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REACTIONS OF 3-AMINO-5-METHYLISOXAZOLE WITH ENOL ETHERS: SYNTHESIS OF NEW ISOXAZOLYLENAMINES DERIVATIVES AND SUBSTITUTED ISOXAZOLO[2,3-*a*]PYRIMIDINONES

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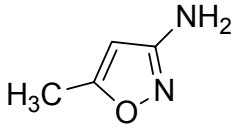
A new series of isoxazolylenamines and substituted isoxazolo[2,3-*a*]pyrimidinones were prepared via condensation of ethoxymethylenemalonate **2a-d** and ethoxymethylenecyanoacetate **2e-h** with 3-amino-5-methylisoxazole **1**. When reactions were carried out under reflux in xylene, the thermal cyclisation of isoxazolylenamines intermediates **3a-d** afforded exclusively the isoxazolo-[2,3-a]pyrimidinones **4a-d**. All the synthesized compounds were characterized by elemental analysis, MS, IR and NMR spectrometry.

INTRODUCTION

Isoxazoles are a major class of five-membered nitrogen heterocycles. They are considered important core components in natural products, and are valuable molecules of medicinal interest.[1] The isoxazole provides a valuable scaffold in medicinal chemistry as well as a useful synthon in organic synthesis.[2] In addition, the aromatic isoxazole displays wide ranging biological activities, including pharmacological applications such as hypoglycemic,[3] anticancer,[3,4] antimicrobial[5], antitumor[6] analgesic,[3a-c,7] antiviral,[8] antiinflammatory,[9] antibacterial,[10] and HIV-inhibitory[11] as well as herbicidal and insecticidal activities.[12]

In the present work and in connection with our synthetic investigations directed to an effective means of preparing new molecular scaffords,[13] a detailed study was carried out on the reaction of 3-amino-5-methyl-isoxazole **1** with electrophilic reagents such as ethoxymethylenecyanoacetate (EMCA) and ethoxymethylene-malonate (EMM), of type **2**, in order to generate new isoxazolylenamine and isoxazolo[2,3-*a*]pyrimidinone derivatives.



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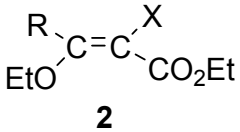

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The enol ethers; ethoxymethylenemalonate (EMM) and ethoxymethylenecyanoacetate (EMCA) **2**,[14, 15] are well known electrophilic reagents and are extremely valuable starting materials for synthesis of the nitrogen containing heterocyclic ring systems.[16-19] The chemistry of enol ethers indicates that this functional group is susceptible to nucleophilic substitution, that usually occurs with elimination of the ethoxy group.[20]

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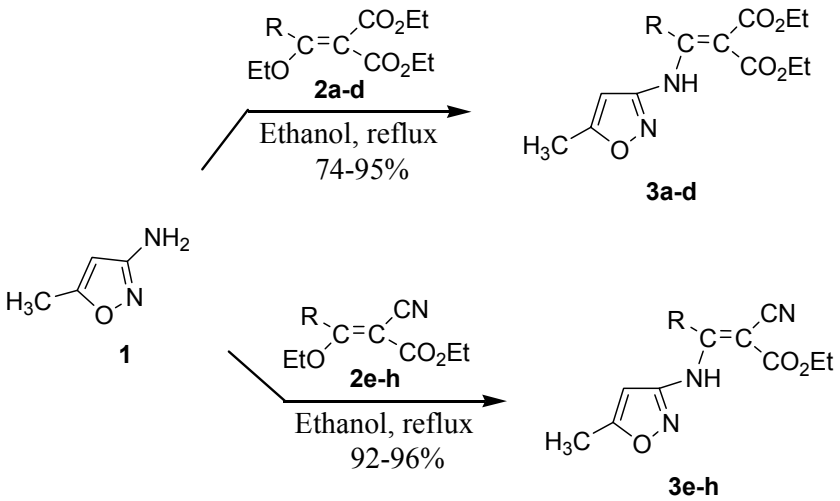
To our knowledge, the synthesis of the new isoxazolylenamines **3a-h** and isoxazolo[2,3-*a*]pyrimidinones **4a-d** derivatives cited in this paper has not been reported in the literature.

