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ARTICLE *in* JOURNAL OF HETEROCYCLIC CHEMISTRY · JULY 2013

Impact Factor: 0.79 · DOI: 10.1002/jhet.719

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An Isocyanide-Based Multicomponent Reaction: New Route for Synthesis of Isoxazolinedione Derivatives

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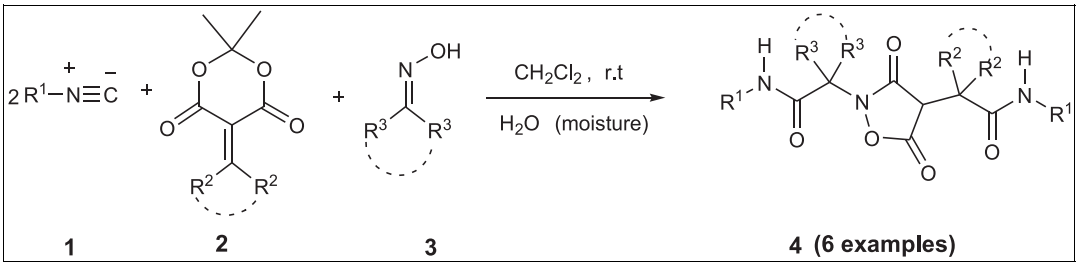
Received July 17, 2010
DOI 10.1002/jhet.719
Published online 00 Month 2013 in Wiley Online Library (wileyonlinelibrary.com).



An efficient and novel multicomponent reaction for synthesis of new isoxazolinedione has been described. This protocol involves reaction of two molecules of isocyanide, aliphatic oxime, alkylidene substituted Meldrum's acid, and water (moisture). Elemental analyses, IR, ^{1}H NMR, and ^{13}C NMR spectroscopic data of products are consistent with the structure defined by X-ray diffraction analysis.

J. Heterocyclic Chem., **00**, 00 (2013).

INTRODUCTION

Multicomponent reactions (MCRs) have an important role for the efficient and simple synthesis of wide variety of different compounds. The diversity, efficiency, and rapid access to small and highly functionalized organic molecules makes this approach of central current interest in the construction of combinatorial libraries and optimization in drug discovery process. These reactions have one-pot procedure and ready operation, facile execution, generally high yield, and convergence virtue.

Among MCRs, isocyanides-based MCRs are important tools for the rapid and ready synthesis of a wide variety of interested organic molecules. On the basis of isocyanides chemistry, several synthesis of drug-like and heterocyclic compounds needed in medicinal chemistry were reported and extensive researches are being made [1–3].

Because of the great rule of Meldrum's acid derivatives in organic synthesis, we are interested to investigate MCR using isocyanide, alkylidene Meldrum's acid, and RXH moieties. Meldrum's acid has several features that make it a magic molecule. It has high acidity [4], susceptible to nucleophilic attack at C_4 and C_6 and electrophilic attack at C_5, undergoing ring opening reactions, and it is applied as an alternative for acyclic malonic esters. In addition, a lot of Meldrum's acid derivatives have been used as intermediate compounds in organic synthesis. Several reports have been published in which acyl Meldrum's is used for preparation of 1,3-dicarbonyl compounds [5]; mono- and di-alkyl and aryl substituted of Meldrum's at C_5 is used for synthesis of different malonic ester derivatives [6]; 5,5-dibromo Meldrum's acid is applied for mild α-brominating of aldehyde and ketones [7]. Also, other derivatives were used in Diels–Alder reactions, conjugate addition, cyclization, and so on [8–10].

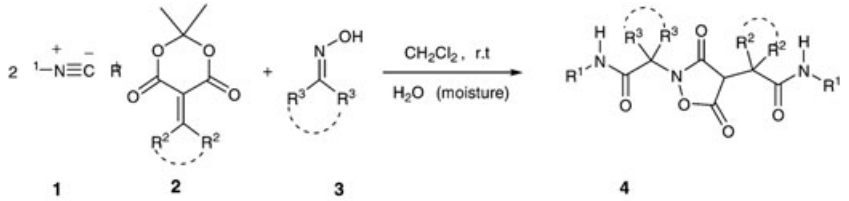
RESULTS AND DISCUSSION

To expand our current work on investigation, three-component reaction of isocyanide and alkylidene Meldrum's acid in the presence of RXH moieties [11,12], here we wish to report the result of reaction between isocyanide **1**, alkylidene Meldrum's acid **2**, and Ketoxime **3** (Scheme 1). So, one-pot MCR of alkyl isocyanide **1**, alkylidene Meldrum's acid **2** in the presence of ketoxime **3** occurred in CH_2Cl_2 as solvent and at room temperature. After 48 h the reaction was completed with moderate yield and crude products were purified with column chromatography using hexane/ethyl acetate as eluent.

