-dihydro-1,2-benzisoxazol-4(5*H*)-one (4)*

A solution of hydroxylamine was prepared by combining warm (60°) methanol solutions of hydroxylamine hydrochloride (0·72 g, 10·4 mmol, in 4 ml) and potassium hydroxide (0·68 g, 12·1 mmol, in 3 ml). The mixture was filtered and added dropwise over 5 min to a stirred solution of 2-acetyldimedone[15] (1·82 g, 10·0 mmol) in benzene (20 ml) chilled in ice. The resultant solution was stirred overnight; then water (25 ml) was added and the mixture extracted with diethyl ether (2×50 ml). The organic phase was washed with 10% sodium carbonate solution (2×50 ml), water (50 ml), and brine (2×75 ml), then dried ($MgSO_4$) and evaporated to give 3,6,6-trimethyl-6,7-dihydro-1,2-benzisoxazol-4(5*H*)-one (4) (1·13 g, 63%) as a white solid. Recrystallization from light petroleum (b.p. 40–60°) gave (4) as white granules, m.p. 53·2–54·7° (lit.[19] 55–57°) (Found: $MH^{+\bullet}$, 180·1012. Calc. for $C_{10}H_{13}NO_2$: $MH^{+\bullet}$, 180·1025). ^{13}C n.m.r. ($CDCl_3$) δ 10·57, 3-CH_3; 28·20, 6,6-$(CH_3)_2$; 35·47,

* A referee has suggested an alternative mechanism (Scheme 5) based on molybdenum complexation to the nitrogen rather than the oxygen.

C 6; 36·51, C 7; 52·16, C 5; 113·88, C 3a; 159·96, C 3; 180·33, C 7a; 192·46, C 4. ^{1}H n.m.r. ($CDCl_3$) δ 1·02, s, 6H, CH_3; 2·26, s, 2H, H 7; 2·30, s, 3H, 3-CH_3; 2·72, s, 2H, H 5. ν_{max} (KBr) 2964, 1684s, 1602, 1550, 1472s, 1428, 1386, 1046 cm^{-1}.

The aqueous washings from above were chilled and cautiously acidified to pH 3 with 10% hydrochloric acid. A precipitate formed and the mixture was extracted with diethyl ether (2×75 ml). The extracts were washed with water (2×50 ml), dried ($MgSO_4$), and evaporated to yield crude 2-[1-(hydroxyimino)ethyl]-5,5-dimethylcyclohexane-1,3-dione (3) as a white solid (0·61 g, 31%). The crude material was washed with diethyl ether, and recrystallized from benzene to afford a pure sample of (3), m.p. 105·5–107·5°. Upon cooling, the melt, which had transformed to (4), solidified and remelted at 51·8–53·5° (Found: $MH^{+\bullet}$, 198·1144. $C_{10}H_{15}NO_3$ requires $MH^{+\bullet}$, 198·1130). The compound is present in the enol form (3-hydroxy-2-[1-(hydroxyimino)ethyl]-5,5-dimethylcyclohex-2-enone) in acetone solution. ^{13}C n.m.r. (CD_3COCD_3) δ 28·23, C(=N)**C**H$_3$; 36·80, C 4; 52·72, C 6; 107·90, C 2; 161·76, C=N; 192·93, C 3; 207·36, C 1. ^{1}H n.m.r. (CD_3COCD_3) δ 1·10, s, 6H, CH_3; 2·38, s, 7H, C(=N)CH_3, H 4 and H 6; 3·08, br, 2H, OH. ν_{max} (KBr) 2100–3300, 1480–1680, 1380–1470 cm^{-1}. Within 5 days in the n.m.r. tube, compound (3) cyclizes and dehydrates to (4).

*(E)- and (Z)-(3,6,6-Trimethyl-6,7-dihydro-1,2-benzisoxazol-4(5*H*)-one Oxime) (5a,b)*

