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Synthesis of Highly Functionalized Isoxazolinediones from One-pot Reaction of Alkylidene *Meldrum*'s Acid with Alkyl Isocyanides in the Presence of Arylhydroxylamines

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Summary. Alkyl isocyanides undergo a smooth reaction with alkylidene *Meldrum*'s acids in the presence of arylhydroxylamines to produce N^1-alkyl-2-(3,5-dioxo-2-aryltetrahydro-4-isoxazolyl)alkanamides in high yields.

Keywords. Isoxazolinedione; Arylhydroxylamine; Alkyl isocyanide; Alkylidene *Meldrum*'s acid.

Introduction

Isoxazolidines have been found to exhibit antimicrobial activity [1, 2] and have been used as enzyme inhibitors [3–5]. Isoxazolidine nucleoside analogues are a particularly interesting group of compounds due to their potential antiviral activity [6–8]. Isoxazolidines have also been employed as useful building blocks in the synthesis of various natural and unnatural compounds, including alkaloids, biologically active β-aminoacids, β-lactams, amino sugars, as well as simple 1,3-aminoalcohols owing to the facile cleavage of the N–O bond [9, 10]. The 1,3-dipolar cycloaddition of nitrones to alkenes has been the most efficient approach employed for the construction of isoxazolidines, since the stereochemistry of the reaction is predictable, and the mechanism has been established [11, 12].

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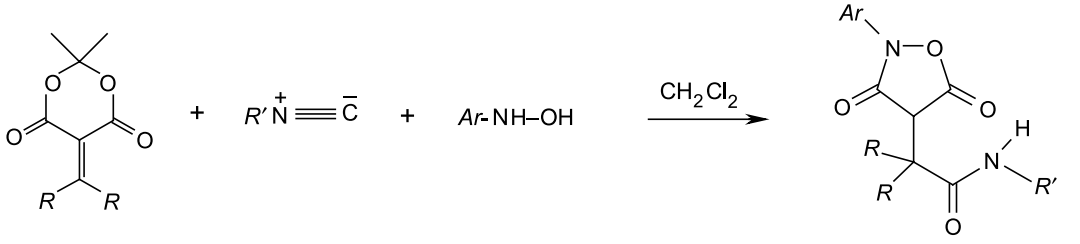
Results and Discussion

As part of our current studies [13] on the reaction between alkylidene *Meldrum*'s acid and alkyl isocyanides in the presence of proton sources, we now report a simple and one-pot synthesis of functionalized isoxazoline diones from the reaction between alkyl isocyanides and alkylidene *Meldrum*'s acids in the presence of arylhydroxylamines. This three-component reaction proceeded slowly at room temperature in CH_2Cl_2 and completed within 24 h, to afford the corresponding N^1-alkyl-2-(3,5-dioxo-2-aryl-tetrahydro-4-isoxazolyl)alkanamides **4a**–**4g** in good yields (Scheme 1).

The ^{1}H and ^{13}C NMR spectra of the crude product clearly indicated the formation of isoxazoline diones **4**. Any product other than **4** could not be detected by NMR spectroscopy. Products **4a**–**4g** were purified by SiO_2 CC using *n*-hexane-*Et*O*Ac* as eluent and identified on the basis of their spectroscopic data. The IR spectrum of **4f** exhibits a NH stretching band at 3418 cm^{-1} and signals for three carbonyl groups at 1824 and 1728 cm^{-1}. The ^{1}H NMR spectrum of **4f** exhibited a single sharp line readily recognized as arising from *tert*-butyl ($\delta = 1.32$ ppm), five methylene ($\delta = 1.23$–2.77 ppm), methine ($\delta = 3.57$ ppm), and NH ($\delta = 5.48$ ppm) protons. Five aromatic protons show three signals at $\delta = 7.25$–7.66 ppm. The ^{13}C NMR



	R		R′		Ar
1a	*Me*	**2a**	^{t}*Bu*	**3a**	4-*Me*-C_6H_4
1b	$(CH_2)_5$	**2b**	Cyclohexyl	**3b**	*Ph*
				3c	4-Br-C_6H_4

	R	R′	Ar
4a	Me	^{t}*Bu*	4-*Me*-C_6H_4
4b	*Me*	^{t}*Bu*	*Ph*
4c	*Me*	^{t}*Bu*	4-Br-C_6H_4
4d	*Me*	Cyclohexyl	*Ph*
4e	*Me*	Cyclohexyl	4-*Me*-C_6H_4
4f	$(CH_2)_5$	^{t}*Bu*	*Ph*
4g	$(CH_2)_5$	Cyclohexyl	4-*Me*-C_6H_4

Scheme 1

spectrum shows 14 distinct resonances for aliphatic (seven signals) and aromatic carbons (four signals) together with three resonances at $\delta = 165.5$, 167.8, and 173.5 ppm for the carbonyl groups.

