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Features of 3-amino-5-methylisoxazole in heterocyclizations involving pyruvic acids

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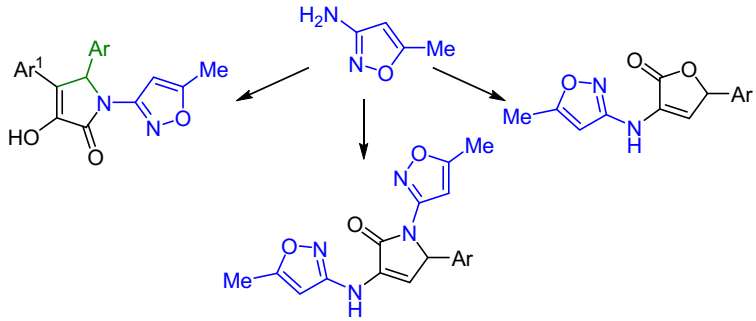


The chemical properties of 3-amino-5-methylisoxazole in the reactions involving pyruvic acid derivatives are reported. The multicomponent condensation of 3-amino-5-methylisoxazole, aromatic aldehyde, and pyruvic acid was not effective while the treatment of the starting amine with pyruvic acid derivatives led to suitable synthetic procedures for selective synthesis of furanones and pyrrolones. It was established that only NH_2-nucleophilic center of 3-amino-5-methylisoxazole takes part in the heterocyclizations with pyruvic acid derivatives.

Keywords: 3-amino-5-methylisoxazole, furanones, pyrrolones, pyruvic acids, heterocyclization.

The cascade hetorocyclizations involving α-aminoazoles and carbonyl compounds is a simple and efficient way for the construction of different five- and six-membered heterocycles. Among them, there are aza-Diels–Alder,[1–4] Biginelli,[4,5] Doebner, Povarov reactions,[6,7] etc.[4] The most well-studied amines in such heterocyclizations are different 3(5)-aminopyrazoles, 2-aminobenzimidazoles, 3-amino-1,2,4-triazoles, and 5-aminotetrazoles.[8–13] However, the α-aminoazoles based on isoxazole moiety had not been well studied in such reactions before our research:[14–18] there are significantly fewer publications devoted to the treatments of 5-amino-3-methylisoxazole[1,19–27] and 3-amino-5-methylisoxazole[6,28–33] in one-pot reactions.

Concerning 5-amino-3-methylisoxazole, it was shown that its two- and multicomponent heterocyclizations in the most cases led to isoxazolopyridines (Fig. 1). It was found by our group that 5-amino-3-methylisoxazole was not stable in two- and multicomponent reactions with pyruvic acid and its arylidene derivatives while two-component condensations with ethyl 4-aryl-2-oxobut-3-enoate in the presence of $Sc(OTf)_3$ gave not only isoxazolo[5,4-*b*]-pyridines **I**, but also both di- and tetrahydropyridines **II** and **III**.[18]

Thus, 5-amino-3-methylisoxazole usually reacts as 1,3-bi-nucleophile involving exocyclic amino group and position C-4 in the isoxazole moiety as reaction centers. It is also

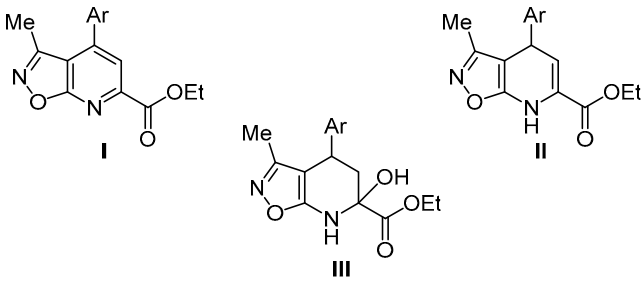


Figure 1. Some products of heterocyclization involving 5-amino-3-methylisoxazole.

worth noting that two-component reactions between 5-amino-isoxazole and carbonyl compounds where 5-amino-isoxazole exhibits properties of C-mononucleophile are described,[26,34–40] as well as its condensations with the formation of imides.[20]

On the other hand, the literature data on the behavior of 3-amino-5-methylisoxazole in such heterocyclizations are ambiguous. For instance, its reaction with mercaptoacetic acid and aromatic aldehydes was described as a step-by-step process leading to the formation of thiazolidinones **IV**[32] (Fig. 2), while similar condensation with isatin as carbonyl component gave isoxazolo[2,3-*c*][1,3,5]thiadiazepinones **V**.[33] Among the treatments affecting only amino group there are not only the reactions leading to thiazolidinone formation: the condensation of 3-amino-5-methylisoxazole, aromatic aldehyde, and pyruvates in TMSCl/DMF gave 3-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones **VI**;[41] the product of the reaction of aryl isothiocyanate and 3-amino-5-methylisoxazole undergoes Boulton–Katritzky rearrangement with the opening of the isoxazole ring and formation of 1,2,4-thiadiazole moiety (compounds **VII**).[39,40]