A solution of hydroxylamine was prepared from hydroxylamine hydrochloride (1·62 g, 23·4 mmol) in methanol (6 ml) with potassium hydroxide (1·31 g, 23·4 mmol). This was added to the ketone (4) (1·66 g, 9·0 mmol) in benzene (20 ml). The mixture was stirred and heated to reflux for 1 h, then allowed to stand at room temperature overnight. The methanol was then evaporated, water added, and the resultant solid filtered off and recrystallized from ethanol to give the *E* oxime (5a) (1·90 g, 44%) of *c.* 97% purity as white needles, m.p. 199·4–199·9° (lit.[19] for unspecified geometry 192°) (Found: $MH^{+\bullet}$, 195·1155. Calc. for $C_{10}H_{14}N_2O_2$: $MH^{+\bullet}$, 195·1133). ^{13}C n.m.r. ($CDCl_3$) δ 12·02, C(=N)**C**H$_3$; 28·47, 6,6-$(CH_3)_2$; 28·47, C 6; 36·01 and 36·23, C 5 and C 7; 109·82, C 3a; 150·42, C 4; 156·42, C 3; 172·14, C 7a. ^{1}H n.m.r. (CD_3Cl_3) δ 1·12, s, 6H, CH_3; 2·45, s, 3H, C(=N)CH_3; 2·60, s, 2H, H 5; 2·65, s, 2H, H 7. ν_{max} (KBr) 3100–3500, 2960, 1650, 1612,1492, 1468s, 1424, 926 cm^{-1}.

The recrystallization filtrate was evaporated and the residue subjected to radial chromatography on silica by using a gradient from neat dichloromethane to dichloromethane/methanol (20:1) as eluent to give the minor product of lower R_F; this proved to be the *Z* oxime (5b) (1·94 g, 45%), m.p. 167·2–168·0° (lit.[19] for unspecified geometry 192°) (Found: $MH^{+\bullet}$, 195·1117. Calc. for $C_{10}H_{14}N_2O_2$: $MH^{+\bullet}$, 195·1133). ^{13}C n.m.r. ($CDCl_3$) δ 14·59, C(=N)**C**H$_3$; 27·86, 6,6-$(CH_3)_2$; 32·87, C 6; 37·00, C 5 or C 7; 43·35, C 5 or C 7; 108·71, C 3a; 146·43, C 4; 157·71, C 3; 173·89, C 7a. ^{1}H n.m.r. ($CDCl_3$) δ 1·04, s, 6H, CH_3; 2·25, s, 2H, H 5; 2·48, s, 3H, C(=N)CH_3; 2·62, s, 2H, H 7. ν_{max} (KBr) 2500–3500br, 1668, 1584, 1390–1530, 1096, 992 cm^{-1}.

2-Acetyl-3-amino-5,5-dimethylcyclohex-2-enone (6)

(A) Molybdenum hexacarbonyl (0·362 g, 1·34 mmol) was added to an approximately equimolar solution of *E* and *Z* oximes (5a,b) (0·532 g, 2·69 mmol) in acetonitrile (25 ml) and water (0·05 ml, 2·77 mmol), and the mixture was heated at reflux for 2 h under nitrogen. The reaction mixture was cooled, filtered through Celite, and the solvent evaporated. Radial chromatography on silica with dichloromethane/methanol (10:1) as eluent afforded 2-acetyl-3-amino-5,5-dimethylcyclohex-2-enone (6) and 3,6,6-trimethyl-6,7-dihydro-1*H*-indazol-4(5*H*)-one (7) (see below) in a ratio of approximately 2:1.

2-Acetyl-3-amino-5,5-dimethylcyclohex-2-enone (6) (0·30 g, 62%) was isolated as an off-white solid and recrystallized from benzene to give white flakes, m.p. 160·5–161·7° (lit.[15] 161–163°) (Found: $MH^{+\bullet}$, 182·1181. Calc. for $C_{10}H_{15}NO_2$: $MH^{+\bullet}$, 182·1181). ^{13}C n.m.r. ($CDCl_3$) δ 27·88, $(CH_3)_2$; 31·01, C 5; 32·69, CO**C**H$_3$; 45·82, C 4; 52·40, C 6; 108·37, C 2; 172·08, C 3; 195·03, C 1; 200·90, **C**OCH$_3$. ^{1}H n.m.r. ($CDCl_3$) δ 1·05, s, 6H, CH_3; 2·30, s, 2H, H 4; 2·45, s, 2H, H 6; 2·53, s, 3H, $COCH_3$; 6,67, br, 1H, NH; 11·18, br, 1H, NH. ν_{max} (KBr) 2900–3650br, 1586, 1480, 1330, 1250 cm^{-1}.