Unambiguous evidence for the structure of **4f** was obtained from a single-crystal X-ray analysis. An ORTEP [14] diagram of **4f** is shown in Fig. 1. There are 8 molecules of **4f** in the unit cell. The phenyl group is forced out of the plane of the heterocyclic ring and it is twisted by about 6°.

Although the mechanism of reaction between alkylidene *Meldrum*'s acid and alkyl isocyanides in the presence of arylhydroxylamines was not established in an experimental manner, a plausible explanation is proposed in Scheme 2. On the basis of the well established chemistry of isocyanides [15] the reaction starts from [4 + 1] cycloaddition of **2** and **1**, producing an iminolactone intermediate **5**. Conjugate addition by the hydroxylamine on the enone moiety of **5** followed by cleavage of the five-membered ring gives **6** and hence the ketene **7** by electrocyclic ring opening of the O-alkylated *Meldrum*'s acid. The ketene **7** can then undergo intermolecular reaction between the nitrogen of the hydroxylamine and ketene moiety to give product **4**.

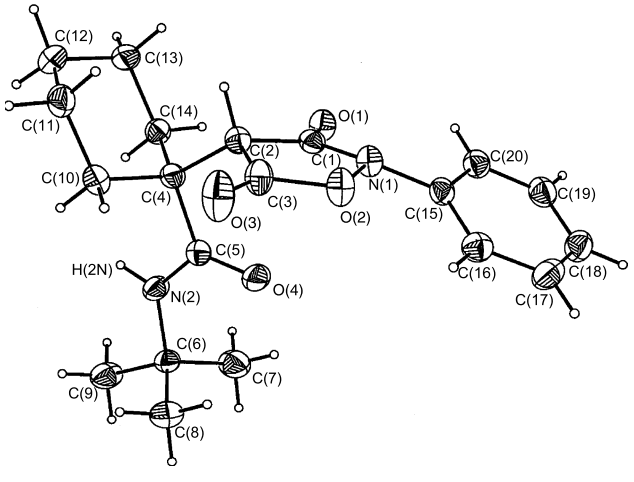
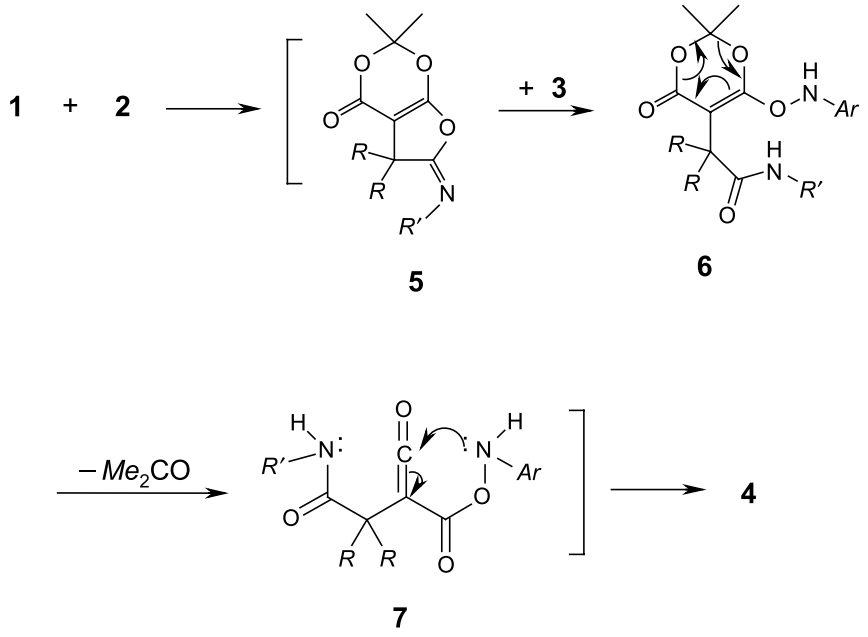


