Synthesis and thermolysis rate constants of diastereomeric oxadiazoline sources of acetoxy(methoxy)carbene — Reaction of acetoxy(methoxy)carbene with isocyanates

Wojciech Sokol and John Warkentin

Abstract: Oxidation of the methoxycarbonylhydrazone of *p*-methoxyacetophenone affords both the *cis*- and *trans*-2-acetoxy-2-methoxy-5-(*p*-methoxyphenyl)-5-methyl-Δ^3-1,3,4-oxadiazolines (also known as corresponding 2,5-dihydro-1,3,4-oxadiazoles) as well as methyl 1-acetoxy-1-(*p*-methoxyphenylethyl)diazenecarboxylate. The three isomers were separated and identified by spectroscopic means. Methyl 1-acetoxy-1-(*p*-methoxyphenylethyl)diazenecarboxylate is the major product from oxidation in dichloromethane. Oxidation in acetic acid did not afford the oxadiazolines but gave the diazenecarboxylate and, in addition, 1-(*p*-methoxyphenyl)ethyl acetate. Attempts to isomerize the diazenecarboxylate to the oxadiazolines by acid catalysis were not successful. Thermolysis of the oxadiazolines at 50.4 °C occurred with approximately the same rate constant (ca. 3.6×10^{-5} s^{-1}) to afford acetoxy(methoxy)carbene, which rearranges to methyl pyruvate by acetyl transfer. The carbene, which reacts with relatively unhindered isocyanates to transfer the methoxycarbonyl group to carbon and the acetyl group to nitrogen, can be considered an acyl anion equivalent in that reaction.

Key words: acetoxy(methoxy)carbene, diazene, oxadiazoline, isocyanate, (acetylamino)oxoacetate.

Résumé : L'oxydation de la méthoxycarbonylhydrazone de la *p*-méthoxyacétophénone conduit à la formation d'un mélange des 2-acétoxy-2-méthoxy-5-(*p*-méthoxyphényl)-5-méthyl-Δ^3-1,3,4-oxadiazolines *cis* et *trans* (aussi connues sous le nom des 2,5-dihydro-1,3,4-oxadiazoles correspondantes) accompagné de 1-acétoxy-1-(*p*-méthoxyphényléthyl)diazènecarboxylate de méthyle. On a séparé les trois isomères et on les a identifiés par des méthodes spectroscopiques. Le 1-acétoxy-1-(*p*-méthoxyphényléthyl)diazènecarboxylate de méthyle est le produit majeur de l'oxydation dans le dichlorométhane. L'oxydation dans l'acide acétique ne fournit pas d'oxadiazolines, mais conduit à la formation du diazènecarboxylate ainsi qu'à de l'acétate de 1-(*p*-méthoxyphényl)éthyle. On n'a pas réussi dans nos tentatives d'isomériser le diazènecarboxylate en oxadiazolines par catalyse acide. Les constantes de vitesse des thermolyses de chacune des oxadiazolines effectuées à 50,4 °C sont approximativement les mêmes, soit environ $3,6 \times 10^{-5}$ s^{-1}, et elles conduisent toutes les deux à la formation d'acétoxy(méthoxy)carbène qui se réarrange en pyruvate de méthyle par transfert d'un groupe acétyle. Le carbène, qui réagit avec les isocyanates non encombrées pour conduire à un transfert du groupe méthoxycarbonyle vers le carbone et du groupe acétyle vers l'azote, peut être considéré comme équivalent à un anion acyle dans cette réaction.

Mots clés : acétoxy(méthoxy)carbène, diazène, oxadiazoline, isocyanate, (acétylamino)oxoacétate.

[Traduit par la Rédaction]

Introduction

Generation of dimethoxycarbene from 2,2-dimethoxy-5-(*p*-methoxyphenyl)-5-methyl-Δ^3-1,3,4-oxadiazoline was reported recently (1). The *p*-methoxyphenyl substituent provided an extra methoxy signal in the ^{1}H NMR spectrum and it lowered the temperature for generation of the carbene from about 110 °C (for the 5,5-dimethyl analogue) to about 50 °C. We decided to make the isomeric 2-acetoxy-2-methoxy-5-(*p*-methoxyphenyl)oxadiazolines because acetoxy(methoxy)carbene (also known as (acetyloxy)methoxymethylene), which had been generated earlier at 110 °C (2), might have interesting properties, similar to those of acetoxy(methylthio)carbene that were reported in 2005, Scheme 1 (2). The diastereomers were separated and identified. We now report their spectra and rate constants for their thermolysis to carbonyl ylides that, in turn, fragment rapidly to acetoxy(methoxy)carbene. The carbene was intercepted with various isocyanates to afford methyl (acetylamino)oxoacetates.

Received 27 February 2006. Accepted 9 June 2006. Published on the NRC Research Press Web site at http://canjchem.nrc.ca on 27 July 2006.