RESULTS AND DISCUSSION

The reaction of 3-amino-5-methylisoxazole **1** with ethoxymethylenemalonates (EMM) **2a-d** and ethoxymethylenecyanoacetates (EMCA) **2e-h** was performed in refluxing ethanol, to give the corresponding isoxazolylenamines **3a-h** in excellent yields (74-96%) (Scheme 1).

The amino group of 3-amino-5-methylisoxazole is the nucleophilic site that attacks the methylene carbon of the ethoxy group of the enol ether leading to the formation of isoxazolylenamines **3a-h**.



Entry	a	b	c	d	e	f	g	h
R	H	Me	Et	Ph	H	Me	Et	Ph

Scheme 1 – Synthesis of isoxazolylenamines **2a-d** and **2e-h**.

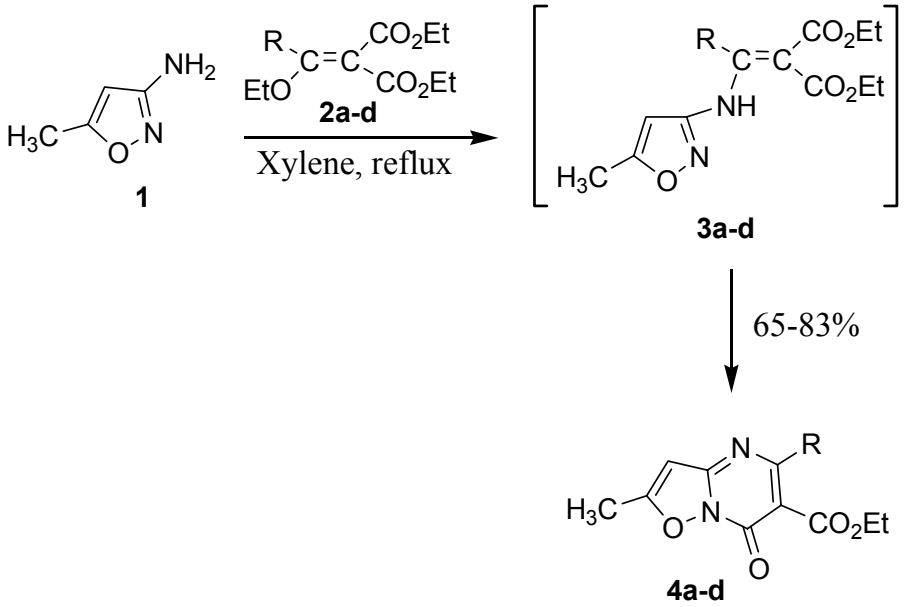
The ^{1}H NMR spectra of isoxazolylenamines **3a-d** showed the N–H protons as broad singlets in the range 10.1-11.3 ppm (doublet for **3a**) and C(4)–H protons of the isoxazole ring in the range 4.9-6.7 ppm. The IR spectra of compounds **3a-d** showed absorption bands for the C=O ester groups in the range 1700-1725 cm^{-1} and for N–H at 3290-3300 cm^{-1}. Similarly, the ^{13}C NMR spectra showed the expected signals. The chemical shifts of the carbon C-4 in the compounds **3a-d** appeared in the range 95.0- 98.0 ppm, whereas the methyl group was observed in the range 12.2-14.5 ppm. The two carbonyl carbons in the carboethoxy groups showed two signals in the range 167.5-171.7 ppm. The two signals at 150.0-157.8 ppm and 157.6-159.0 ppm are attributed to the C-3 and C-5 of the isoxazole ring, respectively.

The ^{1}H NMR spectra of isoxazolylenamines **3e-h** showed the N–H protons as broad singlets in the range 10.5-11.8 ppm (doublet for **3e**) and C(4)–H protons of the isoxazole ring in the range 4.6-5.9 ppm. The IR spectra of compounds **3e-h** showed absorption bands for the C=O ester group in the range 1700-1725 cm^{-1}. The absorption band for the CN group was observed at 2220 cm^{-1} and for N–H group appeared in the range 3290-3300 cm^{-1}. In the ^{13}C NMR spectrum of the target isoxazolylenamines **3e-h**, the positions of the different carbon signals were approximately the same as those observed for compounds **3a-d** (C-3: 151.8-158.6 ppm, C-4: 93.4-97.0 ppm, C-5: 157.6-158.6 ppm, one signal C=O: 170.2-173.2 ppm). The carbon signals for the isoxazolylenamines **3e-h** in the range 166.4-117.1 ppm were attributed to the cyano group. The mass spectra of all the isoxazolylenamines showed [M$^{+\cdot}$] ion peaks which were consistent to their molecular formulas.