The reactions of 3-amino-5-methylisoxazole involving both nitrogen atoms (exo- and endocyclic) without isoxazole ring opening are also described.[28–31] However, of greatest interest for our studies is the article published by Llona-Minguez et al.[6] reporting an aza-Diels–Alder cycloaddition leading to isoxazolo[2,3-*a*]pyrimidines **VIII**, structure of which was proved by X-ray studies. On the other hand, our attempts to synthesize isoxazolo[2,3-*a*]-pyrimidines by multicomponent condensation of 3-amino-5-methylisoxazole, aromatic aldehyde, and Meldrum's acid resulted in the acylation of the starting amine by the

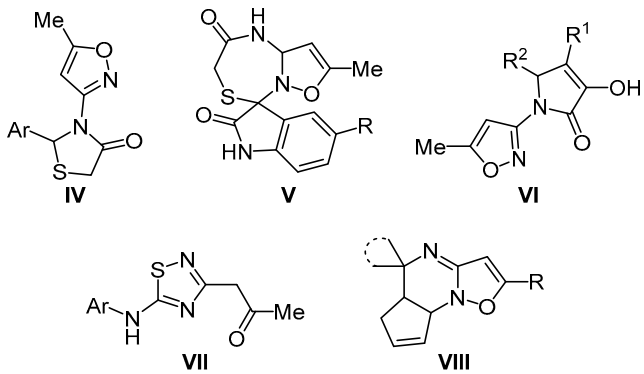


Figure 2. Some products of heterocyclization involving 3-amino-5-methylisoxazole.

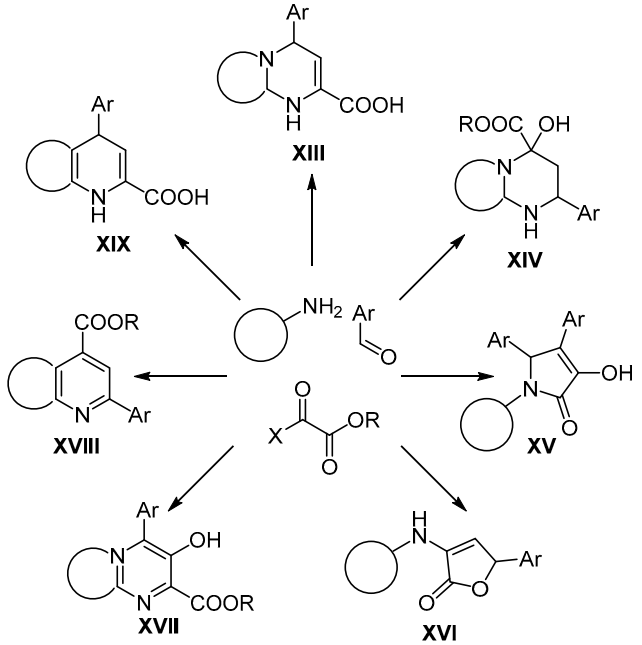


Figure 3. Reactions of α-aminoazoles, aromatic aldehydes, and pyruvic acids.

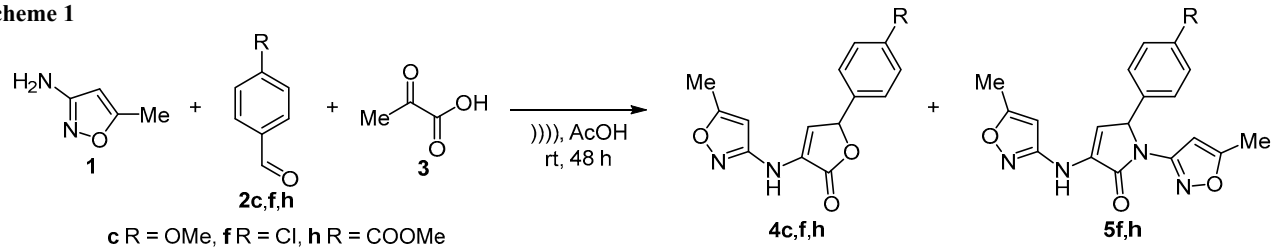
Meldrum's acid under reflux and the formation of the ylidene derivatives of aromatic aldehyde and Meldrum's / *N*,*N*-dimethylbarbituric acids at room temperature, while similar treatment of 5-amino-3-methylisoxazole gave isoxazolo[5,4-*b*]pyridines.[17] Rahmati et al.[24] described the multicomponent reaction of isatin, barbituric acid derivative, and 5-amino-3-methylisoxazole to yield isoxazolo[5,4-*b*]-dihydropyridine moiety, however the product of the same condensation involving 3-amino-5-methylisoxazole was not isolated.

The interest in the 3-amino-5-methylisoxazole as a reactant for condensations involving pyruvic acids and carbonyl compounds is connected with a variety of target compounds that have been obtained in similar experiments: the formation of several types of azoloazines **XIII**, **XIV**, furanones **XVI**, and pyrrolones **XV** has been described (Fig. 3). On the other hand, the behavior of 3-amino-5-methylisoxazole in such reactions is unclear, since it is known that some aminoisoxazoles may be unstable in acidic medium,[42] however the condensation of the selected amines with/in the presence of acids has been described.