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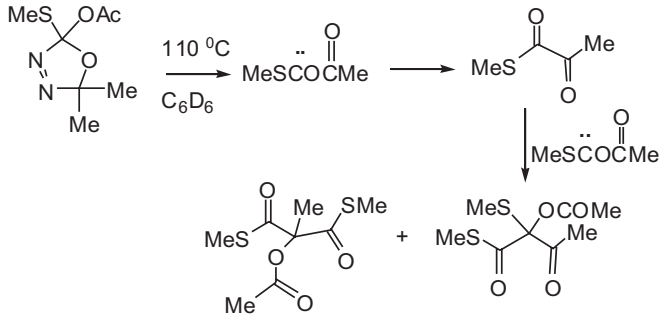
Results and discussion

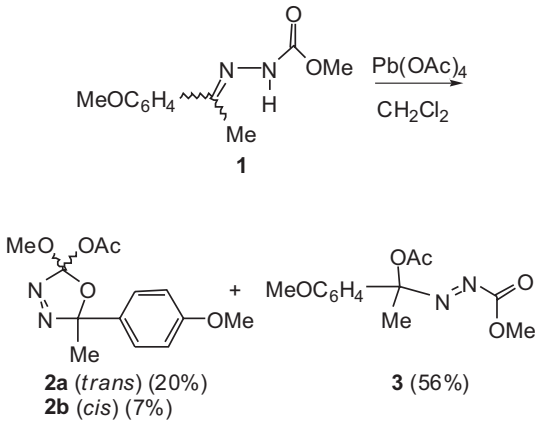
The isomeric oxadiazolines, **2a** and **2b** (also known as corresponding 2,5-dihydro-1,3,4-oxadiazoles), were prepared by oxidative cyclization (3) of a mixture of the (*E*)- and (*Z*)-methoxycarbonylhydrazones (**1**) of *p*-methoxy-

 doi:10.1139/V06-109

Scheme 1.



Scheme 2.



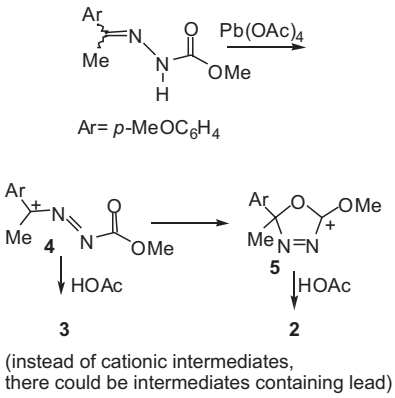
acetophenone with lead tetraacetate in dichloromethane. The products isolated were **2a** (20%), **2b** (7%), and a surprisingly large amount of an acyclic isomer **3** (ca. 56%) (Scheme 2). Oxidation in dry acetic acid did not produce **2** but gave **3** (28%) as well as 1-(*p*-methoxyphenyl)ethyl acetate (22%).

The formation of **3** as a major oxidation product (Scheme 2) suggests that there are cationlike precursors of the type **4** and **5** (Scheme 3). Exchange of acetoxy for methoxy, allyloxy (4), or other hydroxyl-containing groups under conditions of acid catalysis supports the intermediacy of ions such as **4** under exchange conditions. Probably, ion **4** does not cyclize easily to **5** because the stabilization afforded by the *p*-methoxyphenyl group is lost if the species cyclizes.

Cyclization in acetic acid was explored in the expectation that better solvation of cationlike intermediates would lessen the energy difference between **4** and **5**. Oxidation in acetic acid did not result in any oxadiazolines **2**. Attempts to isomerize **3** into a mixture of the diastereomers **2** by means of acid catalysis (CF_3CO_2H–CH_3CO_2H in CH_2Cl_2) did not succeed either. In the latter case, equal amounts of *p*-methoxyacetophenone and 1-(*p*-methoxyphenyl)ethyl acetate (**6**) (22%) were obtained. We suggest that those arise through the reactions shown in Scheme 4.

The ratio in which oxadiazolines **2a** and **2b** were formed by oxidation of **1** (Scheme 2) suggested that **2b** is more hindered and that it was expected to thermolyse more rapidly than **2a**. Oxadiazolines **2a** and **2b** are expected to undergo thermolysis by concerted 1,3-dipolar cycloreversion, to afford carbonyl ylides **7a**–**7d** (Scheme 5). The cycloreversion

Scheme 3.



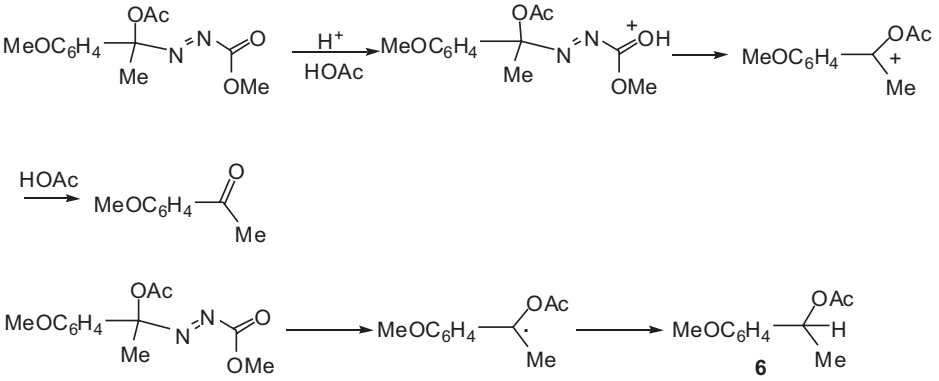
of an oxadiazoline is a disrotatory process, requiring that cis substituents at C-2 and C-5 rotate either both inward (endo) or both outward (exo) (5). Substituents in a trans relationship place one group endo and the other exo. Assuming that the aryl group has the largest steric requirement at C-5 and that polar effects are less important, one would predict that oxadiazoline **2a** would form ylide **7b** in preference to **7a**. Similarly, **2b** should form **7c** in preference to **7d** (Scheme 5). There was little hope of trapping those ylides, whose lifetimes are probably very short (6, 7), with barriers to fragmentation to carbene and ketone of only a few kcal mol^{-1} (1 cal = 4.184 J), but rate constants for thermolysis of the isomeric precursors could be measured. Those rate constants are a measure of the difference between ground-state and transition-state energies.