This reaction was performed according to our previous study. It is expected this reaction occurred in a 1:1:1 manner, but on the base of first spectroscopic data; we found that this reaction occurred in different approach. Initial ^{1}H NMR spectroscopy study of the product appeared that absorption pattern with a 1:1:1 product is not compatible. Noticable with an additional signal, it can be concluded that the two residual structures of isocyanides in the product molecule is present, but still two more hydrogen signals is seen. To understand the structure of our products, we decided to study X-ray structure of the product. It is notable that when the reaction was performed in the presence of 2–3 drops of water, the reaction did not had any progress.

The structure of compound **4a** was elucidated by an X-ray diffraction analysis [13]. Molecular structure of

Scheme 1



4	R^1	R^2	R^3
a	Cyclohexyl	Cyclopentyl	Cyclohexyl
b	Cyclohexyl	Me	Cyclopentyl
c	Cyclohexyl	Me	Me
d	Cyclohexyl	Cyclopentyl	Cyclopentyl
e	Cyclohexyl	Me	Cyclohexyl
f	^{t}Bu	Cyclopentyl	Cyclohexyl

compound **4a** is shown in Figure 1. Clearly, we can see the isoxazole ring where three cyclohexyl and cyclopentyl have normal shape and aligned perpendicular with respect to the isoxazole core.

The IR, ^{1}H NMR, and ^{13}C NMR data of the products have similar signal and bands. This information undoubtedly indicates the formation of isoxazolinedione derivatives (**4a–4f**). Also, elemental analyses data are consistent with this result.

General procedure for synthesis of products and selected spectroscopic data are mentioned in the experimental. The IR spectrum of **4a** shows NH band at 3326 cm^{-1} and four bands for carbonyl stretching at 1806, 1721, 1643, and 1625 cm^{-1}. Molecular ion in mass spectrum appeared at 501. The ^{1}H NMR spectrum of **4a** exhibited a complex signal (δ = 1.29–2.79 ppm) for the cyclohexyl and cyclopentyl protons along with two signals (δ = 3.03 and 3.75 ppm) because of the three methine protons. Two signals (appeared at δ = 5.32 and 7.62 ppm) belong to NH protons. The proton-decoupled ^{13}C NMR spectrum of **4a** exhibited 28 distinct resonances in agreement with the isoxazoline derivative structure. The spectral data of **4b–4f** were similar to **4a** except for differences in the proton and carbon resonances of the substituents.

According to our knowledge on the chemistry of isocyanides [1–3], a plausible mechanism of the five molecules reaction between isocyanides **1**, alkylidene Meldrum's acid **2**, ketoxime **3**, and water is introduced in Scheme 2. The first step of mechanism involves the [4+1] cycloaddition reaction of the electron-deficient heterodiene moiety of alkylidene Meldrum's acid with the isocyanide, producing an iminolactone intermediate **5**. Nucleophilic attack of oxime on the carbonyl of lactone followed ring opening, losing acetone and hydrogen transfer leads to intermediate **6**. Nucleophilic attack of second molecule of isocyanide, produces intermediate **7**. This intermediate undertakes intramolecular ring closure via a "5-exo trig" that leads to form intermediate **8**; after that, addition of one molecule of water (moisture) leads to form new amide group and finally obtains isoxazolinedione derivatives **4**.

In conclusion, our one-pot and novel protocol as a MCR (two molecule of) isocyanide, alkylidene Meldrum's acid, aliphatic ketoxime, and water provides a simple entry into the synthesis of new derivatives of isoxazolinedione.

