Highly peri-, regio- and diastereoselective 1,3-dipolar cycloaddition of mesitonitrile oxide to 1,7-dimethyl-2,3-dihydro-1*H*-1,4-diazepines: unexpected one-step formation of a new triheterocyclic framework

Abdesselam Baouid,*[a] Saïd Elhazazi,[a] Aïssa Hasnaoui,[a] Philippe Compain,*[b] Jean-Pierre Lavergne[c] and François Huet[d]

[a] *Laboratoire de Chimie des Substances Naturelles et des Hétérocycles, Département de Chimie, Faculté des Sciences-Semlalia, BP 2390, Université Cadi Ayyad, Marrakech, Maroc. E-mail: baouid.abdesselam@caramail.com*

[b] *Institut de Chimie Organique et Analytique (CNRS UMR 6005), Rue de Chartres, BP 6759, 45067 Orléans cedex 2, France. E-mail: philippe.compain@univ-orleans.fr*

[c] *Laboratoire des Aminoacides, des Peptides et des Protéines (CNRS UMR 5810), Université Montpellier II, 34095 Montpellier cedex 5, France*

[d] *Laboratoire de Synthèse Organique, Faculté des Sciences, Université du Maine, 72085 Le Mans cedex 9, France*

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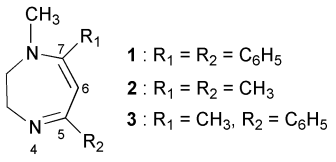
We report here an efficient one-step synthesis of new [1,2,4]oxadiazolo[4,5-*d*][1,4]diazepines and [1,2,4]oxadiazolo[4,5-*d*][1,4]-diazepine-8-spiro-5′-isoxazolines by way of highly *peri*-, regio- and diastereoselective 1,3-dipolar cycloadditions of mesitonitrile oxide to 1,7-dimethyl-2,3-dihydro-1*H*-1,4-diazepines. The structures were elucidated by spectral methods and X-ray crystallographic analysis. The regiochemistry of the cycloaddition is dictated by frontier orbital interactions.

The 1,3-dipolar cycloaddition reaction is one of the most powerful strategies for the synthesis of polyfunctional heterocycles.[1] Among them, 2-isoxazolines, obtained by reaction of nitrile oxides with alkene dipolarophiles, have been extensively studied due to their usefulness in medicine and agriculture, as well as their synthetic versatility.[2,3] Isoxazoline systems are often used in total synthesis as latent synthons, such as masked new heterocyclic or aromatic rings. As part of a program aimed at studying the *peri*- and regioselectivity of 1,3-dipolar cycloadditions of nitrile oxides, we have recently explored the reactivity of 1,5-benzodiazepines,[4–6] 1,4-benzodiazepines,[7] 1,2-diazepines[8] and 1,2,4-triazepines.[9] The *peri*- and regioselectivity observed in this previous work led us to examine the 2,3-dihydro-1*H*-1,4-diazepines **1**–**3**,[10] which contain two possible dipolarophile sites: N4=C5 and C6=C7.

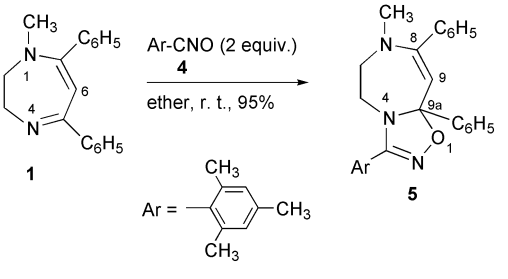


1 : $R_1 = R_2 = C_6H_5$
2 : $R_1 = R_2 = CH_3$
3 : $R_1 = CH_3$, $R_2 = C_6H_5$

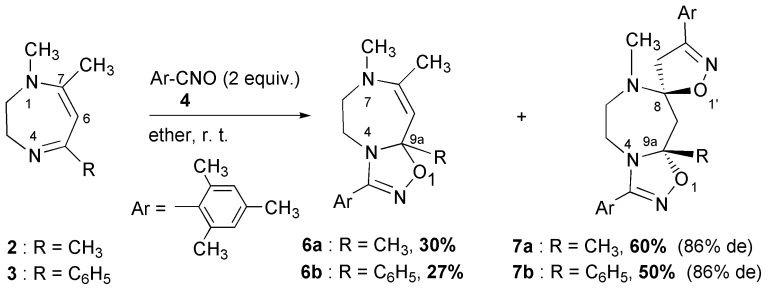
Besides the mechanistic aspects of this study, our aim was also to develop a rapid access to new types of potentially bioactive bi- or triheterocyclic systems. Herein, we wish to report our preliminary results on the reaction of mesitonitrile oxide **4** with the 1,4-diazepines **1**–**3**, which has led to the unexpected formation of the spiroisoxazolines **7**.

