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Synthesis and Characterization of Ethyl 2-methyl-7-oxo-7*H*-isoxazolo[2,3-*a*]pyrimidine-6-carboxylate Derivatives

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ABSTRACT

Reactions of 5-methylisoxazol-3-amine with diethyl ethoxymethylenemalonate derivatives are described. By this method ethyl 2-methyl-7-oxo-7*H*-isoxazolo[2,3-*a*]pyrimidine-6-carboxylate derivatives were prepared and characterized.

KEYWORDS

Isoxazolo[2,3-*a*]pyrimidine-6-carboxylate, heterocyclic, aminoisoxazole.

1. Introduction

Pyrimidine and fused heterocyclic pyrimidine derivatives are known to be associated with a wide spectrum of biological activity.[1–6] Isoxazolo[5,4-*d*]pyrimidines have received considerable attention due to their pharmacological applications as antibacterial, antifungal, antimicrobial, anti-inflammatory and anticancer agents.[7–10] Aminoisoxazole derivatives are widely used with different active methylene compounds for preparing new heterocyclic compounds.[5,6,11–14]

In this work, we describe the synthesis of ethyl 2-methyl-7-oxo-7*H*-isoxazolo[2,3-*a*]pyrimidine-6-carboxylate derivatives from 5-methylisoxazol-3-amine and diethyl ethoxymethylenemalonate derivatives.

2. Results and Discussion

The reaction of 5-methylisoxazol-3-amine with diethyl ethoxymethylenemalonate derivatives in dry xylene under reflux conditions gives exclusively the corresponding ethyl 2-methyl-7-oxo-7*H*-isoxazolo[2,3-*a*]pyrimidine-6-carboxylate **2** (Scheme 1) in good yield after purification by column chromatography (Table 1). This reaction is mainly condensation followed by cyclization. Initially the NH_2 group of 5-methylisoxazol-3-amine attacks the carbon attached to the ethoxy group of diethyl ethoxymethylenemalonate, which is prone to nucleophilic attack. The cyclization proceeds at the ester carbonyl (CO_2Et) function to give products **2**.

Using absolute ethanol as a solvent under reflux, the condensation of 5-methylisoxazol-3-amine with diethyl ethoxymethylenemalonate derivatives gives exclusively the intermediates **1** in high yield (Table 1). Compounds **2** can be obtained from the enamines **1** by reflux in dry xylene, but the yields are lower.

Formation of the ethyl 2-methyl-7-oxo-7*H*-isoxazolo[2,3-*a*]pyrimidine-6-carboxylate structure **2** can be discussed *via* intramolecular cyclization of the intermediate **1** *via* EtOH elimination (Scheme 2).

In conclusion, new ethyl 2-methyl-7-oxo-7H-isoxazolo-[2,3-*a*]pyrimidine-6-carboxylate derivatives were prepared and characterized. The biological activity of the products is under investigation.

3. Experimental

The ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 300 (Wissembourg Cedex, France) at 300 and 75 MHz respectively.

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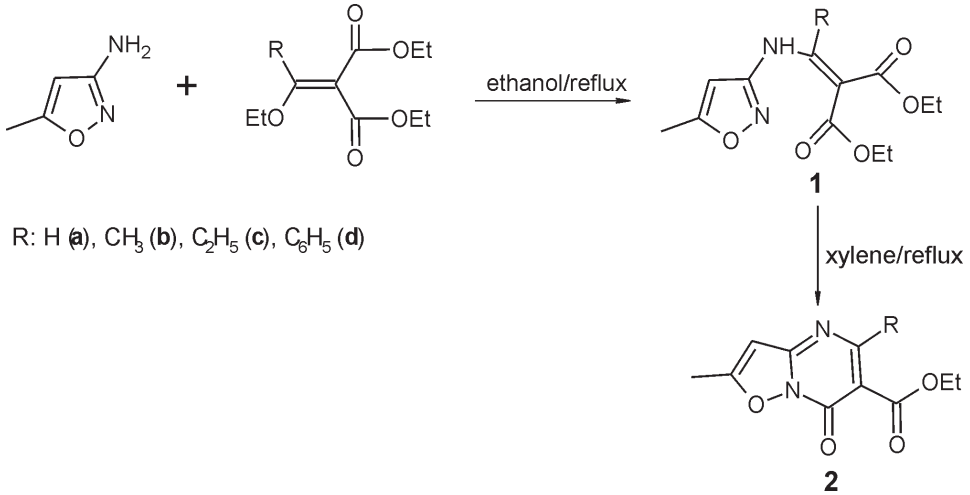
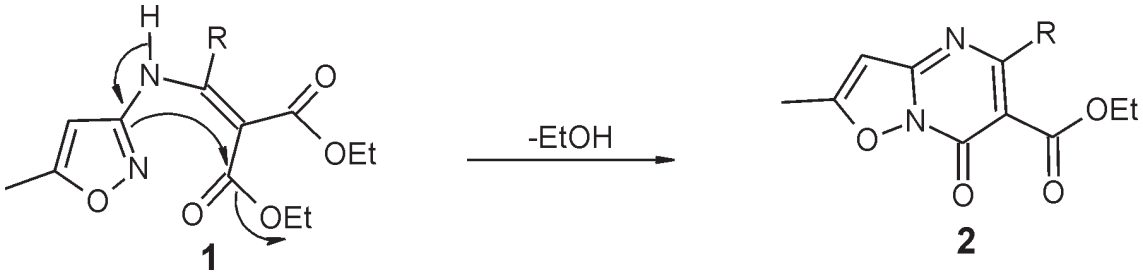