EXPERIMENTAL

Melting points were measured on Electrothermal 9100 apparatus. Elemental analyses for C and H were performed using a Heraeus CHN-S-O-rapid analyzer. IR spectra were measured on a shimadzu IR-460 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded at 300.1 and 75.47 MHz, respectively, on a bruker

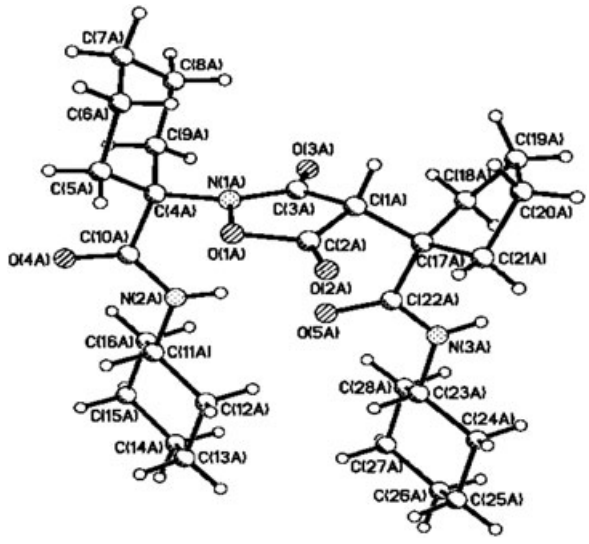
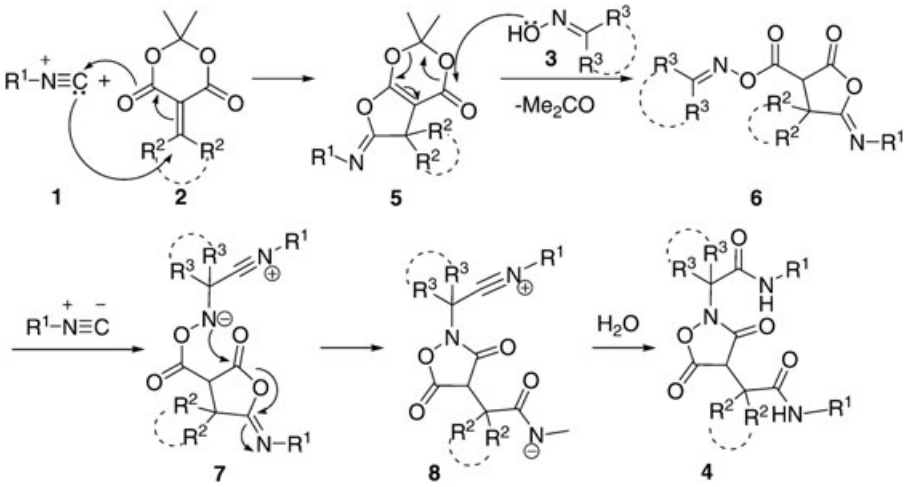


Figure 1. Molecular structure of **1** (ORTEP-III plot).

Scheme 2



DRX-300 Avance instrument with $CDCl_3$ and C_3D_6O as solvent and tetramethylsilane (TMS) as internal standard. Meldrum's acid and isocyanides were obtained from fluka (Buches, Switzerland) and used without further purification. Alkylidene Meldrum's acids were prepared according to reported procedures [6,8,10]. Oximes were obtained according to a classic procedure.

General procedure for the synthesis of 4a-4f. Exemplified for *N*^{1}-cyclohexyl-1-[4-{1-[(cyclohexylamino)carbonyl]cyclopentyl}-3,5-dihydro-2(*3H*)-isoxazolyl]-1-cyclohexanecarboxamide (4a). To a magnetically stirred solution of 2 mmol (0.42 gr) of cyclopentylidene Meldrum's acid and 2 mmol (0.226 gr) of cyclohexanone oxime in 10 mL of CH_2Cl_2, added dropwise solution of 4 mmol (0.484 mL) cyclohexyl isocyanide in CH_2Cl_2 during 10 min. The reaction mixture was allowed to stir for 48 h at room temperature. The solvent was removed under reduced pressure, and the residue was purified by silica gel (Merck 230-240 mesh) column chromatography using hexane–ethyl acetate 4:1 mixture as eluent. The solvent was removed and the product was obtained as follows:

