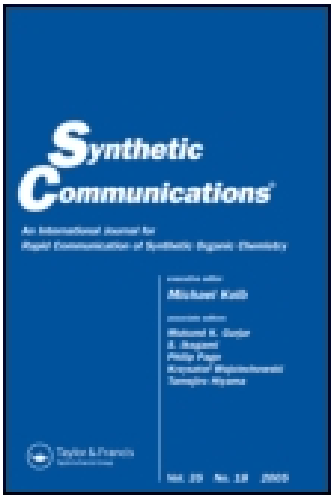

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Microwave-Assisted Facile Synthesis of Dispiro 4-Imino-1,3-Dioxolanes

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Microwave-Assisted Facile Synthesis of Dispiro 4-Imino-1,3-Dioxolanes

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Abstract: The condensation reactions of isocyanides **1** with 1,3-dimethyl alloxan **2** to afford dispiro 4-imino-1,3-dioxolane heterocycles, in excellent yields under microwave irradiation, are reported.

Keywords: Alloxan, dispiro, iminodioxolane, isocyanide, microwave-assisted reaction

INTRODUCTION

Organic isocyanides are useful reagents for organic synthesis.[1,2] They enter cycloaddition reactions giving different types of heterocycles.[3,4] The reaction of isocyanides with carbon-centered double bonds occurs in a stepwise manner and is initiated by a zwitterionic intermediate, whose ultimate fate appears to be dictated by the nature of the original double bond in the substrate.[5,6] Isocyanides can insert preferentially into the carbon-oxygen double bond of electron-deficient carbonyl compounds.[7–9]

Alloxan and its derivatives have four electrophilic C═O sites. The alloxan molecule is biologically a highly important molecule, since it destroys pancreatic insulin-producing beta cells and causes diabetes in animals. The toxicity of a number of *N*-substituted alloxan derivatives has

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been studied and it has been shown that comparatively small changes to the alloxan molecule have a major impact upon diabetogenicity.[10]

The central carbonyl group of the cyclic vicinal triones such as alloxan derivatives is sufficiently reactive to participate in different reactions. This highly electron-deficient moiety is entered in Diels-Alder reactions, Friedel-Crafts reactions, ene reactions, photochemical conversions, and reactions with active methylene compounds.[11] Numerous examples of reactions of alloxan that produce heterocycles have been described.[11,12]

In continuation of my interest on microwave-assisted organic transformation[13] and chemistry of isocyanides leading to the spiro-fused heterocycles synthesis,[9,14] herein I describe an efficient and high yielding protocol for the preparation of dispiro iminodioxolane derivatives.

Wallach's compound has been assigned the 4-imino-1,3-dioxolane structure.[15] A few natural products intramolecularly incorporating a spiro 1,3-dioxolane ring are known,[16] while its usefulness as a building block in asymmetric organic synthesis has been often reported.[17] In recent years, 1,3-dioxolan-4-one derivatives have served as precursors to a variety of synthetic targets. They have been used as substrates for the total synthesis of (*S*)-oxybutynin,[18] eicosanoids,[19] beta lactams,[20] and a muscarinic receptor antagonist.[21]

RESULTS AND DISCUSSION

The pseudo three-component condensation reactions of alkyl or aryl isocyanides **1** with 1,3-dimethyl alloxan **2** proceeded spontaneously in dimethyl formamide (DMF) under microwave irradiation and were completed within 2 min. The ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra of the crude products clearly indicated the formation of C_s symmetry dispiro iminodioxolanes **3**. Any product other than **3** could not be detected by NMR spectroscopy. The structure of these adducts were established as **3** by their elemental analysis and their infrared (IR), ^{1}H NMR, and ^{13}C NMR spectra. The nature of these compounds as 1 : 2 adduct was also apparent from the elemental analysis as well as from the mass spectra. The mass spectra of compounds **3a–g** displayed molecular ion peaks at the appropriate m/z values.

The ^{1}H NMR spectrum of **3a** exhibited three single sharp lines readily recognized as arising from *tert*-butyl (δ 1.44 ppm) and two *N*-methyl (δ 3.32 and 3.42 ppm) protons. The ^{1}H decoupled ^{13}C NMR spectrum of **3a** showed 11 distinct resonances that are in agreement with C_s symmetry of the structure, and the characteristic signals due to two spiro carbons were discernible at δ 80.64 and 96.01 ppm.

The ^{1}H decoupled ^{13}C NMR spectra of **3b–g** are similar to those of **3a** except for the alkyl or arylimino group, which exhibit characteristic signals with appropriate chemical shifts.