We first turned our attention to the 1,4-diazepine **1** substituted with two phenyl groups at C5 and C7. The best results were obtained by using mild and simple experimental conditions: 2 equiv. of mesitonitrile oxide **4**[11] in diethyl ether at room temperature. Although relatively slow (7 days), the cycloaddition of dipole **4** to dipolarophile **1** afforded the bicyclic monoadduct **5** in 95% yield, after a simple filtration on silica gel, and occurred with complete *peri*- and regioselectivity (Scheme 1). It is noteworthy that the potential dipolarophilic alkene C6=C7 did not react, even in the presence of a large excess of nitrile oxide.[12] The structure of **5** was determined on the basis of mass and NMR spectral data (^{1}H and ^{13}C). In particular, the presence of the enamine double bond in adduct **5** is attested to by a doublet at δ 106.9 (C-9, $J = 25$ Hz) in the ^{13}C NMR spectrum and a singlet at δ 5.03 in the ^{1}H NMR spectrum (=C9–H). Moreover, the chemical shift observed for the quaternary carbon C9a (δ 99.6) rules out unambiguously the formation of the other possible regioisomer, the C9a shift of which is expected to be between δ 50 and 60.[13]

Next, we tested under the same mild experimental conditions the cycloaddition of diazepines **2** and **3** substituted on C7 by a methyl group and on C5 by a methyl or a phenyl group. In each case, two products were obtained in a 2 : 1 ratio and in very good overall yield (Scheme 2). After purification by flash chromatography, the minor product was found to be the bicyclic monoadducts **6** obtained with complete regioselectivity and with the same direction of addition on the imine N4=C5 as for the fused heterocycle **5**. The structures of the major cycloadducts were unambiguously determined to be the spiro-isoxazolines **7** on the basis of mass and NMR (^{1}H and ^{13}C) spectral data and X-ray analysis of a single crystal of



Scheme 1



Scheme 2

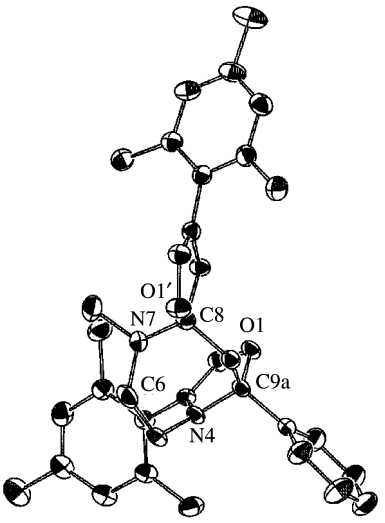
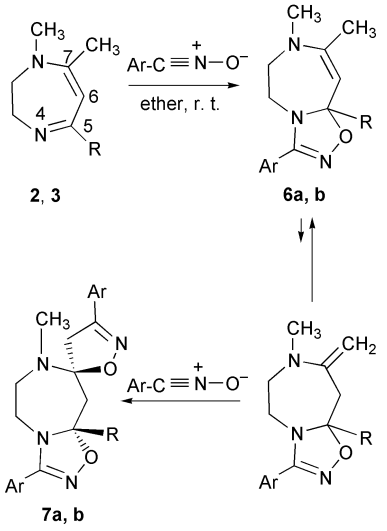


Fig. 1 Crystal structure of the triheterocycle **7b**.

compound **7b** (Fig. 1).[14,15] The 1,4-diazepine cycle was found to have a boat-like conformation with a quasi-planar central part (N4–C8–C9a–N7).

The triheterocyclic systems **7** result from the cycloaddition of mesitonitrile **4** to the imine N4=C5 and to the exocyclic double bond C7=CH_2 generated from the isomerization of the endocyclic double bond C7=C6 (Scheme 3).[16] The preferred sense of addition of the second molecule of mesitonitrile oxide was *anti* with respect to the oxadiazolo ring and occurred with high diastereofacial selectivity (93 : 7 as indicated by NMR analysis). This high selectivity may be explained by a boat conformation of precursors **6** similar to that of **7b** depicted in



Scheme 3

Fig. 1 in which the most hindered face of the exocyclic double bond is on the side of the oxadiazole. The identical diastereomeric excess found, whatever the nature of the R group (phenyl or methyl), is consistent with this hypothesis. As for 1,4-diazepine **1**, no trace amount of dipolar addition on the enamine endocyclic double bond was observed, even under forced conditions. This dramatic difference in reactivity between the two dipolarophile sites allowed the trapping of the imperceptible exocyclic enamine. The efficient one-step formation of the complex triheterocycles **7** is also remarkable in light of the fact that this process was found to be completely *peri*- and regioselective, and highly diastereoselective.