***N*^{1}-Cyclohexyl-1-[4-{1-[(cyclohexylamino)carbonyl]cyclopentyl}-3,5-dioxodihydro-2(3H)-isoxazolyl]-1-cyclohexanecarboxamide (4a).** White powder; mp 184–186°C; yield: 58%. IR (KBr) υ cm^{-1} 3326 (NH), 1806, 1721, 1643, 1625 (C O), 1538 (NH bending). ^{1}H NMR (300.1 MHz, CD_6CO) δ ppm 1.29–2.79 (m, 38H, 19 CH_2), 3.03 (s, 1H, CH), 3.75 (m, 1H, CH), 5.32 (d, 1H, ^{3}J = 8.0, NH), 7.62 (d, 1H, ^{3}J = 8.0, NH). ^{13}C NMR (75.47 MHz, CD_6CO) δ ppm 21.8, 22.3, 24.7, 24.8, 25.4, 25.4, 25.6, 25.7, 31.4, 31.8, 32.6, 32.8, 32.8, 32.9, 35.8, 36.7, 47.7, 49.1, 49.3, 57.4, 70.6, 76.6, 77.0, 77.4, 165.6, 168.5, 170.1, 175.6. MS (ESI): *m*/*z* (%) = 501 (4, M^+), 375 (80), 279 (41), 262 (87) 248 (80), 194 (25), 180 (50), 154 (64), 114 (53), 109 (53), 98 (100), 96 (81), 83 (53), 67 (52), 56 (71), 55 (81), 41 (59). Anal.calcd. for $C_{28}H_{43}N_3O_5$(501.66): C, 67.04; H, 8.64; N, 8.38% found: C, 66.90; H, 8.80; N, 8.34%.

***N*^{1}-Cyclohexyl-1-[4-[2-(cyclohexylamino)-1,1-dimethyl-2-oxoethyl]-3,5-dioxodihydro-2(3H)-isoxazolyl]-1-cyclohexanecarboxamide (4b).** White powder; mp 174–176°C; yield: 46%. IR (KBr) υ cm^{-1} 3369 (NH), 1817, 1730, 1650, 1645 (C O), 1549 (NH bending). ^{1}H NMR (300.1 MHz, CD_6CO) δ ppm 1.17–2.31 (m, 28H, 14 CH_2), 1.61 and 1.64 (2s, 6H, 2 CH_3), 2.91 (s, 1 H, CH), 3.73 (m, 1H, CH), 5.56 (d, 1H, ^{3}J = 8.1, NH), 7.59 (d, 1H, ^{3}J = 8.1, NH). ^{13}C NMR (75.47 MH_Z, CD_6CO) δ ppm 23.8, 24.4, 24.9, 25.3, 25.3, 25.7, 26.0, 29.7, 32.6, 32.7, 32.8, 32.9, 35.6, 35.8, 47.5, 49.3, 50.0, 76.0, 165.0, 167.8, 169.7, 174.7. MS (ESI): *m*/*z* (%) = 461 (11, M^+), 336 (71), 268 (31), 114 (55), 111 (51), 98 (100), 83 (46), 67 (52), 55 (81), 41 (56). Anal.calcd. for $C_{25}H_{39}N_3O_5$ (461.59): C, 65.05; H, 8.52; N, 9.10% found: C, 64.95; H, 8.68; N, 9.05%.

***N*^{1}-Cyclohexyl-2-[2-[2-(cyclohexylamino)-1,1-dimethyl-2-oxoethyl]-3,5-dioxodihydro-4(3H)-isoxazolyl]-2-methylpropanamide (4c).** White powder; mp 189–191°C; yield: 51%. IR (KBr) υ cm^{-1} 3393, 3337 (NH), 1812, 1783, 1704, 1640 (C O), 1530 (NH bending). ^{1}H NMR (300.1 MHz, CD_6CO) δ ppm 1.15–1.90 (m, 20H, 10 CH_2), 1.46, 1.61, 1.64 and 1.72 (4s, 12H, 4 CH_3), 2.87 (s, 1H, CH), 3.73 (m, 1H, CH), 5.44 (d, 1H, ^{3}J = 7.8, NH), 7.38 (d, 1H, ^{3}J = 7.8, NH). ^{13}C NMR (75.47 MH_Z, CD_6CO) δ ppm 24.7, 24.8, 24.9, 25.3, 25.4, 25.7, 26.0, 32.6, 32.7, 32.9, 47.5, 49.1, 49.3, 50.0, 66.3, 165.3, 167.8, 170.6, 174.6. MS (ESI): *m*/*z* (%) = 435 (56, M^+), 309 (27), 236 (100), 225 (10), 83 (80), 55 (74). Anal.calcd. for $C_{23}H_{37}N_3O_5$ (435.56): C, 63.42; H, 8.56; N, 9.65% found: C, 63.31; H, 8.62; N, 9.59%.