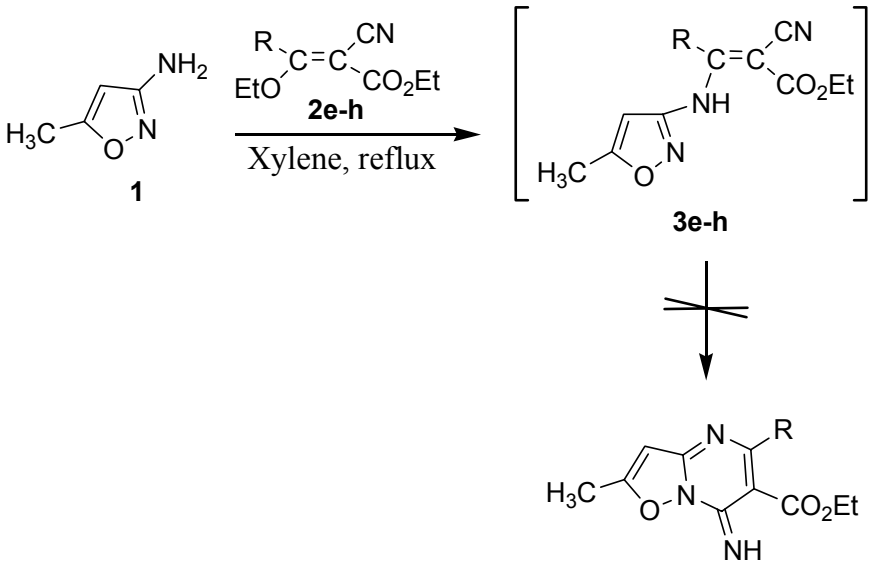
When the reaction of 3-amino-5-methylisoxazole **1** with ethoxymethylene-malonate (EMM) **2a-d** was performed in reluxing xylene, the intermediates isoxazolylenamines **3a-d** formed *in situ*, were converted to the corresponding isoxazolo[2,3-*a*]pyrimidinones **4a-d** by intramolecular cyclisation in good to excellent yields (65-83%) as depicted in Scheme 2. The compounds **3a-d** proved to be a key intermediates and served for the

formation of several new fused heterocycles related to isoxazolopyrimidine ring system (Scheme 2). In this step, the nitrogen atom of the isoxazole ring acts as a nucleophile which attacks one of the carbonyl groups leading to cyclisation and the formation of the target compounds **4a-d** as outlined in Scheme 2.

However, under the same conditions, the reaction of 3-amino-5-methylisoxazole with ethoxy-methylenecyanoacetate (EMCA) afforded only the isoxazolylenamines **3e-f**. In other words, cyclisation of the isoxazolylenamines **3e-f** was unsuccessful and the latter derivatives failed to cyclize in the desired manner (Scheme 3).



Scheme 2 – Synthetic pathway for the preparation of isoxazolo[2,3-a]pyrimidinones **4a-d**.



Scheme 3 – Reactivity of **1** with ethoxymethylenecyanoacetate **2e-h**.

The spectral data of isoxazolo[2,3-a]pyrimidinones **4a-d** are in full agreement with the assumed structures. In the ^{1}H NMR spectra all the proton signals of the principal structural fragments of the molecule were retained with disappearance of the N–H group and one the two ethoxy groups' signals. The IR spectra of isoxazolo[2,3-a]pyrimidinones **4a-d** revealed the presence of the absorption bands of the C=O lactam in the region 1685-1700 cm^{-1}, the C=O ester

group in the range 1740-1745 cm^{-1} and the absence of NH group. The ^{13}C NMR spectra exhibited the expected resonances at 99.7-100.2 ppm for (C-H of isoxazole ring), C=O of the lactam group at 165.6-168.0 ppm and C=O of the ester group at 168.2-169.6 ppm. The three signals at 150.9-151.2 ppm, 111.6-112 ppm and 165.3-163.9 ppm are due to C-2, C-3 and C-9 of the pyrimidine ring, respectively. The presence of molecular ion peak in mass spectra, the signal due to C-H of isoxazole ring in ^{13}C NMR and the absence of N-H absorption in IR spectra confirmed the proposed structures of target products **4a-d**.