Scheme 1.
Synthesis of isoxazolopyrimidine.



Scheme 2.
Intramolecular cyclization of **1**.

Table 1 Reaction times, yields and melting points of compounds **1** and **2.**

Compound	R	Reaction time/h	Yield/%	M.p./°C
1a	H	6	95	114
1b	CH_3	36	87	Oil
1c	C_2H_5	36	82	Oil
1d	C_6H_5	36	78	Oil
2a	H	48	68	145
2b	CH_3	48	85	176
2c	C_2H_5	48	88	214
2d	C_6H_5	48	80	217

TMS was used as standard reference for ^{1}H and ^{13}C NMR spectra. Melting points were determined in capillaries and they are uncorrected. IR spectra were recorded on a Bruker IFS 66V/S spectrometer (Bioaccess, Les Berges du Lac, Tunisia). Mass spectra were determined on a GCMS-QP 1000 EX instrument (Champs Sur Marne, France) at 70 eV (EI). Silica gel 60 (Merck) was used for chromatographic column separations.

3.1. Preparation of Diethyl 2-((5-methylisoxazol-3-ylamino)methylene)malonate (1a)

A solution of 5-methylisoxazol-3-amine (0.49 g, 5 mmol) and diethyl ethoxymethylenemalonate (1.08 g, 5 mmol) in absolute ethanol (20 mL) was refluxed for 6 h. The mixture was cooled, the solid was filtered and recrystallized from ethanol.

δ_H (300 MHz, $CDCl_3$): 1.35 (6H, m, 2CH_3CH$_2$O), 2.40 (3H, s, CH_3), 4.25 (4H, m, 2CH$_3$CH_2O), 5.90 (1H, s, C*H*=C-O), 8.45 (1H, d, *J* 13.78 Hz, C*H*=C) and 10.70 ppm (1H, d, *J* 13.78 Hz, N*H*); δ_C (75 MHz, $CDCl_3$): 12.52, 13.87 (2C, 2CH_3CH$_2$O), 14.07 (CH_3), 60.24, 60.62 (2C, 2CH$_3$$CH_2$O), 95.05 (*C*H=CO), 150.90 (*C*H=C), 151.53 (CH=*C*-O), 159.14 (CH=*C*), 164.60 (N-*C*=N), 168.15 and 171.16 ppm (2C, 2*C*=O); ν_{max}: 3240 (NH) and 1700 cm^{-1} (C=O); MS (EI): m/z 268 (M$^+$), 222, 177, 162, 134 and 120.

3.2. Preparation of Enamines 1b–d: General Procedure

A solution of 5-methylisoxazol-3-amine (0.49 g, 5 mmol) and diethyl ethoxymethylenemalonate derivative (5 mmol) in absolute ethanol (20 mL) was refluxed for 36 h. The solvent was removed and the residue was purified by column chromatography over silica gel (eluent: ethyl acetate/cyclohexane: 1/5) to obtain **1b–d**.