Fig. 1. X-Ray crystal structure of **4f** (ORTEP-III plot [14]; arbitrary numbering of atoms)

In conclusion, we have describe a convenient route to N^1-alkyl-2-(3,5-dioxo-2-aryl-tetrahydro-4-isoxazolyl)alkanamides by means of a one-pot reaction of alkylidene *Meldrum*'s acid with alkyl isocyanides in the presence of arylhydroxylamines. These products may be considered as potentially useful synthetic intermediates because they possess atoms with different oxidation states. The advantage of the present procedure is that the reaction is performed under neutral conditions by simple mixing of the starting materials.

Experimental

Compounds **1**–**3** were obtained from Fluka and were used without further purification. M.p.: Electrothermal-9100 apparatus. IR spectra: Shimadzu IR-460 spectrometer. ^{1}H and ^{13}C NMR spectra: Bruker DRX-500 AVANCE instrument; in $CDCl_3$ at 500.1 and 125.7 MHz. EI-MS (70 eV): Finnigan-MAT-8430 mass spectrometer. Elemental analyses (C, H, N) were performed with a Heraeus CHN-O-Rapid analyzer; the results



Scheme 2

were found to be in favourable agreement with the calculated values.

General Procedure for the Preparation of Compounds ***4***

To a stirred soln. of 2 mmol **1** and 2 mmol **3** in 10 cm^3 anh. CH_2Cl_2 was added a solution of 2 mmol **2** in 5 cm^3 anh. CH_2Cl_2 at −5° over 10 min. The mixture was then allowed to warm to r.t., and stirred for 24 h. The solvent was removed under reduced pressure, and the residue was purified by silica gel (SiO_2; *n*-hexane/*AcOEt* 4/1) to afford the pure compounds.

N^1-(tert-Butyl)-2-methyl-2-[2-(4-methylphenyl)-3,5-dioxo-tetrahydro-4-isoxazolyl]-propanamide (**4a**, $C_{18}H_{24}N_2O_4$)

White powder; yield 0.30 g (91%), mp 166–167°C. IR (KBr): $\bar{\nu} = 3421$ (NH), 1823 and 1716 (C=O) cm^{-1}; EI-MS: $m/z = 332$ (M^+, 6), 57 (100), 55 (48); ^{1}H NMR: $\delta = 1.31$ (s, C*Me*$_3$), 1.60, 1.63 (2s, CMe_2), 2.36 (s, *Me*), 3.22 (s, CH), 5.40 (s, NH), 7.22, 7.53 (2*d*, $^3J = 7.5$, 4CH) ppm; ^{13}C NMR: $\delta = 21$ (*Me*), 24.4, 25.1 (C*Me*$_2$), 28.5 (C*Me*$_3$), 48.1 (*CMe*$_2$), 49.8 (CH), 51.6 (*CMe*$_3$), 120.0, 129.5 (2CH), 133.2 (C–N), 136.8 (*CMe*), 165.1, 167.8, 173.7 (3C=O) ppm.

N^1-(tert-Butyl)-2-(3,5-dioxo-2-phenyl-tetrahydro-4-isoxazolyl)-2-methyl-propanamide (**4b**, $C_{17}H_{22}N_2O_4$)

Colorless crystals; yield 0.22 g (70%), mp 149–151°C. IR (KBr): $\bar{\nu} = 3406$ (NH), 1800, 1714 and 1822 (C=O) cm^{-1}; EI-MS: $m/z = 318$ (M^+, 6), 91 (64), 57 (90), 58 (100), 41 (69); ^{1}H NMR: $\delta = 1.31$ (s, C*Me*$_3$), 1.58, 1.62 (2s, C*Me*$_2$), 3.21 (s, CH), 5.39 (s, NH), 7.23 (*t*, $^3J = 7.8$, CH), 7.40 (*t*, $^3J = 7.8$, 2CH), 7.64 (*d*, $^3J = 7.8$, 2CH) ppm; ^{13}C NMR: $\delta = 24.5$, 25.3 (C*Me*$_2$), 28.5 (C*Me*$_3$), 48.3 (*CMe*$_2$), 49.9 (CH), 51.6 (*CMe*$_3$), 119.3 (2CH), 126.5 (CH), 129.0 (2CH), 135.7 (C–N), 165.1, 167.7, 173.8 (3C=O) ppm.