The table below indicates reaction times, yields and melting points of isoxazolylenamines **3a-h** and isoxazolo[2,3-a]pyrimidinones **4a-d** obtained in this study.

Table 1

Reaction times, yields and melting points of the isoxazolylenamines **3a-h** and the isoxazolo[2,3-a]pyrimidinones **4a-d**

Entry	R	X	Reaction time (h)	Yield (%)	Mp (°C)
3a	H	CO_2Et	6	95	114-115
3b	Me	CO_2Et	36	85	Oily
3c	Et	CO_2Et	36	78	Oily
3d	Ph	CO_2Et	36	74	Oily
3e	H	CN	1.5	96	116-117
3f	Me	CN	2.5	93	98-99
3g	Et	CN	4	92	94-95
3h	Ph	CN	6	92	164-165
4a	H	CO_2Et	48	83	145-146
4b	Me	CO_2Et	48	65	176-177
4c	Et	CO_2Et	48	75	214-215
4d	Ph	CO_2Et	48	80	217-218

The spectral data IR, ^1H NMR, ^{13}C NMR, mass and elemental analyses were used to confirm the structures of isoxazolylenamines **3a-h** and isoxazolo[2,3-*a*]pyrimidinones **4a-d**. Physical properties, molecular ion peaks and elemental analysis are presented in the Experimental section. The extension of this strategy to other enol ethers is under progress.

EXPERIMENTAL

The 3-amino-5-methylisoxazole and solvents were purchased from commercial suppliers and used without further purification. Melting points were taken on a Reichert-Heizbank apparatus and are uncorrected. IR was recorded on a Perkin-Elmer 298. Mass Spectra were obtained by GC/MS with electron impact ionization using a 5971 Hewlett Packard instrument at 70 eV. ^1H and ^{13}C spectra were recorded on a Bruker AC 300 Spectrometer (300 MHz and 75 MHz for ^1H and ^{13}C, respectively). Chemical shifts are expressed in ppm relative to TMS. Microanalyses were performed on a Perkin-Elmer 240-B microanalyser.

General procedure for the synthesis of isoxazolylenamines 3a-h

An ethanol (20 ml) solution of 3-amino-5-methylisoxazole **1** (5 mmol) and diethyl ethoxymethylenemalonate **2a-d** (5 mmol) or ethoxymethylenecyanoacetate (5 mmol) **2e-h** was heated under reflux, until the reaction was completed. The solvent was then removed under reduced pressure, and the residue was washed with ether. The enamines **3a-d** were purified by column chromatography over silica gel (eluant: AcOEt/Cylohexane: 1/5) and the enamines **3e-h** were recrystallized from hexane.

Diethyl 2-(5-methylisoxazol-3-ylamino)methylenemalonate **(3a):** MS (EI): m/z = 268 ($M^{+\cdot}$), 177, 162, 134, 120; ^1H NMR ($CDCl_3$) δ 1.3 (6H, m, 2 C<u>H</u>$_3$CH$_2$-O); 2.4 (3H, s, CH_3); 4.2 (4H, m, 2 CH_3C<u>H</u>$_2$-O); 5.9 (1H, s, C<u>H</u>=C-O); 8.4 (1H, d, NH-C<u>H</u>=C, J = 13.7 Hz); 10.7 (1H, d, N<u>H</u>-CH=C, J = 13.7 Hz); ^{13}C NMR ($CDCl_3$): δ 12.5, 13.8, 14.0, 60.2, 60.6, 95.0, 150.9, 151.5, 159.1, 164.6, 168.1, 171.1; I.R. ($CHCl_3$) $\overline{\nu}$: 3240, 1725; Anal. Calcd. for $C_{12}H_{16}N_2O_5$: C, 53.73; H, 5.97; N, 10.44%. Found: C, 53.63; H, 5.88; N, 10.14%.