3.2.1. *Diethyl 2-(1-(5-methylisoxazol-3-ylamino)ethylidene)malonate* (**1b**)

δ_H (300 MHz, $CDCl_3$): 1.30 (6H, m, 2CH_3CH$_2$O), 2.30 (3H, s, CH_3C=C), 2.45 (3H, s, CH_3C-O), 4.20 (4H m, 2CH$_3$CH_2O), 5.90 (1H, s, C*H*=C-O) and 11.30 ppm (1H, s, NH); δ_C (75 MHz, $CDCl_3$): 12.45 and 13.64 (2C, 2CH_3CH$_2$O), 14.03 (CH_3C), 24.00 (CH_3C=C), 60.20, 60.32 (2C, 2CH$_3$$CH_2$O), 97.15 (CH=CO), 151.53 (CH=C), 151.58 (CH=*C*-O), 158.90 (CH=*C*), 164.34 (N-*C*=N), 168.03 and 171.06 ppm (2C, 2*C*=O); ν_{max}: 3238 (NH) and 1700 cm^{-1} (C=O); MS (EI): m/z 282 (M$^+$), 209, 164 and 135.

3.2.2. *Diethyl 2-(1-(5-methylisoxazol-3-ylamino)propylidene)malonate* (**1c**)

δ_H (300 MHz, $CDCl_3$): 1.22 (3H, t, *J* 7.42 Hz, CH_3CH$_2$), 1.31 (6H, m, 2CH_3CH$_2$O), 2.40 (3H, s, CH_3C-O), 2.60 (2H, q, *J* 7.42 Hz, CH$_3$CH_2), 4.24 (4H, m, 2CH$_3$CH_2O), 5.72 (1H, s, C*H*=C-O) and 10.10 ppm (1H, s, N*H*); δ_C (75 MHz, $CDCl_3$): 12.25, 13.10 (2C, 2CH_3CH$_2$O), 12.50 (CH$_3$$CH_2$C), 14.21 ($CH_3$C), 26.55 (CH$_3$$CH_2$C), 60.35, 60.45 (2C, 2CH$_3$$CH_2$O), 98.04 (CH=CO), 150.10 (CH=C), 151.51 (CH=*C*-O), 159.07 (CH=*C*), 163.50 (N-*C*=N), 167.58 and 170.70 ppm (2C, 2*C*=O); ν_{max}: 3236 (NH) and 1700 cm^{-1} (C=O); MS (EI): m/z 296 (M$^+$), 223, 178 and 149.

3.2.3. *Diethyl 2-(1-(5-methylisoxazol-3-ylamino)(phenyl)methylene)malonate* (**1d**)

δ_H (300 MHz, $CDCl_3$): 1.21 (6H, m, 2CH_3CH$_2$O), 2.41 (3H, s, CH_3), 4.20 (4H, m, 2CH$_3$CH_2O), 5.91 (1H, s, C*H*=C-O), 7.50 (5H, m, ArH) and 11.30 ppm (1H, s, N*H*); δ_C (75 MHz, $CDCl_3$): 12.30, 12.87 (2C, 2CH_3CH$_2$O), 14.50 (CH_3C), 60.45, 60.50 (2C, 2CH$_3$$CH_2$O), 96.71 (*C*H=CO), 128.40, 130.81, 131.10, 136.24 (6C, ArC), 151.52 (CH=*C*-O), 157.55 (C_6H_5C=C), 159.14 (CH=*C*), 166.08 (N-*C*=N), 167.20 and 170.54 ppm (2C, 2*C*=O); $\nu_{max.}$ 3242 (NH) and 1700 cm^{-1} (C=O); MS (EI): m/z 344 (M$^+$), 271, 126.

3.3. Preparation of Isoxazolopyrimidines 2: General Procedure

A solution of 5-methylisoxazol-3-amine (0.49 g, 5 mmol) and diethyl ethoxymethylenemalonate derivative (5 mmol) in dry xylene (20 mL) was refluxed for 48 h. The solvent was removed and the residue was purified by column chromatography over silica gel (eluent: ethyl acetate/cyclohexane: 1/3) to obtain **2**.