Herein we present our recent results of the study of two- and three-component heterocyclizations of 3-amino-5-methylisoxazole with aromatic aldehydes, pyruvic acid, and its derivatives, as well as of the comparison of the chemical behavior of 3-amino-5-methyl- and 5-amino-3-methylisoxazole in such reactions.

The multicomponent reaction of 3-amino-5-methylisoxazole (**1**), pyruvic acid (**3**), and aromatic aldehyde **2** under ultrasonication in acetic acid for 48 h (the procedure used for the similar reaction earlier[4]) resulted in the formation of furanones **4** (R = OMe) or their mixtures with pyrrolones **5** (R = Cl, COOMe) (Scheme 1). The precipitate was usually contaminated by pyruvic acid which was difficult to separate from the mixture. This result in the

Scheme 1



c R = OMe, **f** R = Cl, **h** R = COOMe

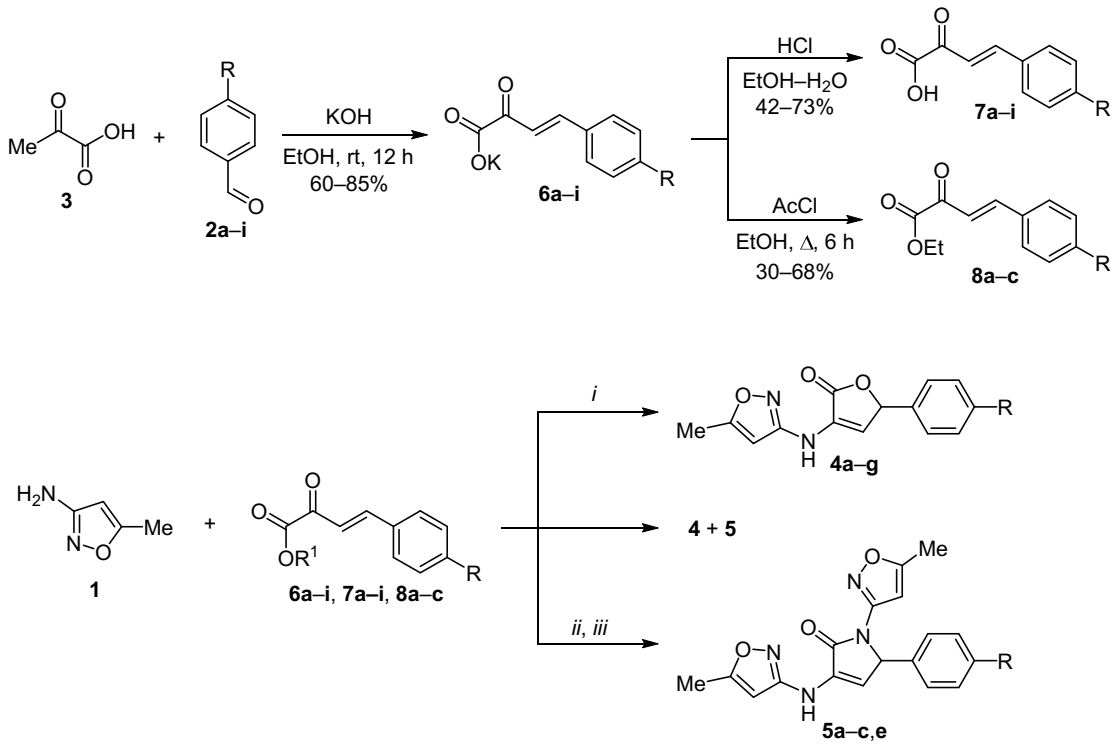
combination with the rather poor yields (<35%) forced us to look for more efficient procedures to synthesize compounds **4** and **5**.

Firstly, the scheme of the reaction was changed from multicomponent to sequential *via* preliminary synthesis of arylidene derivatives of pyruvic acid **7**.[43] Further condensation of amine **1** with unsaturated acid **7a**–**c** under ultrasonication (an ultrasonic bath) in acetic acid gave pure furanone **4a**–**c** in 37–55% yields (Scheme 2, Table 1, entries 1–3). To optimize the reaction conditions, variation of activation methods and solvents was used. We found that refluxing of the reaction mixture resulted in its tarring, however, heating in AcOH at 50–70°C for 1 h led to isolation of the same products in slightly better yields (Table 1, entries 6–8).

At the same time, 3-amino-5-methylisoxazole (**1**) is unstable in acidic medium,[42] therefore the application of methanol instead of the acetic acid can improve yields due to increasing the stability of the starting material. Indeed, using MeOH in the combination with an ultrasonic horn instead of the ultrasonic bath (to improve grinding of the reagents) reduced the reaction time from 48 to 3 h without raising the temperature (Scheme 2, Table 1, entries 12–15). This procedure showed good results for acids **7a**,**c**–**e**, however, acid **7b** was completely insoluble in MeOH, therefore the corresponding product was obtained only in acetic acid.