2-[2-(4-Bromophenyl)-3,5-dioxo-tetrahydro-4-isoxazolyl]-N^1-(tert-butyl)-2-methyl-propanamide (**4c**, $C_{17}H_{21}BrN_2O_4$)

Colorless crystals; yield 0.22 g (70%), mp 134–137°C. IR (KBr): $\bar{\nu} = 3392$ (NH), 1804 and 1729 (C=O) cm^{-1}; EI-MS: $m/z = 396$ (M^+-1, 2), 296 (4), 184 (23), 171 (16), 83 (44), 57 (100), 55 (70), 43 (38), 41 (52); ^{1}H NMR: $\delta = 1.30$ (s, C*Me*$_3$), 1.61, 1.65 (2s, C*Me*$_2$), 3.16 (s, CH), 5.54 (s, NH), 7.56 (*m*, 4CH) ppm; ^{13}C NMR: $\delta = 24.6$, 25.4 (C*Me*$_2$), 28.4 (C*Me*$_3$), 48.1 (*CMe*$_2$), 49.8 (CH), 51.6 (*CMe*$_3$), 119.0 (C_{ipso}-Br), 120.4 (2CH), 132.0 (2CH), 134.2 (C_{ipso}-N), 165.1, 167.8, 173.7 (3C=O) ppm.

N^1-Cyclohexyl-2-(3,5-dioxo-2-phenyl-tetrahydro-4-isoxazolyl)-2-methyl-propanamide (**4d**, $C_{19}H_{24}N_2O_4$)

Colorless crystals; yield 0.28 g (83%), mp 151–153°C. IR (KBr): $\bar{\nu} = 3375$ (NH), 1707, 1811 and 1822 (C=O) cm^{-1}; EI-MS: $m/z = 344$ (M^+, 3), 236 (17), 154 (32), 93 (38), 83 (100), 55 (66); ^{1}H NMR: $\delta = 1.127$, 1.319 (2s, CMe_2), 1.57–1.89 (*m*, 5CH_2), 3.20 (s, CH), 3.69 (*d*, N–CH), 5.39 (s, NH), 7.23 (*t*, $^3J = 7.6$ Hz, CH), 7.40 (*t*, $^3J = 7.6$ Hz, 2CH), 7.65 (*d*, $^3J = 7.6$ Hz, 2CH) ppm; ^{13}C NMR: $\delta = 24.5$, 24.5 (C*Me*$_2$), 25.4, 25.4, 32.9 (5CH_2), 47.7 (*CMe*$_2$), 48.7 (CH), 49.9 (N–CH), 118.8 (2CH), 126.3 (CH), 129.0 (2CH), 135.7 (C_{ipso}-N), 164.1, 167.0, 173.2 (3C=O) ppm.

N^1-Cyclohexyl-2-methyl-2-[2-(4-methylphenyl)-3,5-dioxo-tetrahydro-4-isoxazolyl]-2-methyl-propanamide (**4e**, $C_{20}H_{26}N_2O_4$)

Colorless crystals; yield 0.26 g (75%), mp 152–154°C. IR (KBr): $\bar{\nu} = 3391$ (NH), 1828, 1816 and 1707 (3C=O) cm^{-1}; EI-MS: $m/z = 359$ ($M^+ + 1$, 3), 236 (38), 154 (100), 107 (42), 83 (88), 56 (72), 41 (41); ^{1}H NMR: $\delta = 1.60$–2.70 (*m*, 5CH_2), 1.63, 1.66 (2s, CMe_2), 2.36 (s, *Me*-Ph), 3.22 (s, CH),

3.72 (*m*, N–CH), 5.39 (br, s, NH), 7.21 (*d*, $^3J = 7.2$ Hz, 2CH), 7.54 (*d*, $^3J = 7.2$ Hz, 2CH) ppm; ^{13}C NMR: $\delta = 21.0$ (*Me*), 24.5, 25.3 (C*Me*$_2$), 24.5, 25.3, 25.4, 32.8, 32.9 (5CH$_2$), 47.6 (CH), 48.7 (*CMe*$_2$), 49.8 (CH–N), 119.6 (2CH), 129.5 (2CH), 133.2 (C$_{ipso}$-*Me*), 136.5 (C$_{ipso}$-N), 164.8, 167.7, 173.6 (3C=O) ppm.