Although I have not established a mechanism for the formation of the compounds **3** in an experimental manner, a possible explanation is shown in Scheme 1. The first step may involve addition of the isocyanide to the 1,3-dimethyl alloxan and formation of the 1 : 1 adduct **4**. Subsequent nucleophilic attack of this adduct to another molecule of the 1,3-dimethyl alloxan would yield zwitterionic intermediate **5** that can be cyclized to product **3**.

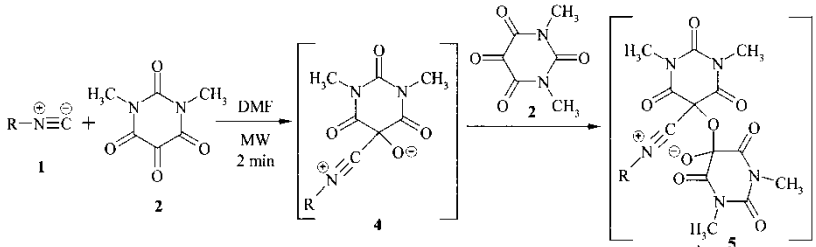
The starting 1,3-dimethylalloxan is conveniently prepared from its hydrate by either chemical removal of the water (acetic anhydride in boiling acetic acid) or by azeotropic drying using chlorobenzene as solvent but I prepared it from the thermal decomposition of 1,3-dimethyl-5,5-dinitrobarbituric acid[22] by a novel, effective, and facile procedure (see EXPREMENTAL).

CONCLUSION

In summary, I found that the reaction of isocyanides with two equivalents of 1,3-dimethyl alloxan leads to facile synthesis of dispiro 4-imino-1,3-dioxolane derivatives in excellent yields under microwave irradiation and without any catalyst after two minutes.

EXPERIMENTAL

Melting points were measured on a BÜCHI 535 apparatus and are uncorrected. Elemental analyses were performed using a Heraeus CHN-O-Rapid



3	R	Yield (%)
a	*tert*-Butyl	89
b	Cyclohexyl	93
c	Benzyl	88
d	2,6-Dimethylphenyl	91
e	CH_2CO_2Et	90
f	Tosylmethyl	86
g	2-Morpholinoethyl	77

Scheme 1.

analyzer. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. The infrared (IR) spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER DRX-500 AVANCE spectrometer at 500.13 and 125.77 MHz, respectively. The ^{1}H and ^{13}C NMR spectra were obtained on solutions in $CDCl_3$. Microwave irradiation were carried out in a National domestic oven, model 5250 (700 W). The reagents and solvents used in this work except for benzyl isocyanide were purchased from Fluka (Buchs, Switzerland) chemical company and the benzyl isocyanide was obtained from Aldrich Chemical Company.

Preparation of 1,3-Dimethyl Alloxan 2

Thermolysis of (2.461 g, 10 mmol) 1,3-dimethyl-5,5-dinitrobarbituric acid at 170°C for 20 min, after elimination of N_2O and NO resulted in 1,3-dimethyl alloxan **2** as a pure product (1.667 g, 9.8 mmol, 98%). Yellow powder, Mp 284–286°C. IR (KBr) (ν_{max}, cm^{-1}): 1762, 1700 and 1666 (C═O). ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 3.17 (6 H, s, 2 NMe). ^{13}C NMR (DMSO-d_6, 100 MHz): δ_C 28.91 (2 NMe), 151.09(N*C*ON), 156.67 (2 N*C*OC), 168.58 (OC*C*OCO). MS (*m*/*z*, %) 170 (M^+, 68), 142 (100). Anal. Calcd. for $C_6H_6N_2O_4$ (170.12): C, 42.36; H, 3.55; N, 16.47%. Found: C, 42.4; H, 3.5; N, 16.4%.

Typical Procedure

Synthesis of 2,4,10,12-tetramethyl-15-(tert-butylimino)-7,14-dioxa-2,4,10,12-tetraazadispiro[5.1.5.2]pentadecane-1,3,5,9,11,13-hexone **(3a)**