Our attempts to carry out the reaction of 3-amino-5-methylisoxazole (**1**) with unsaturated acid **7h** (R = COOMe) in acetic acid medium led to a mixture of compounds **4** and **5**, that could not be separated by recrystallization or column chromatography (Scheme 2, Table 1, entries 5, 9). The reaction in MeOH under ultrasonication by the horn gave the mixtures of compounds **4** and **7**; an excess of amine **1**

Scheme 2



i: **6a**–**g** ⟶ **4a**–**g**; AcOH, 25°C, 3 h, 46–66%
ii: **8a**–**c** ⟶ **5a**–**c**; $Sc(OTf)_3$ (20 mol %), MeCN, –15°C, 7 days, 23–51%
iii: **7h** ⟶ **5e**; MeOH, Δ, 45 min, 36%

2, **4** **a** R = H, **b** R = Me, **c** R = OMe, **d** R = OEt, **e** R = F, **f** R = Cl, **g** R = Br, **h** R = COOMe, **i** R = CN
5 **a** R = H, **b** R = Me, **c** R = Cl, **d** R = Br, **e** R = COOMe
6 R^1 = K; **a** R = H, **b** R = Me, **c** R = OMe, **d** R = OEt, **e** R = F, **f** R = Cl, **g** R = Br, **h** R = COOMe, **i** R = CN
7 R^1 = H; **a** R = H, **b** R = Me, **c** R = OMe, **d** R = OEt, **e** R = F, **f** R = Cl, **g** R = Br, **h** R = COOMe, **i** R = CN
8 R^1 = Et; **a** R = H, **b** R = Me, **c** R = Cl

Table 1. Reaction between 3-amino-5-methylisoxazole (**1**) and pyruvic acid derivatives **6**–**8** under different conditions

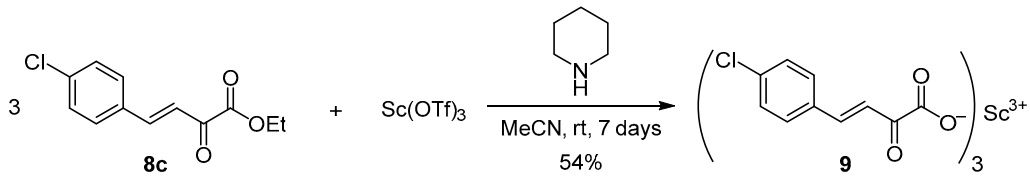
Entry	Compound	R	R^1	Molar ratio **1**:**6**(**7**, **8**)	Conditions	Yield, %	
						4	**5**
1	**7a**	H	H	1:1	US (bath), AcOH, rt, 48 h	37	–
2	**7b**	Me	H	1:1	US (bath), AcOH, rt, 48 h	48	–
3	**7c**	OMe	H	1:1	US (bath), AcOH, rt, 48 h	55	–
4	**7f**	Cl	H	1:1	US (bath), AcOH, rt, 48 h	53	6
5	**7h**	COOMe	H	1:1	US (bath), AcOH, rt, 48 h	Traces	Traces
6	**7a**	H	H	1:1	AcOH, 50–70°C, 1 h	46	–
7	**7b**	Me	H	1:1	AcOH, 50–70°C, 1 h	57	–
8	**7c**	OMe	H	1:1	AcOH, 50–70°C, 1 h	64	–
9	**7h**	COOMe	H	1:1	AcOH, 50–70°C, 1 h	25	10
10	**7f**	Cl	H	1:1	AcOH, 50–70°C, 1 h	45	5
11	**7g**	Br	H	1:1	AcOH, 50–70°C, 1 h	36	9
12	**7a**	H	H	1:1	US (horn), MeOH, rt, 3 h	51	–
13	**7c**	OMe	H	1:1	US (horn), MeOH, rt, 3 h	64	–
14	**7d**	OEt	H	1:1	US (horn), MeOH, rt, 3 h	61	–
15	**7e**	F	H	1:1	US (horn), MeOH, rt, 3 h	56	–
16	**7h**	COOMe	H	2:1	US (horn), MeOH, rt, 3 h	24*	–
17	**7i**	CN	H	2:1	US (horn), MeOH, rt, 3 h	Traces**	–
18	**7f**	Cl	H	1:1	US (horn), MeOH, rt, 3 h	55	6
19	**7g**	Br	H	1:1	US (horn), MeOH, rt, 3 h	40	18
20	**7h**	COOMe	H	1:1	MeOH, Δ, 45 min	18	3
21	**7h**	COOMe	H	2:1	MeOH, Δ, 45 min	–	36
22	**6a**	H	K	1:1	AcOH, 25°C, 3 h	53	–
23	**6b**	Me	K	1:1	AcOH, 25°C, 3 h	46	–
24	**6c**	OMe	K	1:1	AcOH, 25°C, 3 h	66	–
25	**6d**	OEt	K	1:1	AcOH, 25°C, 3 h	61	–
26	**6e**	F	K	1:1	AcOH, 25°C, 3 h	50	–
27	**6f**	Cl	K	1:1	AcOH, 25°C, 3 h	63	–
28	**6g**	Br	K	1:1	AcOH, 25°C, 3 h	57	–
29	**6h**	COOMe	K	2:1	AcOH, 25°C, 3 h	5	22
30	**6i**	CN	K	2:1	AcOH, 25°C, 3 h	Traces	3
31	**8a**	H	Et	2:1	$Sc(OTf)_3$ (20 mol %), MeCN, –15°C, 7 days	–-	23
32	**8b**	Me	Et	2:1	$Sc(OTf)_3$ (20 mol %), MeCN, –15°C, 7 days	–	29
33	**8c**	Cl	Et	2:1	$Sc(OTf)_3$ (20 mol %), MeCN, –15°C, 7 days	–	51

* The product was contaminated with equal amount of compound **7h**.
** The precipitate was contaminated with traces of compound **7i**.

did not affect the product ratio (Scheme 2, Table 1, entries 16, 17). Therefore, we firstly tried to dissolve the starting acids **7h**,**i** in boiling MeOH, then added amine **1** and refluxed the mixture for 45 min.