It turned out that **2b** does thermolyse faster than **2a** (3.74×10^{-5} s^{-1} vs. 3.49×10^{-5} s^{-1} in benzene at 50.4 °C). Isomer **2b** should have a higher ground-state energy than isomer **2a**, while the transition states for thermolysis of the isomers could be more nearly isoenergetic. Of course, the fact that **2b** could place both larger substituents exo (**7c**, Scheme 5) should favour its thermolysis additionally, but there would be a statistical penalty (a factor ≤ 2) involved in a restriction that favours outward rotation of the larger groups. The result suggests that the difference between the steric factors that operate in **2a** and **2b** is relatively small and probably partly compensated for by the statistical factor.

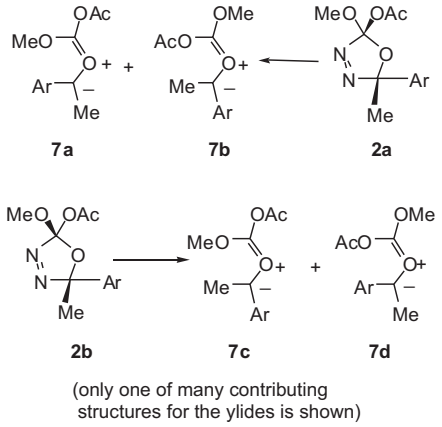
The putative carbonyl ylide intermediate shown in Scheme 5 has never been observed. Computations (7) on the dimethyl analog (rather than aryl methyl as in Scheme 2) indicate that the ylide is a real intermediate with a barrier to fragmentation to acetoxy(methoxy)carbene and ketone of about 2 to 3 kcal mol^{-1}. Although the aryl group of **7** could change that barrier, a change large enough to make the ylide trappable by conventional 1,3-dipolarophiles is hard to imagine. In an attempt to trap the ylide, thermolysis was carried out in neat phenyl isothiocyanate, which has been shown to trap carbonyl ylides (8). The ^1H NMR spectrum of the crude product showed *p*-methoxyacetophenone as the major product (>85%) with the characteristic pair of doublets at low field.

Evidence of the intermediacy of acetoxy(methoxy)carbene (**9**) (also known as (acetyloxy)methoxymethylene) came from two sources. First, it is known from both experiment (9) and theory (6) that the carbene rearranges to methyl

Scheme 4.



Scheme 5.



pyruvate (**10**). That product could be detected by ^{1}H NMR spectroscopy during kinetic runs in C_6D_6, but amounted to only 5% of the signal from *p*-methoxyacetophenone at 30% reaction and only about 2% when essentially all of the oxadiazoline had fragmented (Scheme 6). The reason for the low yield lies in the fact that methyl pyruvate is very self-reactive and does not survive the reaction conditions (10).

Rearrangement of acetoxy(methoxy)carbene to methyl pyruvate could be suppressed, but not eliminated, by an isocyanate (**11**) at high concentration. The pyruvate could always be detected (≤2%) among the crude reaction products. Eight isocyanates, with a variety of functional groups ranging from unhindered alkyl to hindered alkyl and from phenyl to variously substituted phenyls (Scheme 7) at nitrogen were treated with **2** at 50.4 °C. A liquid isocyanate (1 equiv. or more) was mixed with the liquid oxadiazolines **2** prior to degassing and heating. Homogeneous solutions resulted. A solid isocyanate, melting near 50 °C, and **2** gave a homogeneous solution immediately after the mixture had been heated to 50.4 °C. In the cases of aryl or alkyl isocyanates, except for *tert*-butyl isocyanate, reaction occurred to yield methyl (acetylamino)oxoacetates **12** (Scheme 7). Yields, not optimized, ranged from 48% for isopropyl isocyanate to 76% for phenyl isocyanate, after flash chromatography on silica. Product **12c** was obtained simply by washing the crude with ethyl acetate – hexane. Compound **12c** and other solid products from column chromatography were recrystallized from a benzene–hexane mixture. *tert*-Butyl isocyanate afforded many products (many OMe signals in the ^{1}H NMR spectrum), suggestive of extensive rearrangement of the carbene and subsequent reactions of methyl pyruvate. Although the isocyanate appeared to be unchanged (only one *tert*-butyl signal in the ^{1}H NMR spectrum), a low yield of the appropriate **12** (<5%) could not be excluded. Neat phenyl isothiocyanate mixed 1:1 with **2** also did not afford any of the expected product.