From a mechanistic point of view, the *peri*- and regioselectivity in 1,3-dipolar cycloadditions was rationalized satisfactory for the first time in 1973 by frontier orbital theory.[17] These pioneering studies showed that for electron-rich and conjugated dipolarophiles, dipole LUMO–dipolarophile HOMO interactions and the combination of the larger orbital coefficients control the regiochemistry of the reaction. In the case of mesitonitrile, the LUMO has the larger coefficient on the carbon of the dipole (Ar–*C*NO).[17b] The regioselective formation of the oxadiazolo ring in **5**, **6** and **7** may be rationalized by the fact that for compounds **1**–**3**, considered as 1-azadienes substituted with a donor amino group on C4, the larger coefficient in the HOMO is expected to be on the nitrogen of the imine.[18] The formation of the isoxazoline ring in **7** is also explained by fact that the highest HOMO coefficient is on the CH_2 in the exocyclic double bond of the enamine.[18] The difference in reactivity between the endocyclic and exocyclic double bonds may be partly explained by strong steric hindrance induced by the heterocycle formed by the first cycloaddition. The fact that the second dipolar addition occurred with a high *anti*-diastereofacial selectivity with respect to the oxadiazolo ring is in good agreement with this statement.[12b,19]

In conclusion, we have achieved the efficient one-step synthesis of the complex triheterocycles **7** by way of highly *peri*-, regio- and diastereoselective 1,3-dipolar cycloadditions of mesitonitrile oxide **4** to 1,4-diazepines **2** and **3**. This methodology is a good example of complexity-generating reactions that are of great interest in diversity-oriented synthesis. In this concept, introduced recently by Schreiber,[20] the purpose is to rapidly generate structural complexity stereoselectively in order to prepare a specific target compound or a collection of structurally related compounds. It is believed that diversity-oriented synthesis will play a pivotal role in drug discovery in the future. Extension of our methodology to other dipoles for the preparation of libraries of new triheterocyclic compounds is under way in our laboratory.

Experimental

General methods

Melting points were taken in an open capillary tube on a Buchi 510 apparatus and are uncorrected. Spectra were recorded with

the following instruments: ^{1}H NMR spectra: Brücker AC-250, ^{13}C NMR spectra: Brücker WP-200, mass spectra: Jeol JMS DX 300. TMS was used as an internal reference. Column chromatography was carried out using E-Merck silica gel $60F_{254}$. Reagents and solvents were purified in the usual way.

General procedure for preparation of products 5–7

To a solution of 1,4-diazepines **1**–**3** (3.50 mmol) in dry diethyl ether (20 mL) was added mesitonitrile oxide (7 mmol, 2 equiv.).[11] The reaction mixture was stirred for 7 days at room temperature. The mixture was concentrated under reduced pressure. Solid products were purified by chromatography on silica gel (CH_2Cl_2) and recrystallized in ethanol. Compounds **6a,b** were purified by flash chromatography (hexane–$CHCl_3$ 1 : 9).

3-Mesityl-7-methyl-8,9a-diphenyl-4,5,6,9a-tetrahydro-7*H*-[1,2,4]oxadiazolo[4,5-*d*][1,4]diazepine 5. This product was obtained in 95% yield; m.p. 211–213 °C; ^{1}H NMR ($CDCl_3$): δ 2.31, 2.38, 2.45 (3 CCH_3, 3s, 9H), 2.52 (NCH_3, s, 3H), 2.79–3.65 (NCH_2CH_2N, m, 4H), 5.12 (=CH9, s, 1H), 6.91–7.90 (ArH, m, 12H); ^{13}C NMR ($CDCl_3$): δ 19.70, 20.10, 21.15 (3 CCH_3), 37.33 (NCH_3), 42.25, 51.02 (2-CH_2–), 99.61 (C9a), 106.91 (C9), 121.82, 127.78, 127.97, 128.24, 128.39, 128.56, 128.91, 137.78, 138.26, 138.98, 139.70, 142.04, 150.80, 154.56 (C=); MS: m/z 423 $[M]^+$; anal. calc. for $C_{28}H_{29}N_3O$: C, 79.43; H, 6.86; N, 9.93; found: C, 79.29; H, 6.70; N, 10.01%.