To a solution of 1,3-dimethyl alloxan (0.341 g, 2.0 mmol) in DMF (1 mL) in a screw-capped vial, *tert*-butyl isocyanide (0.084 g, 1.0 mmol) was added via a syringe and subjected to microwave irradiation at medium high power for 2 min. After cooling, the reaction mixture was poured onto cold water (10 mL) and stirred for 5 min. The separated solid was filtered under suction, washed with water (20 mL) and then diethyl ether (10 mL) to afford the pure product. Light pink powder (0.377 g, 89%). Mp 241–243°C. IR (KBr) (ν_{max}, cm^{-1}): 1732 and 1684 (C═O), 1573 (N═C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 1.26 (9 H, s, $C(CH_3)_3$), 3.32 and 3.42 (12 H, 2 s, 4 NCH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 29.43 (CMe_3), 29.70 and 29.73 (4 NMe), 56.22 (CMe_3), 80.64 and 96.01 (2 spiro carbons), 142.98 (N═*C*), 149.74 and 150.63 (2 N*C*ON), 162.12 and 162.45 (4 N*C*OC). MS (EI, 70 eV) (*m*/*z*, %) 423 (M^+, 24), 57 (100). Anal. Calcd. for $C_{17}H_{21}N_5O_8$ (423.38): C, 48.23; H, 5.00; N, 16.54%. Found: C, 48.3; H, 5.1; N, 16.5%.

2,4,10,12-Tetramethyl-15-(cyclohexylimino)-7,14-dioxa-2,4,10, 12-tetraazadispiro [5.1.5.2]pentadecane-1,3,5,9,11,13-hexone **(3b)**

Creamy powder. (0.418 g, 93 %). Mp 195–197°C. IR (KBr) (ν_{max}, cm^{-1}): 1735 and 1700 (C═O), 1564 (N═C). ^1H NMR ($CDCl_3$, 400 MHz): δ_H 1.26–1.72 (10 H, m, 5 CH_2), 3.33 and 3.43 (12 H, 2 s, 4 NCH_3), 3.66 (1 H, m, N-CH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 23.77, 25.55 and 32.68 (5 CH_2), 29.74 and 29.83 (4 NMe), 57.01 (N-*C*H), 80.28 and 95.57 (2 spiro carbons), 145.54 (N═*C*), 149.64 and 150.53 (2 N*C*ON), 162.12 and 162.24 (4 N*C*OC). MS (EI, 70 eV) (m/z, %) 449 (M^+, 8), 55 (100). Anal. Calcd. for $C_{19}H_{23}N_5O_8$ (449.41): C, 50.78; H, 5.16; N, 15.58%. Found: C, 50.7; H, 5.2; N, 16.0%.

2,4,10,12-Tetramethyl-15-(benzylimino)-7,14-dioxa-2,4,10, 12-tetraazadispiro [5.1.5.2]pentadecane-1,3,5,9,11,13-hexone **(3c)**

Light pink powder. (0.403 g, 88%). Mp 238–240°C. IR (KBr) (ν_{max}, cm^{-1}): 1762, 1727, 1688, and 1668 (C═O), 1529 (N═C). ^1H NMR ($CDCl_3$, 400 MHz): δ_H 3.32 and 3.44 (12 H, 2 s, 4 NCH_3), 4.65 (2 H, s, CH_2), 7.20–7.33 (5 H, m, C_6H_5). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 29.81 and 29.92 (4 NMe), 52.28 (NCH_2), 80.54 and 95.96 (2 spiro carbons), 127.06, 127.14, 128.53 and 137.63 (arom.), 148.29 (N═*C*), 149.58 and 150.35 (2 N*C*ON), 161.87 and 161.93 (4 N*C*OC). MS (EI, 70 eV) (m/z, %) 457 (M^+, 15), 91 (100). Anal. Calcd. for $C_{20}H_{19}N_5O_8$ (457.39): C, 52.52; H, 4.19; N, 15.31%. Found: C, 52.6; H, 4.3; N, 15.2%.

2,4,10,12-Tetramethyl-15-(2,6-dimethylphenylimino)-7,14-dioxa-2,4,10,12-tetra azadispiro[5.1.5.2]pentadecane-1,3,5,9,11,13-hexone **(3d)**

Light pink powder. (0.429 g, 91%). Mp 278–279°C. IR (KBr) (ν_{max}, cm^{-1}): 1769, 1729, and 1697 (C═O), 1586 (N═C). ^1H NMR ($CDCl_3$, 400 MHz): δ_H 2.09 (6 H, s, $C_6H_3Me_2$), 3.39 and 3.41 (12 H, 2 s, 4 NCH_3), 6.93–7.00 (3 H, m, arom.). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 17.59 ($C_6H_3Me_2$), 29.73 and 29.91 (4 NMe), 80.90 and 96.23 (2 spiro carbons), 124.90, 127.56, 127.85, and 141.40 (arom.), 147.54 (N═*C*), 149.43, and 150.19 (2 N*C*ON), 161.40 and 161.65 (4 N*C*OC). MS (EI, 70 eV) (m/z, %) 471 (M^+, 10), 104 (100). Anal. Calcd. for $C_{21}H_{21}N_5O_8$ (471.42): C, 53.50; H, 4.49; N, 14.86%. Found: C, 53.5; H, 4.5; N, 14.8%.