When the ratio of the reagents was 1:1 the mixture of compounds **4** and **5** was isolated (Scheme 2, Table 1, entry 20), while the twofold excess of aminoazole **1** allowed to isolate pure pyrrolone **5e** (R = COOMe, Table 1, entry 21). However, compound **5f** (R = CN) was not synthesized selectively by this procedure due to the very low solubility of acid **7i**. Carrying out the reaction in refluxing DMF, meant to increase the solubility of the reagents, resulted in the tarring of the reaction mixture, therefore, it could not be applied as a synthetic procedure. The reactions of amine **1** and acids **7f**,**g** (R = Cl, Br) under different conditions (Table 1, entries 4, 10, 11, 18, 19) always gave furanones **4f**,**g**, contaminated with sufficient amounts of pyrrolones **5c**,**d**. It is interesting that pure compounds **4f**,**g** were obtained when the starting unsaturated acids **7f**,**g** were replaced with their potassium salts **6f**,**g** (R^1 = K): the reaction of 3-amino-5-methylisoxazole **1** and the solution of these salts in acetic acid at 25°C yielded furanones **4f**,**g** (Scheme 2, Table 1, entries 27, 28). The same results were obtained in the case of compounds **6a**–**e** (Scheme 2, Table 1,

Scheme 3



entries 22–26). Unfortunately, the reactions of salts **6h**,**i** gave mixtures of furanones **4** and pyrrolones **5** in very low yields (Scheme 2, Table 1, entries 29, 30) even after preliminary dissolving the starting materials.

In the next stage, we used ethyl esters of unsaturated acids **8a**–**c** due to their higher solubility in a wide range of solvents in comparison with compounds **6** and **7**. The treatment of amine **1** with esters **8** in the EtOH, PhMe, MeCN, or CH_2Cl_2 under refluxing or heating at lower temperatures or under ultrasonication at the room temperature did not allow to isolate any reaction product. On the other hand, carrying out the reaction between amine **1** and ester **8c** in acetic acid under reflux gave compound **5c**; the same result was observed in the EtOH–HCl medium. However, the yields of compound **5** were unreproducible (20–40%) due to the partial decomposition of 3-amino-5-methylisoxazole. Therefore, we applied $Sc(OTf)_3$ catalysis which could increase electrophilicity of the C=O group, and thus facilitate the reaction.[44–46] Indeed, the treatment of reagents **1** and **8a**–**c** in MeCN in the presence of $Sc(OTf)_3$ gave the single product of the reaction – furanones **5a**–**c**. The best yields were observed at –15°C with 20 mol % $Sc(OTf)_3$, but they were below 51% (Scheme 2, Table 1, entries 31–33). Additionally, it was established that keeping ester **8c** with $Sc(OTf)_3$ in the presence of piperidine (instead of aminoazole **1** to create basic conditions) in MeCN for 7 days gave a yellow precipitate which according to ^{1}H NMR and X-ray fluorescence data was scandium salt **9** (Scheme 3). Such coordination with unsaturated acid instead of triflate anion apparently affects the catalytic activity of catalyst that may be the reason of lower yields.

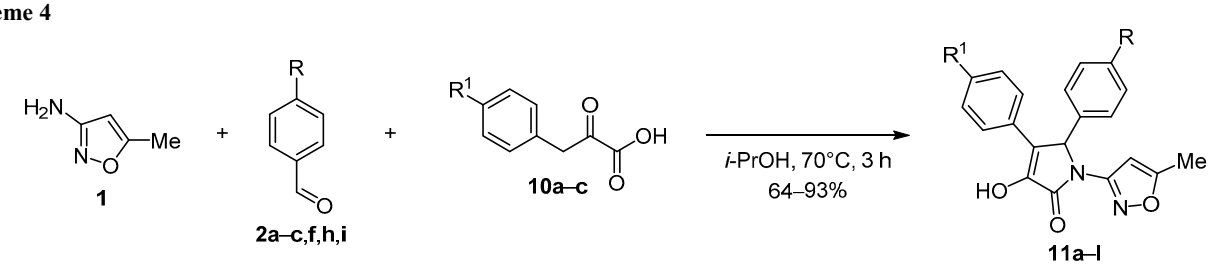
Although esters **8** could be replaced by the synthetic precursors – aromatic aldehydes and ethyl pyruvate, their multicomponent reaction with 3-amino-5-methylisoxazole (**1**) did not yield any reaction product and only tarring of the reaction mixtures was observed in the case of heating them in HOAc, 1,4-dioxane, or acetonitrile with $Sc(OTf)_3$ catalyst.