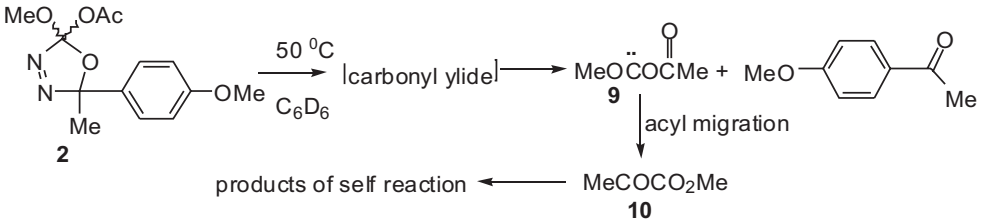
A possible mechanism for the reaction of **9** with isocyanates is shown in Scheme 7. Acetoxy(methoxy)carbene must be nucleophilic toward isocyanates. Although that carbene has not been placed on a nucleophilicity scale (11), it is probably ambiphilic toward alkenes. Trifluoroethoxy(methoxy)carbene is ambiphilic toward alkenes (12) and the acetoxy is only a little poorer than trifluoroethoxy as an electron donor (13). However, philicity depends on the partner; for example, acetic acid is acidic towards water and basic towards sulfuric acid.

A nucleophilic singlet carbene is expected to attack an isocyanate at the carbonyl carbon atom to generate zwitterion **12** or it could add to either double bond in a concerted process. However, the three-membered rings resulting from the latter process would have to undergo ring opening and acetyl transfer (2) to arrive at the product. Model α-lactams or iminooxiranes with *gem*-dialkoxy and carboxylate functions at the ring carbons, which could help to resolve the latter aspect, are unknown and there was no evidence for ring formation in the present case. On the other hand, there are many precedents for formation of zwitterionic intermediates in nonpolar solvents (14).

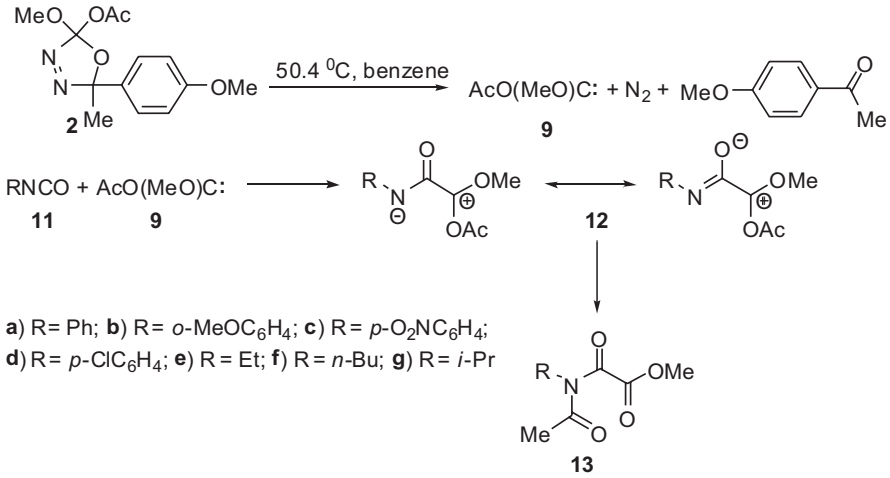
α-Lactams and iminooxiranes that could form by ring closure of **12** may well be unstable at 50 °C. Lengyel et al. (15) reported that α-lactams that are thermally unstable and chemically reactive afford 3-benzylamino products upon reaction with benzyl amine (Scheme 8). A possible explanation of that result is that such lactams open easily to zwitterions of the type **12**. Such an open form of an α-lactam was invoked by Ohshiro et al. (16) to account for the product from a reaction with a vinyl isocyanate (Scheme 9). There is also good evidence that *gem*-dialkoxycyclopropanes undergo thermal ring opening at moderate temperatures (17–20). In the present case, the negative charge of an intermediate is dispersed by conjugation, making it more likely that a three-membered-ring system (not shown in Scheme 7) would either not be formed or would open easily to **12**.

Phenyl isothiocyanate is known to be less reactive, by a

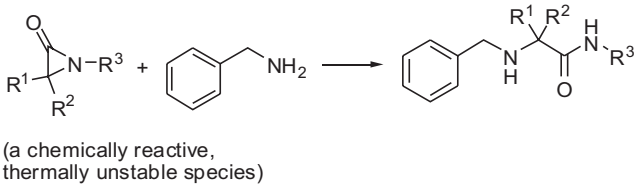
Scheme 6.



Scheme 7.



Scheme 8.



factor of 11, than phenyl isocyanate toward dimethoxycarbene at 140 °C (21). With a less nucleophilic carbene (acetoxy(methoxy)carbene) and a lower temperature (50.4 rather than 140 °C), the difference in reactivity between phenyl isocyanate and phenyl isothiocyanate could well be larger than 11. A product analogous to **12** (Scheme 7) was not obtained with phenyl isothiocyanate.

Summary

Diastereomeric oxadiazoline sources of acetoxy(methoxy)carbene were synthesized, separated, and fully characterized. Their thermolyses in benzene at 50.4 °C occurred with roughly equal rate constants (ca. 3.6×10^{-5} s^{-1}) and they afforded acetoxy(methoxy)carbene. The carbene reacted with various isocyanates to add the methoxycarbonyl group at carbon and the acetyl group at nitrogen. In its addition at carbon, the carbene behaved as an acyl anion equivalent.