Ethyl[(2,4,10,12-tetramethyl-1,3,5,9,11,13-hexaoxo-7,14-dioxa-2,4,10, 12-tetraaza dispiro[5.1.5.2]pentadec-15-ylidene)amino]acetate **(3e)**

Pink powder. (0.409 g, 90%). Mp 221–223°C. IR (KBr) (ν_{max}, cm^{-1}): 1765, 1728, 1720, and 1687 (C═O), 1584 (N═C). ^1H NMR ($CDCl_3$, 400 MHz): δ_H 1.27 (3 H, t, $^3J_{HH} = 7.1$ Hz, CH_3 of Et), 3.34 and 3.44 (12 H, 2 s, 4 NCH_3),

4.20 (2 H, q, $^3J_{HH} = 7.1$ Hz, OCH_2), 4.77 (2 H, s, NCH_2). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 14.10 (CH_3 of Et), 29.74 and 29.83 (4 NMe), 55.23 (NCH_2), 59.84 (OCH_2), 80.61 and 95.94 (2 spiro carbons), 149.12 (N=*C*), 149.78 and 150.38 (2 N*C*ON), 162.03 and 162.18 (4 N*C*OC). MS (EI, 70 eV) (*m*/*z*, %) 453 (M^+, 6), 73 (100). Anal. Calcd. for $C_{17}H_{19}N_5O_{10}$ (453.36): C, 45.04; H, 4.22; N, 15.45%. Found: C, 45.1; H, 4.2; N, 15.5%.

2,4,10,12-Tetramethyl-15-({[(4-methylphenyl)sulfonyl]methyl}imino)-7,14-dioxa-2,4,10,12-tetraazadispiro[5.1.5.2]pentadecane-1,3,5,9,11,13-hexone **(3f)**

Pink powder. (0.461 g, 86%). Mp 241–243°C. IR (KBr) (ν_{max}, cm^{-1}): 1753, 1725, and 1691 (C=O), 1565 (N=C), 1384 and 1170 (SO_2). ^1H NMR ($CDCl_3$, 400 MHz): δ_H 2.47 (3 H, s, CH_3), 3.31 and 3.46 (12 H, 2 s, 4 NCH_3), 4.98 (2 H, s, NCH_2SO_2), 7.34 and 7.91 (4 H, 2 d, $^3J_{HH} = 8.6$ Hz, C_6H_4). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 21.60 (CH_3), 29.83 and 29.85 (4 NMe), 73.47 (NCH_2SO2), 80.95 and 96.68 (2 spiro carbons), 127.70, 132.02, 138.83, and 144.47 (C_6H_4), 147.81 (N=*C*), 149.61 and 150.84 (2 N*C*ON), 162.11 and 163.02 (4 N*C*OC). MS (EI, 70 eV) (*m*/*z*, %) 535 (M^+, 2), 91 (100). Anal. Calcd. for $C_{21}H_{21}N_5O_{10}S$ (535.48): C, 47.10; H, 3.95; N, 13.08%. Found: C, 47.2; H, 4.0; N, 13.1%.

2,4,10,12-Tetramethyl-15-(2-morpholinoethylimino)-7,14-dioxa-2,4,10,12-tetraaza dispiro[5.1.5.2]pentadecane-1,3,5,9,11,13-hexone **(3g)**

Dark pink powder. (0.370 g, 77%). Mp 212–214°C. IR (KBr) (ν_{max}, cm^{-1}): 1760, 1724, and 1683 (C=O), 1576 (N=C). ^1H NMR ($CDCl_3$, 400 MHz): δ_H 2.43 (4 H, m, CH_2NCH_2), 2.56 (2 H, t, $^3J_{HH} = 5.7$ Hz, NCH_2), 3.33 and 3.41 (12 H, 2 s, 4 NCH_3), 3.45 (2 H, t, $^3J_{HH} = 5.7$ Hz, = NCH_2), 3.67 (4 H, m, CH_2OCH_2). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 29.79 and 29.83 (4 NMe), 45.03 (NCH_2), 53.34 (CH_2NCH_2), 57.91 (=NCH_2), 67.11 (CH_2OCH_2), 80.71 and 96.22 (2 spiro carbons), 146.69 (N=*C*), 149.37 and 150.81 (2 N*C*ON), 162.09 and 162.57 (4 N*C*OC). MS (EI, 70 eV) (*m*/*z*, %) 480 (M^+, 10), 87 (100). Anal. Calcd. for $C_{19}H_{24}N_6O_9$ (480.43): C, 47.50; H, 5.04; N, 17.49%. Found: C, 47.6; H, 5.0; N, 17.5%.

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