The multicomponent reaction between 3-amino-5-methylisoxazole (**1**), aromatic aldehydes **2**, and arylpyruvic acids **10** gave pyrrolones **11** (Scheme 4) formation of which was observed under a wide range of conditions (Table 2, entries 1, 2). However, the best results were obtained when the reaction was carried out in boiling *i*-PrOH (Table 2, entry 3). The only drawback was the formation of a thick mixture that inhibited the reaction. Our attempts to increase the amount of the solvent to avoid this effect led to the decreasing of the yields (Table 2, entry 4) while application of the ultrasonication instead of refluxing led to the formation of the mixtures containing azomethine **12**, acid **10**, and product **11** (ratio 1:1:0.3, Scheme 5, Table 2, entry 5). At the same time, surprisingly, dissolving of all starting compounds decreased the yield due to the side reactions (Table 2, entry 6).

There are several possible known side reactions: decomposition of 3-amino-5-methylisoxazole (**1**) and arylpyruvic acid **10**, two-component reaction between amine **1** and aldehyde **2** with the formation of azomethine **12**, or condensation of amine with arylpyruvic acid (Scheme 5), while the product of the reaction between aromatic aldehyde and arylpyruvic acid could not be isolated. Thus, we tried to increase the yields of target pyrrolone **11** by variation of starting material ratio. The application of the excess of amine **1** and/or aldehyde **2** did not affect the yields while a twofold excess of arylpyruvic acid **10** significantly improved them (Table 2, entry 9). Analysis of the mother liquor showed that it contained acid **10**, target compound **11** with traces of starting aldehyde **2**, however, the mass of the solid residue was smaller than calculated value, which indirectly indicated the decomposition of both amine **1** and acid **10**. The replacement of the second equivalent of acid **11** with trifluoroacetic acid did not increase the yield, that points to the influence of the arylpyruvic acid but not additional acidity (Table 2, entry 10) When the potassium salt of arylpyruvic acid was used instead of acid the formation of pyrrolones was not observed.

Carrying out the reaction with twofold excess of acid **10** at 70°C still gave the target compound in comparable yields (Table 2, entries 11, 15–25), however, further

Scheme 4



2 a R = H, **b** R = Me, **c** R = OMe, **f** R = Cl, **h** R = COOMe, **i** R = CN
10 a R^1 = Cl, **b** R^1 = H, **c** R^1 = Me
11 a R = H, R^1 = Cl, **b** R = Me, R^1 = Cl, **c** R = OMe, R^1 = Cl, **d** R = R^1 = Cl, **e** R = COOMe, R^1 = Cl, **f** R = CN, R^1 = Cl, **g** R = R^1 = H, **h** R = OMe, R^1 = H, **i** R = Cl, R^1 = Me, **j** R = COOMe, R^1 = H, **k** R = OMe, R^1 = Me, **l** R = COOMe, R^1 = Me

Table 2. Reaction condition optimization for the synthesis of 4,5-diaryl-3-hydroxy-1-(5-methylisoxazol-3-yl)-1,5-dihydro-2*H*-pyrrol-2-ones **11a**–**l**