Experimental

NMR spectra were taken with Bruker Avance 600 MHz and Bruker Avance 200 MHz instruments operating at frequencies given in each section. IR spectra came from a Bio Rad FTS 40 spectrometer and mass spectra were run with a Waters Micromass GCT instrument. Melting points were measured with a Uni-Melt Thomas Hoover capillary melting point apparatus. Yields were not optimized.

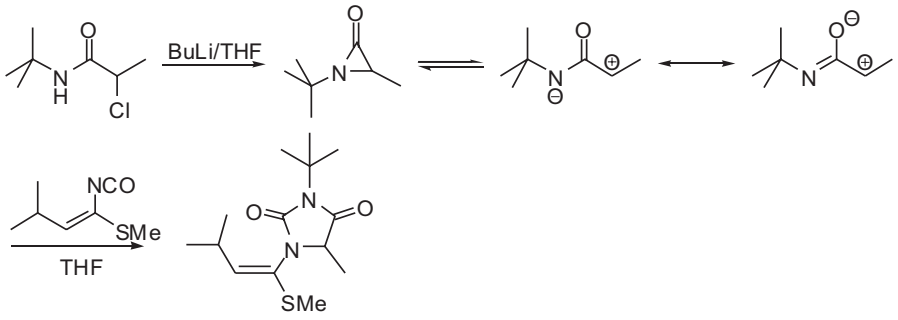
2-Acetoxy-2-methoxy-5-(*p*-methoxyphenyl)-5-methyl-Δ^3-1,3,4-oxadiazoline (2)

Lead tetraacetate (7.49 g, 16.05 mmol, 95% purity) was dissolved in dichloromethane (50 mL), the solution was cooled to about 0 °C, and the methoxycarbonylhydrazones of *p*-methoxyacetophenone (3.61 g, 16.24 mmol) were added in the solid state. After 0.5 h the temperature had risen to 25 °C and the mixture was stirred for an additional 4 h. It was filtered through a bed of Celite to afford a clear solution. The Celite cake was extracted with dichloromethane (2 × 25 mL) and the combined organic solution was washed twice with aqueous sodium bicarbonate (2 × 25 mL) and dried over $MgSO_4$. Evaporation of the solvent at room temperature left 4.84 g of crude product. The ^{1}H NMR spectrum of the mixture revealed the ratios of isomers **3**:**2a**:**2b** as 67.1:24.4:8.5. The products were purified by flash-chromatography on silica with diethyl ether – hexane (25:75) as eluent. Isolated were **3** (2.53 g, 9.02 mmol, 56%) and the diastereomers **2a** and **2b** (1.10 g, 3.91 mmol, 24.4%). Separation of the oxadiazolines was carried out by centrifugal chromatography with a Chromatotron® apparatus.

trans-2-Acetoxy-2-methoxy-5-(*p*-methoxyphenyl)-5-methyl-Δ^3-1,3,4-oxadiazoline (2a, major diastereomer)

Pale pink oil. IR (neat, cm^{-1}): 3000, 2955, 2843, 1774, 1612, 1514, 1446, 1372, 1306, 1253, 1032, 834. ^{1}H NMR

Scheme 9.



(200.2 MHz, $CDCl_3$, ppm) δ: 1.88 (s, 3H, CH_3), 2.15 (s, 3H, $COCH_3$), 3.47 (s, 3H, OCH_3), 3.78 (s, 3H, $C_6H_4OCH_3$), 6.87 (d, J = 8.9 Hz, 2H, CH_{Ar}), 7.44 (d, J = 8.9 Hz, 2H, CH_{Ar}). ^{1}H NMR (200.2 MHz, C_6D_6, ppm) δ: 1.53 (s, 3H, CH_3), 1.95 (s, 3H, CH_3), 3.24 (s, 3H, OCH_3), 3.29 (s, 3H, OCH_3), 6.70 (d, J = 8.9 Hz, 2H, CH_{Ar}), 7.49 (d, J = 8.9 Hz, 2H, CH_{Ar}). ^{13}C NMR (50.3 MHz, $CDCl_3$, ppm) δ: 21.43 ($COCH_3$), 24.95 (CH_3), 52.87 (OCH_3), 55.23 ($C_6H_4OCH_3$), 113.87 (CH_{Ar}), 124.10 (C_{benzyl}), 126.41 (CH_{Ar}), 130.41 (C_{Ar}), 135.11 (C_{ring}), 159.77 (C_{Ar}—O), 166.36 (CO). ^{13}C NMR (50.3 MHz, C_6D_6, ppm) δ: 20.69 (CH_3), 24.85 (CH_3), 52.57 (OCH_3), 54.74 (OCH_3), 114.16 (CH_{Ar}), 124.45 (C_{benzyl}), 126.87 (CH_{Ar}), 131.34 (C_{Ar}), 135.86 (C_{ring}), 160.21 (C_{Ar}—O), 166.23 (CO). HRMS (CI, NH_3) m/z calcd. for $C_{13}H_{17}N_2O_5$: 281.1137 $(MH)^+$; found: 281.1159.