N^1-(tert-Butyl)-1-(3,5-dioxo-2-phenyltetrahydro-4-isoxazolyl)-1-cyclohexane-carboxamide (**4f**, $C_{20}H_{26}N_2O_4$) Colorless crystals; yield 0.28 g (80%), mp 153–155°C. IR (KBr): $\bar{\nu} = 3418$ (NH), 1824 and 1728 (3C=O) cm^{-1}; EI-MS: $m/z = 359$ ($M^+ + 1$, 4), 93 (67), 57 (100), 41 (69); ^{1}H NMR: $\delta = 1.32$ (s, C*Me*$_3$), 1.23–2.77 (*m*, 5CH$_2$), 3.57 (s, CH), 5.48 (br, s, NH), 7.25 (*t*, $^3J = 7.6$ Hz, CH), 7.41 (*t*, $^3J = 8.1$ Hz, CH), 7.66 (*d*, $^3J = 7.6$ Hz, CH) ppm; ^{13}C NMR: $\delta = 22.4$, 22.6, 25.0, 31.2, 32.6 (5CH$_2$), 28.5 (C*Me*$_3$), 43.9 (CH), 51.6 (CH$_2$–*C*), 53.4 (*CMe*$_3$), 119.1 (2CH), 126.6 (CH), 128.9 (2CH), 135.8 (C$_{ipso}$-N), 165.5, 167.8, 173.5 (3C=O) ppm.

X-Ray Crystal-Structure of ***4f***
Structure-determination and refinement of data: formula $C_{20}H_{26}N_2O_4$, $F_w = 358.44$, orthorhombic, space group *pbca*, $Z = 8$, $a = 10.6556(6)$, $b = 18.0132(11)$, $c = 19.5513$ Å, $\alpha = 90$, $\beta = 90$, $\gamma = 90°$, $V = 3725.7(4)$ Å^3, $D_{calcd} = 1.269$ g cm^{-3}, $R = 0.0463$, $R_w = 0.0937$ (for 3059 reflections), $-13 \leq h \leq 13$, $-22 \leq k \leq 23$, $-21 \leq l \leq 24°$, Mo ($\lambda = 0.71073$ Å), $T = 120(2)$ K. The crystallographic data of **4f** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-615110. Copies of the data can be obtained, free of charge, *via* the internet (http://www.ccdc.cam.ac.uk/data_request/cif), e-mail (data_request@ccdc.cam.ac.uk), or fax (+44-1223-336033).

N^1-Cyclohexyl-1-[2-(4-methylphenyl)-3,5-dioxo-tetrahydro-4-isoxazolyl]-1-cyclohexane-carboxamide (**4g**, $C_{23}H_{30}N_2O_4$) Colorless crystals; yield 0.25 g (64%), mp 169–171°C. IR (KBr): $\bar{\nu} = 3364$ (NH), 1804 and 1722 (3C=O) cm^{-1}; EI-MS: $m/z = 398$ (M^+, 3), 276 (14), 107 (100), 83 (38), 56 (71), 41 (47); ^{1}H NMR: $\delta = 1.20$–2.70 (*m*, 10CH$_2$), 2.36 (s, *Me*-Ph), 3.60 (s, CH), 3.71 (*m*, CH–N), 5.49 (*d*, NH), 7.21 (*d*, $^3J = 8.3$ Hz, 2CH), 7.54 (*d*, $^3J = 8.3$ Hz, 2CH) ppm; ^{13}C NMR: $\delta = 21.0$, 22.4, 24.7, 25.3, 31.3, 32.5, 32.8 (10CH$_2$), 43.3 (CH), 48.5 (CH$_2$–*C*), 53.0 (C–N), 119.5 (2CH), 129.5 (2CH), 133.3 (C$_{ipso}$-*Me*), 136.4 (C$_{ipso}$-N), 165.4, 168.2, 173.6 (3C=O) ppm.

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