(B) 2-Acetyl-3-amino-5,5-dimethylcyclohex-2-enone (6) was prepared from 2-acetyl-3-chloro-5,5-dimethylcyclohex-2-enone and ammonia following the procedure of Akhrem and Lakhvich,[15] and was identical in all respects to the product from (A) above. A mixed melting point was not depressed.

(C) To a mixture of 3,6,6-trimethyl-6,7-dihydro-2,1-benzisoxazol-4(5*H*)-one (9) (0·21 g, 1·2 mmol) (see below) in acetonitrile (10 ml) were added water (0·23 ml, 1·3 mmol) and molybdenum hexacarbonyl (0·16 g, 0·59 mmol), and the mixture was heated to reflux for 2 h under nitrogen. The reaction mixture was cooled, filtered through Celite, and the solvent evaporated. Radial chromatography on silica with dichloromethane/methanol (10:1) as eluent afforded 2-acetyl-3-amino-5,5-dimethylcyclohex-2-enone (6) (0·21 g, 96%) which was identical in all respects to the products from (A) and (B) above. A mixed melting point was not depressed.

*3,6,6-Trimethyl-6,7-dihydro-1*H*-indazol-4(5*H*)-one (7)*

(A) The minor product from reaction (A) above, identified as (7) (0·13 g, 27%), was isolated as a cream solid and recrystallized from diethyl ether and further recrystallized from water to give white needles, m.p. 100·3–102·6° (lit.[16] 101–103°) (Found: $MH^{+\bullet}$, 179·1172. Calc. for $C_{10}H_{14}N_2O$: $MH^{+\bullet}$, 179·1184). ^{13}C n.m.r. ($CDCl_3$) δ 11·98, C(=N)**C**H$_3$; 28·39, $(CH_3)_2$; 35·52, C 6; 36·30, C 7; 52·98, C 5; 114·55, C 3a; 144·51, C 7a; 154·03, C 3; 194·57, C 4. ^{1}H n.m.r. ($CDCl_3$) δ 1·05, s, 6H, CH_3; 2·36, s, 2H, H 7; 2·54, s, 3H, C(=N)CH_3; 2·70, s, 2H, H 5; 5·80, br, NH. ν_{max} (KBr) 3440, 3240, 2960, 1646, 1596, 1506, 1464, 1078 cm^{-1}.

(B) Hydrazine hydrate (0·65 g, 13·0 mmol) was added dropwise to a stirred solution of 2-acetyldimedone (2) (2·15 g, 11·8 mmol) in tetrahydrofuran (50 ml). The mixture was heated to reflux for 2 h, allowed to cool to room temperature, filtered through Celite, and the solvent evaporated to give a solid which was recrystallized from diethyl ether and then again from water to give white needles (1·81 g, 86%). The ketone (7), prepared in this way, was identical to that isolated above with respect to ^{13}C and ^{1}H n.m.r. spectra, infrared spectrum, v.p.c. retention time, and t.l.c. R_F. A mixed melting point was not depressed.

*3,6,6-Trimethyl-6,7-dihydro-2,1-benzisoxazol-4(5*H*)-one (9)*

Sodium azide (0·22 g, 3·4 mmol) was added in portions to an ice-chilled, stirred mixture of 2-acetyl-3-chloro-5,5-dimethylcyclohex-2-enone (0·5 g, 2·5 mmol)[15] in acetonitrile (40 ml), then the mixture was stirred at room temperature for 2 days. The solvent was evaporated and water (20 ml) added. The mixture was extracted with ether (3×50 ml), the organic phase washed with water and brine, dried ($MgSO_4$) and evaporated to leave the title compound (9) (0·40 g, 95%) as a cream *solid*, m.p. 64·5–66·7° (Found: $MH^{+\bullet}$, 180·1022. $C_{10}H_{13}NO_2$ requires $MH^{+\bullet}$, 180·1025). ^{13}C n.m.r. ($CDCl_3$) δ 12·86, 3-CH_3; 28·16, 6,6-$(CH_3)_2$; 29·62, C 6; 34·76, C 7; 52·99, C 5; 112·32, C 3a; 163·17, C 7a; 172·47, C 3; 193·18, C 4. ^{1}H n.m.r. ($CDCl_3$) δ 1·04, s, 6H, CH_3; 2·30, s, 2H, H 7; 2·42, s, 3H, 3-CH_3; 2·68, s, 2H, H 5. ν_{max} (KBr) 3436, 2968, 1686, 1610, 1504, 1432s, 1310, 1050 cm^{-1}.

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