Assignments of the NMR signals are based on 2D correlation spectra. Gradient HMBC and gradient HSQC spectra were run in $CDCl_3$ with a Bruker AV 600 instrument. The relative configurations of substituents at C-2 and C-5 was established at the same time on the basis of a selective 1D NOESY experiment with a pulsed field gradient, with the pulse delay set at 5.0 s and the NOESY mixing time set at 0.6 s. Irradiation of the signal at 1.88 ppm caused enhancement of the signal at 7.44 ppm. Similarly, irradiation at 3.47 ppm caused strong enhancement at 2.15 and 7.44 ppm and weak enhancement at 6.87 ppm, while irradiation at 3.78 ppm caused signal enhancement at 6.87 ppm.

cis-2-Acetoxy-2-methoxy-5-(*p*-methoxyphenyl)-5-methyl-Δ^3-1,3,4-oxadiazoline (2b, minor diastereomer)

Pale yellow oil. IR (neat, cm^{-1}): 2993, 2955, 2843, 1776, 1612, 1515, 1445, 1372, 1306, 1253, 1080, 1031, 834. ^{1}H NMR (200.2 MHz, $CDCl_3$, ppm) δ: 1.82 (s, 3H, CH_3), 2.00 (s, 3H, $COCH_3$), 3.62 (s, 3H, OCH_3), 3.78 (s, 3H, $C_6H_4OCH_3$), 6.87 (d, J = 8.9 Hz, 2H, CH_{Ar}), 7.40 (d, J = 8.9 Hz, 2H, CH_{Ar}). ^{1}H NMR (200.2 MHz, C_6D_6, ppm) δ: 1.41 (s, 3H, CH_3), 1.62 (s, 3H, CH_3), 3.22 (s, 3H, OCH_3), 3.35 (s, 3H, OCH_3), 6.70 (d, J = 8.9 Hz, 2H, CH_{Ar}), 7.52 (d, J = 8.9 Hz, 2H, CH_{Ar}). ^{13}C NMR (50.3 MHz, $CDCl_3$, ppm) δ: 21.28 ($COCH_3$), 26.53 (CH_3), 52.95 (OCH_3), 55.23 ($C_6H_4OCH_3$), 113.81 ($2CH_{Ar}$), 123.83 (C_{benzyl}), 126.32 ($2CH_{Ar}$), 129.67 (C_{Ar}), 134.98 (C_{ring}), 159.77 (C_{Ar}—O), 166.06 (CO). ^{13}C NMR (50.3 MHz, C_6D_6, ppm) δ: 20.62 (CH_3), 26.68 (CH_3), 52.53 (OCH_3), 54.7 (OCH_3), 114.10 ($2CH_{Ar}$), 123.86 (C_{benzyl}), 126.83 ($2CH_{Ar}$), 130.58 (C_{Ar}), 135.83 (C_{ring}), 160.21 (C_{Ar}—O), 165.42 (CO).

The relative configurations of substituents at C-2 and C-5 were established on the basis of selective 1D NOESY experiments with a pulsed field gradient, as described previously. Selective irradiation at 1.82 ppm caused signal enhancements at 3.62 and 7.44 ppm, while irradiation at 2.00 ppm caused strong enhancement at 7.40 ppm and medium enhancement at 3.62 ppm. Irradiation at 3.62 and 3.78 ppm caused enhancements of signals at 1.82 and 6.87 ppm, respectively.

Acyclic isomer 3

Lemon yellow oil. IR (neat, cm^{-1}): 2960, 2842, 1770, 1611, 1514, 1439, 1371, 1305, 1252, 1110, 1029, 835. ^{1}H NMR (200.2 MHz, $CDCl_3$, ppm) δ: 2.00 (s, 3H), 2.13 (s, 3H), 3.76 (s, 3H), 3.94 (s, 3H), 6.88 (d, J = 8.9 Hz, 2H), 7.42 (d, J = 8.9 Hz, 2H). ^{1}H NMR (200.2 MHz, C_6D_6, ppm) δ: 1.73 (s, 3H), 2.00 (s, 3H), 3.218 (s, 3H), 3.222 (s, 3H) (these signals not resolved), 6.72 (d, J = 8.9 Hz, 2H), 7.46 (d, J = 8.9 Hz, 2H). ^{13}C NMR (50.3 MHz, $CDCl_3$, ppm) δ: 21.53, 23.87, 54.75, 55.07, 102.07, 113.84, 126.98, 130.43, 159.59, 161.75, 168.31. ^{13}C NMR (50.3 MHz, C_6D_6, ppm) δ: 21.17, 24.29, 54.04, 54.71, 102.28, 114.23, 127.53, 131.42, 160.17, 162.50, 167.81. HRMS (CI, NH_3) m/z calcd. for $C_{13}H_{17}N_2O_5$: 281.1137 $(MH)^+$; found: 281.1130.

Thermolysis of oxadiazolines

A solution of **2b** (0.1837 mmol) and *tert*-butylbenzene (0.1021 mmol) in C_6D_6 (1 mL), in an NMR tube fitted with a ground glass joint, was degassed by means of three freeze–pump–thaw cycles before the tube was sealed and heated at 50.4 °C. Oxadiazoline **2a** (0.2498 mmol) and *tert*-butylbenzene (0.1512 mmol) were treated analogously. Every 3 h, ^{1}H NMR spectra were acquired with the tubes still sealed and with a pulse delay of 6 s to ensure complete relaxation. For **2b**, the signal at 1.41 ppm was integrated and compared with the signal of *tert*-butylbenzene at 1.20 ppm. For **2a**, the signal at 1.95 ppm was integrated and compared with the signal of *tert*-butylbenzene. Standard first-order treatment of the data gave $k_{\mathbf{2b}} = 3.74 \times 10^{-5}$ s^{-1} (seven points, $R2$ = 0.9914) and $k_{\mathbf{2a}} = 3.49 \times 10^{-5}$ s^{-1} (seven points, $R2$ = 0.9920).