Diethyl 2-(1-(5-methylisoxazol-3-ylamino)ethylidene)malonate **(3b):** MS (EI): m/z = 282 ($M^{+\cdot}$), 209, 164, 135; ^1H NMR ($CDCl_3$,); δ 1.3 (6H, m, 2 C<u>H</u>$_3$CH$_2$-O); 2.3 (3H, s); 2.4 (3H, s); 4.2 (4H, m, 2 CH_3C<u>H</u>$_2$-O); 5.9 (1H, s, C<u>H</u>=); 11.3 (1H, s, NH); ^{13}C NMR ($CDCl_3$): δ 13.6, 14.0, 14.2, 23.5, 60.2, 61.0, 97.1, 150.9, 151.5, 158.9, 164.3, 168.0, 171.0; I.R. ($CHCl_3$) $\overline{\nu}$: 3290, 1720; Anal. Calcd. for $C_{13}H_{18}N_2O_5$: C, 55.32; H, 6.38; N, 9.93%. Found: C, 55.22; H, 5.77; N, 9.88%.

Diethyl 2-(1-(5-methylisoxazol-3-ylamino)propylidene)malonate **(3c):** MS (EI): m/z = 296 ($M^{+\cdot}$), 223, 178, 149; ^1H NMR ($CDCl_3$,); δ 1.2 (3H, t, C<u>H</u>$_3$CH$_2$-, J = 7.2Hz); 1.3 (m, 6H, 2 C<u>H</u>$_3$CH$_2$-O); 2.4 (s, 3H); 2.6 (q, 2H, CH_3C<u>H</u>$_2$-, J 7.2Hz); 4.2 (4H, m, 2 CH_3C<u>H</u>$_2$-O); 6.7 (1H, s, C<u>H</u>=); 10.1 (1H, s, NH); ^{13}C NMR ($CDCl_3$): δ 12.7, 13.6, 13.9, 14.3, 26.5, 60.4, 61.0, 98.0, 150.0, 152.2, 159.0, 163.5, 167.5, 170.7; I.R. ($CHCl_3$) $\overline{\nu}$: 3300, 1700; Anal. Calcd. for $C_{14}H_{20}N_2O_5$: C, 56.75; H, 6.75; N, 9.46%. Found: C, 56.64; H, 6.65; N, 9.20%.

Diethyl 2-((5-methylisoxazol-3-ylamino)(phenyl)methylene)malonate **(3d):** MS (EI): m/z = 344 ($M^{+\cdot}$), 271, 226; ^1H NMR ($CDCl_3$) δ 1.2 (6H, m, 2 C<u>H</u>$_3$CH$_2$-O); 2.4 (3H, s); 4.2 (4H, m, 2 CH_3C<u>H</u>$_2$-O); 4.9 (1H, s, C<u>H</u>=); 7.5 (5H, m); 11.3 (1H, s,

NH); ^{13}C NMR ($CDCl_3$) δ 12.5, 14.0, 14.1, 61.4, 61.5, 85.9, 93.3, 93.7, 114.5, 116.3, 151.3, 151.7, 158.2, 158.4, 163.2, 166.4, 171.4, 171.7; I.R. ($CHCl_3$) $\overline{\nu}$: 3300, 1725; Anal. Calcd. for $C_{18}H_{20}N_2O_5$: C, 62.79; H, 5.81; N, 8.14%. Found: C, 62.68; H, 5.70; N, 7.81%.

Ethyl 2-cyano-3-(5-methylisoxazol-3-ylamino)acrylate **(3e):** MS (EI): m/z = 221 ($M^{+\cdot}$), 162, 134, 120; ^{1}H NMR ($CDCl_3$) δ 1.4 (3H, t, C<u>H</u>$_3$CH$_2$-O, J 8Hz); 2.4 (3H, s); 4.3 (2H, q, CH$_3$C<u>H</u>$_2$-O, J 8Hz); 5.9 (1H, s, C<u>H</u>=); 7.9 (1H, d, C<u>H</u>=C, J 13Hz); 10.5 (1H, d, NH, J 13Hz); ^{13}C NMR ($CDCl_3$) δ 12.7, 14.1, 14.3, 61.7, 93.4, 116.4, 151.8, 158.3, 166.6, 171.9; I.R. ($CHCl_3$) $\overline{\nu}$: 3290, 2220, 1725; Anal. Calcd. for $C_{10}H_{11}N_3O_3$: C, 54.29; H, 4.97; N, 19.00%. Found: C, 54.18; H, 4.86; N, 18.84%.