***N*^{1}-Cyclohexyl-1-[4-{1-[(cyclohexylamino)carbonyl]cyclopentyl}-3,5-dioxodihydro-2(3H)-isoxazolyl]-1-cyclopentanecarboxamide (4d).** White powder; mp 169–171°C; yield: 56%. IR (KBr) υ cm^{-1} 3327 (N H), 1809, 1720, 1645, 1630 (C O), 1539 (N H bending). ^{1}H NMR (300.1 MHz, CD_6CO) δ ppm 1.26–2.60 (m, 36H, 18 CH_2), 2.954 (s, 1H, CH), 3.749 (m, 1H, CH), 5.33 (d, 1H, ^{3}J = 7.8, NH), 7.64 (d, 1H, ^{3}J = 7.8, NH). ^{13}C NMR (75.47 MH_Z, CD_6CO) δ ppm 23.8, 24.4, 24.8, 25.4, 25.5, 25.7, 32.6, 32.8, 32.8, 32.9, 35.7, 35.8, 36.6, 47.8, 49.2, 57.7, 76.0, 165.3, 168.5, 169.7, 175.5. MS (ESI): *m*/*z* (%) = 487 (10, M^+), 362 (73), 347 (44), 154 (24), 128 (45), 114 (31), 98 (100), 83 (58), 55 (36). Anal.calcd. for $C_{27}H_{41}N_3O_5$ (487.63): C, 66.50; H, 8.47; N, 8.62% found: C, 66.43; H, 8.54; N, 8.57%.

***N*^{1}-Cyclohexyl-1-[4-[2-(cyclohexylamino)1,1-dimethyl-2-oxoethyl]-3,5-dioxodihydro-2(3H)-isoxazolyl]-1-cyclohexanecarboxamide (4e).** White powder; mp 150°C; yield: 43%. IR (KBr) υ cm^{-1} 3343 (N H), 1821, 1746, 1723, 1637 (C O), 1555 (N H bending). ^{1}H NMR (300.1 MHz, CD_6CO) δ ppm 1.16–2.67 (m, 30H, 15 CH_2), 1.62 and 1.66 (2s, 6H, 2 CH_3), 2.99 (s, 1H, CH),

3.73 (m, 1H, CH), 5.55 (d, 1H, ^3J = 8.1, NH), 7.57 (d, 1H, ^3J = 8.1, NH). ^{13}C NMR (75.47 MH_Z, CD_6CO) δ ppm 21.8, 22.3, 24.7, 24.9, 25.4, 25.8, 26.0, 27.0, 31.5, 32.0, 32.6, 32.8, 32.8, 33.0, 47.3, 49.1, 49.8, 70.7, 165.4, 167.9, 170.1, 174.7 (4C O) ppm. MS (ESI): *m*/*z* (%) = 475 (44, M^+), 349 (95), 333 (92), 253 (35), 236 (84), 154 (35), 128 (64), 114 (43), 98 (100), 95 (63), 83 (85), 55 (72), 41 (50). Anal.calcd. for $C_{26}H_{41}N_3O_5$ (475.62): C, 65.66; H, 8.69; N, 8.83% found: C, 65.51; H, 8.81; N, 8.84%.

N^1-(tert-Butyl)-1-[4-{1-[(tert-butylamino)carbonyl]cyclopentyl}-3,5-dioxodihydro-2(3H)-isoxazolyl]-1-cyclohexanecarboxamide (4f). White powder; mp 175°C; yield: 38%. IR (KBr) υ cm^{-1} 3414, 3358 (N H), 1812, 1706, 1675, 1637 (C O), 1534 (N H bending). ^{1}H NMR (300.1 MHz, CD_6CO) δ ppm 1.13–1.74 (m, 18H, 9 CH_2), 1.32 and 1.38 (2s, 18H, 2 CMe_3), 2.91 (s, 1H, CH), 5.35 (s, 1H, NH), 6.52 (s, 1H, NH). ^{13}C NMR (75.47 MH_Z, CD_6CO) δ ppm 23.7, 24.3, 25.2, 25.7, 28.2, 28.5, 28.6, 47.9, 50.2, 51.6, 66.7, 165.2, 167.6, 169.7, 174.2. MS (ESI): *m*/*z* (%) = 449 (15, M^+), 351 (30), 279 (26), 236 (50), 128 (42), 98 (100), 83 (61), 81 (25), 55 (52). Anal.calcd. for $C_{24}H_{39}N_3O_5$ (449.58): C, 64.12; H, 8.74; N, 9.35% found: C, 64.03; H, 8.80; N, 9.29%.

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[13] Crystallographic data for the structure in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 733794. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [Fax: +44 0 1223 336033 (or) e-mail: deposit@ccdc.cam.ac.u].