Attempt to cyclize 3

A solution of **3** (0.32 g, 1.14 mmol) and trifluoroacetic acid (0.012 g, 0.105 mmol, 10 mol%) in acetic acid (25 mL) was stirred at room temperature for 9 days. The mixture was diluted with water (25 mL) and extracted with dichloromethane (3 × 15 mL). The solution in dichloromethane was then washed with aqueous sodium bicarbonate to remove acids and dried over $MgSO_4$. After flash chromatography on

silica with diethyl ether – hexane (25:75), *p*-methoxyacetophenone (0.038 g, 0.25 mmol, 22%), 1-(*p*-methoxyphenyl)ethyl acetate (0.049 g, 0.25 mmol, 22%), and unreacted **3** (0.178 g, 0.634 mmol, 55%) were obtained.

1-(*p*-Methoxyphenyl)ethyl acetate

Colourless oil. IR (neat, cm^{-1}): 2983, 2938, 2839, 1735, 1614, 1516, 1372, 1242, 1063, 1035, 832. ^1H NMR (200.2 MHz, $CDCl_3$, ppm) δ: 1.50 (d, J = 6.5 Hz, 3H), 2.03 (s, 3H), 3.78 (s, 3H), 5.83 (q, J = 6.5 Hz, 1H), 6.86 (d, J = 8.7 Hz, 2H), 7.28 (d, J = 8.7 Hz, 2H). ^{13}C NMR (50.3 MHz, $CDCl_3$, ppm) δ: 21.33, 21.87, 55.17, 71.93, 113.74, 127.53, 133.64, 159.18, 170.32.

Thermolysis of oxadiazolines in the presence of isocyanates

All isocyanates except **11c** and **11d** are liquids at room temperature. The liquids except isopropyl isocyanate were freshly distilled before use. The isopropyl compound was used as received from Sigma-Aldrich. *p*-Chlorophenyl isocyanate and *p*-nitrophenyl isocyanate melted at 28–30.5 and 56–60 °C, respectively.

A mixture of **2** (1.00 mmol) and isocyanate (0.96–1.63 mmol), placed in an ampoule, was degassed by means of three freeze–pump–thaw cycles before the ampoule was sealed and heated at 50.4 °C for 41 h. A large excess of isocyanate was avoided after initial experiments with a two-fold excess indicated that a considerable amount of residual isocyanate hindered isolation of **12**. The crude reaction mixture was analysed by ^1H NMR spectroscopy before pure products were isolated as described.

Reaction of 2 with phenyl isocyanate

Heating **2** with 1.28 equiv. of *p*-chlorophenyl isocyanate gave **12a**, which was isolated by means of flash chromatography on silica with ethyl acetate – hexane (20:80) as eluent. Yield of colourless oil: 76%. IR (neat, cm^{-1}): 3064, 3018, 2958, 1750, 1729, 1706, 1597, 1439, 1370, 1343, 1273, 1235, 1140, 1046, 756, 733, 698. ^1H NMR (200.2 MHz, $CDCl_3$, ppm) δ: 2.01 (s, 3H), 3.90 (s, 3H), 7.19–7.25 (m, 2H), 7.44–7.52 (m, 3H). ^{13}C NMR (50.3 MHz, $CDCl_3$, ppm) δ: 24.37, 52.90, 128.38, 129.84, 130.08, 135.67, 161.72, 162.52, 172.45. HRMS (CI, NH_3) m/z calcd. for $C_{11}H_{12}NO_4$: 222.0766 $(MH)^+$; found: 222.0760.

Reaction of 2 with *o*-methoxyphenyl isocyanate

Heating **2** with 1.63 equiv. of the isocyanate and flash chromatography of the crude products on silica with ethyl acetate – hexane (32:68) gave **12b** in 74% yield as pale yellow crystals, mp 115.5–118.5 °C. IR (NaCl, cm^{-1}): 3018, 2960, 2946, 1755, 1729, 1705, 1600, 1436, 1346, 1283, 1253, 1146, 1023, 754. ^1H NMR (200.2 MHz, $CDCl_3$, ppm) δ: 1.99 (s, 3H), 3.84 (s, 3H), 3.91 (s, 3H), 7.00–7.09 (m, 2H), 7.16–7.21 (m, 1H), 7.39–7.48 (m, 1H). ^{13}C NMR (50.3 MHz, $CDCl_3$, ppm) δ: 23.48, 52.81, 55.86, 112.25, 121.36, 124.27, 129.68, 131.44, 155.01, 161.88, 162.34, 172.95. HRMS (CI, NH_3) m/z calcd. for $C_{12}H_{14}NO_5$: 252.0872 $(MH)^+$; found: 252.0875.