3.3.1. *Ethyl 2-methyl-7-oxo-7H-isoxazolo[2,3-a]pyrimidine-6-carboxylate* (**2a)**

δ_H (300 MHz, $CDCl_3$): 1.32 (3H, t, *J* 7.18 Hz, CH_3CH$_2$O), 2.40 (3H, s, CH_3), 4.20 (2H q, *J* 7.18 Hz, CH$_3$CH_2O), 6.35 (1H, s, C*H*=C-O) and 8.26 ppm (1H, s, C*H*=C); δ_C (75 MHz, $CDCl_3$): 12.10 (1C, CH_3CH$_2$O), 14.19 (*C*H$_3$C), 61.68 (1C, CH$_3$$CH_2$O), 99.78 (*C*H=C-O), 111.74 (CH=*C*), 150.90 (CH$_3$*C*), 153.46 (*C*H=C), 165.28 (N-*C*=N), 165.60 (N-*C*=O), and 168.23 ppm (*C*O); ν_{max}: 1680 (C=O) and 1735 cm^{-1} (C=O ester); MS (EI): m/z 222 (M$^+$), 177 and 109.

3.3.2. *Ethyl 2,5-dimethyl-7-oxo-7H-isoxazolo[2,3-a]pyrimidine-6-carboxylate* (**2b**)

δ_H (300 MHz, $CDCl_3$): 1.31 (3H, q, *J* 7.18 Hz, CH_3CH$_2$O), 2.41 (s, 3H, CH_3CO), 2.51 (s, 3H,CH_3C=C), 4.20 (2H, q, *J* 7.18 Hz, CH$_3$CH_2O) and 6.35 ppm (1H, s, C*H*=C-O); δ_C (75 MHz, $CDCl_3$): 12.10 (CH$_3$$CH_2$O), 14.52 (CH$_3$C-O), 26.90 (CH$_3$C=C), 60.68

(CH_3CH_2O), 99.78 (*C*H=C-O), 111.74 (CH=*C*), 150.90 (CH_3C), 153.46 (*C*H=C), 165.28 (N-*C*=N), 165.60 (N-*C*=O) and 168.23 ppm (*C*O); ν_{max}: 1680 (C=O) and 1738 cm^{-1} (C=O ester); MS (EI): m/z 236 (M^+), 191, 177 and 123.

3.3.3. *Ethyl 5-ethyl-2-methyl-7-oxo-7H-isoxazolo[2,3-a]pyrimidine-6-carboxylate* (**2c**)

δ_H (300 MHz, $CDCl_3$): 1.20 (3H, t, *J* 7.50 Hz, CH_3CH_2), 1.30 (3H, t, *J* 7.18 Hz, CH_3CH_2O), 2.55 (s, 3H, CH_3), 2.71 (2H, q, *J* 7.50 Hz, CH_3CH_2), 4.21 (2H, q, *J* 7.18 Hz, CH_3CH_2O) and 6.36 ppm (1H, s, C*H*=C-O); δ_C (75 MHz, $CDCl_3$): 12.93 (CH_3CH_2O), 13.11 (CH_3C=C), 14.17 (CH_3C), 29.88 (CH_3CH_2C), 61.73 (CH_3CH_2O), 99.84 (*C*H=C-O), 111.67 (CH=*C*), 151.13 (1C, CH_3C), 153.76 (*C*H=C), 165.26 (N-*C*=N), 168.00 (N-*C*=O) and 169.67 ppm (*C*O); ν_{max}: 1680 (C=O) and 1736 cm^{-1} (C=O ester); MS (EI): m/z 250 (M^+), 204, 183 and 137.

3.3.4. *Ethyl 2-methyl-7-oxo-5-phenyl-7H-isoxazolo[2,3-a]pyrimidine-6-carboxylate* (**2d**)

δ_H (300 MHz, $CDCl_3$): 1.05 (3H, t, *J* 7.18 Hz, CH_3CH_2O), 2.55 (3H, s, 3H, CH_3), 4.15 (2H q, *J* 7.18 Hz, CH_3CH_2O), 6.41 (1H, s, C*H*C-O) and 7.51 ppm (5H, m, ArH); δ_C (75 MHz, $CDCl_3$): 13.06 (CH_3CH_2O), 13.63 (CH_3), 61.70 (CH_3CH_2O), 100.26 (CH=C-O), 112.05 (CH=*C*), 128.02, 128,41, 129,97,138.08 (6C, ArC), 151.20 (CH_3C), 153.61 (*C*H=C), 163.94 (N-*C*=N), 165.61 (N-*C*=O) and 168.37 ppm (*C*O); ν_{max}: 1680 (C=O) and 1740 cm^{-1} (C=O ester); MS (EI): m/z 298 (M^+), 253, 226 and 182.

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