Ethyl 2-cyano-3-methyl-3-(5-methyl-isoxazol-3-ylamino)acrylate **(3f):** MS (EI): m/z = 235 ($M^{+\cdot}$), 189, 148, 134; ^{1}H NMR ($CDCl_3$) δ 1.4 (3H, t, C<u>H</u>$_3$CH$_2$-O, J 8Hz); 2.4 (3H, s); 2.6 (3H, s); 4.3 (2H, q, CH$_3$C<u>H</u>$_2$-O, J 8Hz); 5.9 (1H, s, C<u>H</u>=); 11.7 (1H, s, N<u>H</u>); ^{13}C NMR ($CDCl_3$): δ 12.3, 14.0, 20.4, 61.2, 78.0, 96.8, 117.1, 157.8, 167.4, 167.7, 170.7; I.R. ($CHCl_3$) $\overline{\nu}$: 3300, 2220, 1700; Anal. Calcd. for $C_{11}H_{13}N_3O_3$: C, 56.17; H, 5.53; N, 17.87%. Found: C, 56.04; H, 5.41; N, 17.61%.

Ethyl 2-cyano-3-ethyl-3-(5-methyl-isoxazol-3-ylamino)acrylate **(3g):** MS (EI): m/z = 249 ($M^{+\cdot}$), 188, 160, 148, 176; ^{1}H NMR ($CDCl_3$) δ 1.3 (3H, t, C<u>H</u>$_3$CH$_2$-, J 7.2Hz); 1.4 (3H, t, C<u>H</u>$_3$CH$_2$-O, J 8Hz); 2.4 (3H, s); 2.45 (2H, q, CH$_3$C<u>H</u>$_2$-, J 7.2Hz); 4.2 (2H, q, CH$_3$C<u>H</u>$_2$-O, J 8Hz); 5.9 (1H, s, C<u>H</u>=); 11.7 (1H, s, N<u>H</u>); ^{13}C NMR ($CDCl_3$) δ 12.2, 12.5, 14.2, 26.2, 61.4, 77.4, 97.0, 117.0, 157.6, 168.2, 170.9, 173.2; I.R. ($CHCl_3$) $\overline{\nu}$: 3290, 2220, 1725; Anal. Calcd. for $C_{12}H_{15}N_3O_3$: C, 57.83; H, 6.02; N, 16.86%. Found: C, 57.15; H, 5.92; N, 16.61%.

Ethyl 2-cyano-3-(5-methylisoxazol-3-ylamino)-3-phenylacrylate **(3h):** MS (EI): m/z = 297 ($M^{+\cdot}$), 224, 210, 196; ^{1}H NMR ($CDCl_3$) δ 1.4 (3H, t, C<u>H</u>$_3$CH$_2$-O, J 8Hz); 2.4 (3H, s); 4.4 (2H, q, CH$_3$C<u>H</u>$_2$-O, J 8Hz); 4.6 (1H, s, C<u>H</u>=); 7.5 (5H, m); 11.8 (1H, s, N<u>H</u>); ^{13}C NMR ($CDCl_3$): δ 11.7, 12.5, 14.2, 61.7, 79.8, 95.8, 96.1, 116.8, 128.3, 129.2, 131.2, 131.6, 158.6, 166.5, 167.4, 170.2; I.R. ($CHCl_3$) $\overline{\nu}$: 3290, 2220, 1725; Anal. Calcd. for $C_{16}H_{15}N_3O_3$: C, 64.64; H, 5.05; N, 14.14%. Found: C, 64.52; H, 4.92; N, 13.92%.

General procedure for the synthesis of isoxazolo[2,3-a]pyrimidinones 4a-d

To a solution of 3-amino-5-methylisoxazole **1** (5 mmol) in xylene (15 ml), ethoxy-methylenemalonate **2a-d** (5 mmol) was added and refluxed for 48 h. The solvent was removed and the residue was purified by column chromatography over silica gel (eluant: AcOEt/Cyclohexane:1/3) to yield isoxazolo[2,3-a]pyrimidinones **4a-d**.