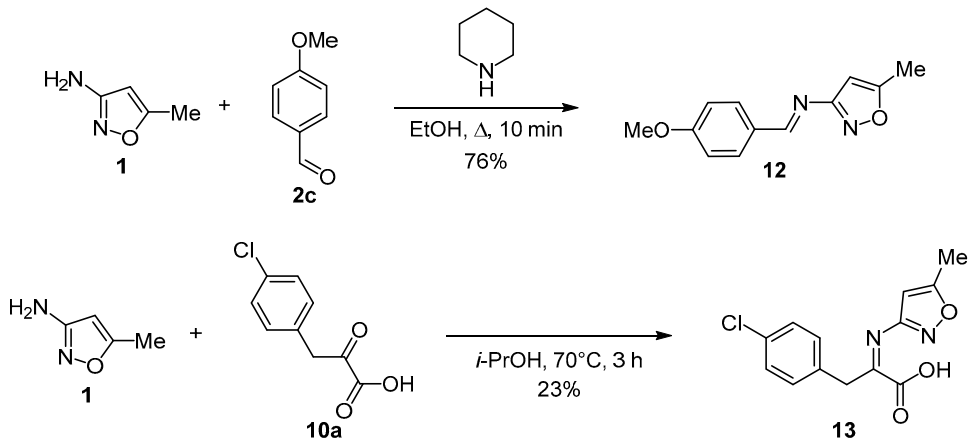
Entry	Compound	R	Compound	R^1	Ratio **1**:**2**:**10**	Conditions	Product	Yield, %
1	**2c**	OMe	**10a**	Cl	1:1:1	AcOH (1.5 ml), Δ, 3 h	**11c**	28
2	**2c**	OMe	**10a**	Cl	1:1:1	EtOAc (1.5 ml), Δ, 3 h	**11c**	30
3	**2c**	OMe	**10a**	Cl	1:1:1	*i*-PrOH (1.5 ml), Δ, 3 h	**11c**	33
4	**2c**	OMe	**10a**	Cl	1:1:1	*i*-PrOH (5 ml), Δ, 3 h	**11c**	8
5	**2c**	OMe	**10a**	Cl	1:1:1	US (horn), *i*-PrOH (3 ml), rt, 3 h	**11c**	Traces*
6	**2c**	OMe	**10a**	Cl	1:1:1	*i*-PrOH (1.5 ml), Δ, 3 h	**11c**	20**
7	**2c**	OMe	**10a**	Cl	2:1:1	*i*-PrOH (1.5 ml), Δ, 3 h	**11c**	23
8	**2c**	OMe	**10a**	Cl	2:2:1	*i*-PrOH (1.5 ml), Δ, 3 h	**11c**	30
9	**2c**	OMe	**10a**	Cl	1:1:2	*i*-PrOH (1.5 ml), Δ, 3 h	**11c**	56
10	**2c**	OMe	**10a**	Cl	1:1:1	TFA (1 equiv), *i*-PrOH (1.5 ml), Δ, 3 h	**11c**	36
11	**2c**	OMe	**10a**	Cl	1:1:2	*i*-PrOH, 70°C, 3 h	**11c**	56
12	**2c**	OMe	**10a**	Cl	1:1:2	*i*-PrOH, 70°C, 0.5 h	**11c**	30
13	**2c**	OMe	**10a**	Cl	1:1:2	*i*-PrOH, 70°C, 1 h	**11c**	44
14	**2c**	OMe	**10a**	Cl	1:1:2	*i*-PrOH, 70°C, 2 h	**11c**	50
15	**2a**	H	**10a**	Cl	1:1:2	*i*-PrOH, 70°C, 3 h	**11a**	72
16	**2b**	Me	**10a**	Cl	1:1:2	*i*-PrOH, 70°C, 3 h	**11b**	64
17	**2f**	Cl	**10a**	Cl	1:1:2	*i*-PrOH, 70°C, 3 h	**11d**	65
18	**2h**	COOMe	**10a**	Cl	1:1:2	*i*-PrOH, 70°C, 3 h	**11e**	81
19	**2i**	CN	**10a**	Cl	1:1:2	*i*-PrOH, 70°C, 3 h	**11f**	91
20	**2a**	H	**10b**	H	1:1:2	*i*-PrOH, 70°C, 3 h	**11g**	93
21	**2c**	OMe	**10b**	H	1:1:2	*i*-PrOH, 70°C, 3 h	**11h**	87
22	**2f**	Cl	**10c**	Me	1:1:2	*i*-PrOH, 70°C, 3 h	**11i**	70
23	**2h**	COOMe	**10b**	H	1:1:2	*i*-PrOH, 70°C, 3 h	**11j**	92
24	**2c**	OMe	**10c**	Me	1:1:2	*i*-PrOH, 70°C, 3 h	**11k**	83
25	**2h**	COOMe	**10c**	Me	1:1:2	*i*-PrOH, 70°C, 3 h	**11l**	84

* A mixture containing aryl pyruvic acid **10a**, product **11a**, and azomethine **12** was obtained.
** All reactants were separately dissolved in *i*-PrOH prior to the reaction.

decreasing of the temperature did not allow to isolate the target heterocycles. Our attempts to decrease the reaction time resulted in declining yields (Table 2, entries 12–14) while its increasing results in the formation of a thick mixture with poor mass transfer.

Thus, we developed synthetic procedures to obtain compounds **4**, **5**, and **11**: the optimal conditions for the synthesis of furanones **4a**–**g** are stirring of 3-amino-5-methylisoxazole **1** and potassium 4-aryl-2-oxobut-3-enoate **6** at 25°C in AcOH for 3 h, however the suitable procedure for selective synthesis of compounds **4h**,**i** was not developed; pyrrolones **5a**–**c** could be synthesized *via* $Sc(OTf)_3$-catalyzed heterocyclization of 3-amino-5-methylisoxazole (**1**) and ethyl 4-aryl-2-oxobut-3-enoate **8a**–**c** in MeCN at 5°C; pyrrolone **5e** could be obtained by the reaction of 4-(4-(methoxycarbonyl)phenyl)-2-oxobut-3-enoic acid **7h**

Scheme 5



and twofold excess of 3-amino-5-methylisoxazole (**1**) in methanol under refluxing, on the other hand, these conditions aren't suitable for the synthesis of compounds **5d**,**f** and corresponding methods weren't developed; the optimal procedure for the synthesis of pyrrolones **11a**–**l** is the heating of 3-amino-5-methylisoxazole (**1**), aromatic aldehyde **2**, and twofold excess of arylpyruvic acid **10a**–**c** at 70°C in *i*-PrOH for 3 h.

The results of our study concerning the two- and three-component heterocyclization reactions involving 3-amino-5-methylisoxazole and pyruvic acid derivatives show that the chemical behavior of 3-amino-5-methylisoxazole (**1**) sufficiently differs from the chemical behavior of 5-amino-3-methylisoxazole that has been described earlier.[18] It is clear that in the most cases, the nucleophilic sites of the latter in such reactions are NH_2 group and 4-CH center of isoxazole ring while in the analogous reactions of the former, 4-CH center is never involved in the formation of final heterocycles.