3-Mesityl-7,8,9a-trimethyl-4,5,6,9a-tetrahydro-7*H*-[1,2,4]-oxadiazolo[4,5-*d*][1,4]diazepine 6a. This compound was obtained in 30% yield as an oil; ^{1}H NMR ($CDCl_3$): δ 1.63, 2.22, 2.23, 2.28 (5 CCH_3, 4s, 15H), 2.30 (NCH_3, s, 3H), 2.9–3.4 (NCH_2CH_2N, m, 4H), 3.97 (=CH9, s, 1H), 6.87 (ArH, s, 2H); ^{13}C NMR ($CDCl_3$): δ 19.52, 20.21, 21.06, 23.57, 35.31, 35.93 (6 CH_3), 41.40, 50.48 (NCH_2CH_2N), 98.55 (C9a), 106.00 (C9), 121.43, 128.35, 136.96, 137.79, 138.51, 139.92, 155.67, 162.33, 167.47 (C=); MS: m/z 299 $[M]^+$; anal. calc. for $C_{18}H_{25}N_3O$: C, 72.24; H, 8.36; N, 14.05; found: C, 72.39; H, 8.18; N, 14.18%.

3,3′-Dimesityl-7,9a-dimethyl-4,4′,5,5′,6,8,9,9a-octahydro-7*H*-[1,2,4]oxadiazolo[4,5-*d*][1,4]diazepine-8-spiro-5′-isoxazole 7a. This compound was obtained in 60% yield; m.p. 203–205 °C; ^{1}H NMR ($CDCl_3$): δ 1.75, 2.25, 2.26, 2.28, 2.35 (7 CCH_3, 5s, 21H), 2.53 (NCH_3, s, 3H), 2.4–3.5 (4-CH_2–, m, 8H), 6.9 (ArH, s, 4H); ^{13}C NMR ($CDCl_3$): δ 19.14, 19.53, 19.95, 29.96, 21.11, 21.30 (7 CCH_3), 37.45 (NCH_3), 44.11, 48.60, 51.84, 53.10 (4-CH_2–), 96.30 (C8), 102.30 (C9a), 121.17, 126.32, 128.26, 128.41, 128.60, 136.50, 137.77, 137.84, 138.78, 139.79, 154.15, 155.45 (C=); MS: m/z 460 $[M]^+$; anal. calc. for $C_{28}H_{36}N_4O_2$: C, 73.04; H, 7.83; N, 12.17; found: C, 73.20; H, 7.71; N, 12.05%.

3-Mesityl-7,8-dimethyl-9a-phenyl-4,5,6,9a-tetrahydro-7*H*-[1,2,4]oxadiazolo[4,5-*d*][1,4]diazepine 6b. This compound was obtained in 27% yield as an oil; ^{1}H NMR ($CDCl_3$): δ 1.96, 2.16, 2.47 (4 CCH_3, NCH_3, 3s, 15H), 2.93–3.07 (NCH_2CH_2N, m, 4H), 3.97 (=CH9, s, 1H), 6.93–7.50 (ArH, m, 7H); ^{13}C NMR ($CDCl_3$): δ 19.31, 19.83, 20.83, 33.92 (4 CCH_3), 35.47 (NCH_3), 41.75, 50.23 (NCH_2CH_2N), 99.44 (C9a), 106.14 (C9, d, $J=27$ Hz), 120.96, 126.25, 127.93, 128.27, 128.75, 136.79, 137.84, 138.18, 138.76, 139.79, 154.82, 167.04 (C=); MS: m/z 361 $[M]^+$.

3,3′-Dimesityl-7-methyl-9a-phenyl-4,4′,5,5′,6,8,9,9a-octahydro-7*H*-[1,2,4]oxadiazolo[4,5-*d*][1,4]diazepine-8-spiro-5′-isoxazole 7b. This compound was obtained in 50% yield; m.p. 184–186 °C; ^{1}H NMR ($CDCl_3$): δ 1.90, 2.16, 2.32, 2.47 (6 CCH_3, 4s, 18H), 2.60 (NCH_3, s, 3H), 2.87, 2.90, 3.37, 3.83, 4.16 (4-CH_2–, 5m, 8H), 6.90–7.50 (ArH, m, 9H); ^{13}C NMR ($CDCl_3$): δ 19.25, 19.52, 20.00, 20.93 (6 CCH_3), 37.53 (NCH_3), 42.61, 45.92, 46.63, 49.52 (4-CH_2–), 97.79 (C8), 102.71 (C9a), 121.01, 124.57, 126.24, 126.65, 127.96, 128.21, 128.41, 128.54, 128.67, 136.42, 138.16, 138.51, 138.88, 139.74, 144.01, 155.75, 157.23 (C=); MS: m/z 522 $[M]^+$.

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