Ethyl 5-methyl-7-oxo-7H-isoxazolo[2,3-a]pyrimidine-6-carboxylate **(4a):** MS (EI): m/z = 222 ($M^{+\cdot}$), 177, 163, 109; ^{1}H NMR ($CDCl_3$) δ 1.3 (3H, t, C<u>H</u>$_3$CH$_2$-O, J 7.18Hz); 2.4 (3H, s, CH$_3$); 4.2 (2H, q, CH$_3$C<u>H</u>$_2$-O, J 7.18Hz); 6.3 (1H, s, C<u>H</u>=C-O), 8.2 (1H, s, CH=C); ^{13}C NMR ($CDCl_3$) δ 12.1, 14.2, 61.7, 99.8, 111.7, 150.9, 153.4, 165.3, 165.6, 168.2; I.R. ($CHCl_3$) $\overline{\nu}$: 1680, 1735; Anal. Calcd. for $C_{10}H_{10}N_2O_4$: C, 54.05; H, 4.51; N, 12.61%. Found: C, 53.99; H, 4.48; N, 12.57%.

Ethyl 2,5-dimethyl-7-oxo-7H-isoxazolo-[2,3-a]pyrimidine-6-carboxylate **(4b):** MS (EI): m/z = 236 ($M^{+\cdot}$), 191, 177, 123; ^{1}H NMR ($CDCl_3$) δ 1.3 (3H, t, C<u>H</u>$_3$CH$_2$-O, J 8Hz); 2.4 (3H, s); 2.5 (3H, s); 4.2 (2H, q, CH$_3$C<u>H</u>$_2$-O, J 8Hz); 6.3 (1H, s, C<u>H</u>=); ^{13}C NMR ($CDCl_3$) δ 12.1, 14.1, 26.9, 61.6, 99.7, 111.7, 150.9, 153.4, 165.2, 165.6, 168.2; I.R. ($CHCl_3$) $\overline{\nu}$: 1700, 1740; Anal. Calcd. for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.08; N, 11.86%. Found: C, 55.82; H, 4.91; N, 11.73%.

Ethyl 5-ethyl 2-methyl-7-oxo-7H-isoxazolo[2,3-a]pyrimidine-6-carboxylate **(4c):** MS (EI): m/z = 250 ($M^{+\cdot}$), 204, 183, 137; ^{1}H NMR ($CDCl_3$) δ 1.3 (3H, t, C<u>H</u>$_3$CH$_2$-O, J 8Hz); 1.2 (3H, t, C<u>H</u>$_3$CH$_2$-, J 7.2Hz); 2.5 (3H, s); 2.7 (2H, q, CH$_3$C<u>H</u>$_2$-, J 7.2Hz); 4.2 (2H, q, CH$_3$C<u>H</u>$_2$-O, J 8Hz); 6.4 (1H, s, C<u>H</u>=); ^{13}C NMR ($CDCl_3$) δ 12.9, 13.1, 14.1, 29.8, 61.7, 99.8, 111.6, 151.1, 153.7, 165.2, 168.0, 169.6; I.R. ($CHCl_3$) $\overline{\nu}$: 1685, 1745; Anal. Calcd. for $C_{12}H_{14}N_2O_4$: C, 57.60; H, 5.60; N, 11.20%. Found: C, 57.51; H, 5.52; N, 10.99%.

Ethyl 5-phenyl 2-methyl-7-oxo-7H-isoxazolo[2,3-a]pyrimidine-6-carboxylate **(4d):** MS (EI): m/z = 298 ($M^{+\cdot}$), 253, 226, 182; ^{1}H NMR ($CDCl_3$) δ 1.0 (3H, t, C<u>H</u>$_3$CH$_2$-O, J 8Hz); 2.5 (3H, s); 4.1 (2H, q, CH$_3$C<u>H</u>$_2$-O, J 8Hz); 6.4 (1H, s, C<u>H</u>=); 7.5 (5H, m); ^{13}C NMR ($CDCl_3$): δ 13.0, 13.6, 61.7, 100.2, 112.0, 128.0, 128.4, 129.9,138.0, 151.2, 153.6, 163.9, 165.6, 168.3; I.R. ($CHCl_3$) $\overline{\nu}$: 1685, 1740; Anal. Calcd. for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.69; N, 9.39%. Found: C, 64.34; H, 4.58; N, 9.23%.

CONCLUSIONS

In conclusion, we have reported a convenient, simple, and an efficient route to new isoxazolylenamines **3a-h** and isoxazolo[2,3-*a*]pyrimidinones **4a-d** which were synthesized from 3-amino-5-methylisoxazole and enol ethers **2** in good to excellent yields. The structures of the new synthesized compounds were confirmed by mass spectra, NMR spectroscopy, IR and elemental analysis data. All isolated products were expected to have potential interesting biological activities.

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