Reaction of 2 with *p*-nitrophenyl isocyanate

Heating **2** with 1.50 equiv. of *p*-nitrophenyl isocyanate gave a crude product that was not chromatographed, but was washed with ethyl acetate – hexane (35:65) to afford yellow crystals of **12c** (mp 107.0–110.0 °C) in 72% yield. IR (NaCl, cm^{-1}): 3118, 3082, 2955, 1752, 1732, 1710, 1597, 1530, 1352, 1271, 1236, 1141, 855, 750, 699. ^1H NMR (200.2 MHz, $CDCl_3$, ppm) δ: 2.08 (s, 3H), 3.90 (s, 3H), 7.45 (d, J = 9.08 Hz, 2H), 8.37 (d, J = 9.08 Hz, 2H). ^{13}C NMR (50.3 MHz, $CDCl_3$, ppm) δ: 24.54, 53.18, 125.36, 129.93, 141.22, 148.42, 161.04, 162.11, 170.97. HRMS (CI, NH_3) m/z calcd. for $C_{11}H_{11}N_2O_6$: 267.0617 $(MH)^+$; found: 267.0609.

Reaction of 2 with *p*-chlorophenyl isocyanate

Heating **2** with 1.08 equiv. of the isocyanate gave, after flash chromatography and recrystallization from benzene–hexane (50:50), 57% of **12d** as white crystals melting at 115.5–117.5 °C. IR (NaCl, cm^{-1}): 3098, 3076, 2956, 1752, 1727, 1706, 1341, 1275, 1237, 1145, 1095, 1041, 832, 770, 720, 675, 635. ^1H NMR (200.2 MHz, $CDCl_3$, ppm) δ: 2.03 (s, 3H), 3.90 (s, 3H), 7.17 (d, J = 8.75 Hz, 2H), 7.47 (d, J = 8.75 Hz, 2H). ^{13}C NMR (50.3 MHz, $CDCl_3$, ppm) δ: 24.44, 53.03, 129.86, 130.41, 134.17, 136.09, 161.49, 162.41, 171.98. HRMS (CI, NH_3) m/z calcd. for $C_{11}H_{11}NO_4Cl$: 256.0377 $(MH)^+$; found: 256.0339.

Reaction of 2 with ethyl isocyanate

Heating **2** with 1.37 equiv. of the isocyanate gave, after flash chromatography on silica with ethyl acetate – hexane (35:65) as eluent, product **12e** as a pale yellow oil in 55% yield. IR (neat, cm^{-1}): 2986, 2960, 1752, 1720, 1695, 1438, 1380, 1350, 1260, 1217, 1142, 1071, 1009, 781, 735, 635. ^1H NMR (200.2 MHz, $CDCl_3$, ppm) δ: 1.20 (t, J = 7.1 Hz, 3H), 2.30 (s, 3H), 3.69 (q, J = 7.1 Hz, 2H), 3.81 (s, 3H). ^{13}C NMR (50.3 MHz, $CDCl_3$, ppm) δ: 13.66, 23.16, 39.02, 52.63, 161.93, 162.60, 172.47. HRMS (CI, NH_3) m/z calcd. for $C_7H_{12}NO_4$: 174.0766 $(MH)^+$; found: 174.0768.

Reaction of 2 with *n*-butyl isocyanate

Flash chromatography on silica with ethyl acetate – hexane (20:80) gave, after heating **2** with 0.96 equiv. of **11f** and 55% of **12f** as a colourless oil. IR (neat, cm^{-1}): 2963, 2877, 1754, 1724, 1701, 1464, 1437, 1379, 1349, 1282, 1233, 1202, 1145, 1078, 1019, 735, 638. ^1H NMR (200.2 MHz, $CDCl_3$, ppm) δ: 0.89 (t, J = 7.2 Hz, 3H), 1.22–1.41 (m, 2H), 1.47–1.62 (m, 2H), 2.29 (s, 3H), 3.57–3.64 (m, 2H), 3.81 (s, 3H). ^{13}C NMR (50.3 MHz, $CDCl_3$, ppm) δ: 13.49, 19.84, 23.16, 30.65, 43.73, 52.60, 161.94, 162.81, 172.65. HRMS (CI, NH_3) m/z calcd. for $C_9H_{16}NO_4$: 202.1079 $(MH)^+$; found: 202.1040.

Reaction of 2 with isopropyl isocyanate

Heating **2** with 1.08 equiv. of **11g** gave **12g** by means of flash chromatography on silica, with ethyl acetate – hexane (28:72) as eluent. The product was obtained as a pale yellow oil in 48% yield. IR (neat, cm^{-1}): 3012, 2980, 2957, 1750, 1718, 1696, 1438, 1403, 1368, 1331, 1283, 1212, 1183, 1110, 1055, 1009, 770, 728, 638. ^1H NMR (200.2 MHz, $CDCl_3$, ppm) δ: 1.42 (d, J = 6.9 Hz, 6H), 2.29 (s, 3H), 3.79 (s, 3H), 4.16 (sept, J = 6.9 Hz, 1H). ^{13}C NMR (50.3 MHz,

$CDCl_3$, ppm) δ: 19.65, 23.96, 50.19, 52.55, 161.48, 163.53, 173.41. HRMS (CI, NH_3) *m/z* calcd. for $C_8H_{14}NO_4$: 188.0923 $(MH)^+$; found: 188.0922.

Acknowledgements

The authors thank the Natural Sciences and Engineering Research Council of Canada (NSERC) for continued financial support and the Department of Chemistry of McMaster University for office and laboratory space as well as access to spectroscopy facilities.

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