The reason for such contrast most likely is due to difference in the electronic structure of these two amino-isoxazoles that may influence both the center for primary attack by electrophilic reagent and on the further cascade of the reactions including energy of possible transition states and stability of intermediates. This hypothesis calls for the further detailed studies by means of quantum chemistry, but even in crystalline state X-ray diffraction analysis allowed to find significant differences in the structures of these aminoazoles (Fig. 4).

The analysis of the bond lengths for two isomeric aminomethylisoxazoles has shown the essential influence of the amino group position on the electron density distribution within the cycle in the crystal phase (Fig. 4). The conjugation between the nitrogen lone pair and the endocyclic double bond is stronger in 5-amino-3-methylisoxazole: its C–N exocyclic bond is shorter and the degree of the amino group pyramidalization is smaller as compared to 3-amino-5-methylisoxazole (the sum of bond angles centered at the nitrogen atom of the amino group is 346° in 3-amino-5-methylisoxazole (**1**) and 357° in 5-amino-3-methylisoxazole). It may be caused also by the participation of the high electronegative oxygen atom in the conjugation with the same endocyclic double bond in 5-amino-3-methylisoxazole. It is confirmed additionally by the elongation of C=C double bond and shortening of the C–O bond as compared to 3-amino-5-methylisoxazole (**1**).

The differences in electronic structure between the two isomers are also observed in solutions according to ^{13}C and ^{15}N NMR data. Thus, the analysis of the ^{13}C NMR data obtained for 3-amino-5-methylisoxazole (**1**) and 5-amino-3-methylisoxazole showed that electronic density on the C-4 atom of isoxazole ring is higher in the case of 5-amino-3-methylisoxazole which is manifested the upfield shift of the signal by 16.57 ppm. Reverse situation is observed with the signals of the NH_2 groups: the ^{15}N NMR experiments showed that exocyclic nitrogen atom of 3-amino-5-methylisoxazole (**1**) is more shielded by the electrons in comparison with the same atom of 5-amino-3-methylisoxazole (difference in 12.4 ppm).[42]

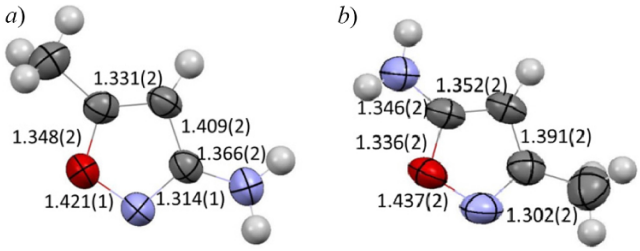


Figure 4. The molecular structure of *a*) 3-amino-5-methylisoxazole (**1**) and *b*) 5-amino-3-methylisoxazole with atoms represented by thermal vibration ellipsoids of 50% probability.

The structures of the all compounds synthesized were established *via* ^{1}H, ^{13}C NMR studies, mass spectroscopy, and elemental analysis.

The structure of compounds **4** was also confirmed by 2D NMR analysis of its representative **4c**. Compound **4c** can exist as 4 different structures **A**–**D** (Fig. 5). However, the IR spectrometry data showed the absence of any carboxyl group, therefore, the structures **C** and **D** should be excluded.

The choice in favor of structure **A** was made on the basis of a set of two-dimensional NMR spectra. The most important data was acquired by ^{1}H–^{13}C HMBC, COSY, and NOESY experiments (Fig. 6). COSY and NOESY spectra show that position 4'-CH of the isoxazole moiety is unsubstituted: COSY spectra contain spin-spin coupling between 4'-CH proton and CH_3 group protons in the position C-3 with ^{4}J = 1.0 Hz. The ^{1}H–^{13}C HMBC spectrum confirms the existence of the furanone ring without correlations between the signals of the furanone and isoxazole moieties; on the other hand, the NH group has cross peaks with both rings. The IR spectroscopy data confirms the presence of furan-2(5*H*)-one fragment (C=O 1743 cm^{-1}) and NH group (N–H 3336 cm^{-1}). The comparison of ^{1}H and ^{13}C NMR spectra of compounds **4** with literature data[47] for similar furanones confirms the structure **A** as well.

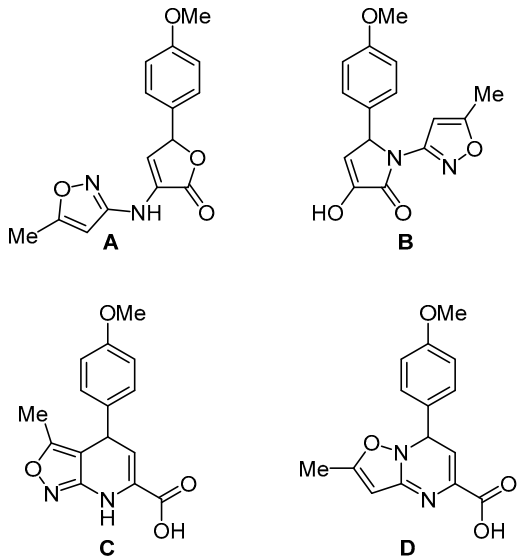


Figure 5. Feasible structures of compound **4c**.

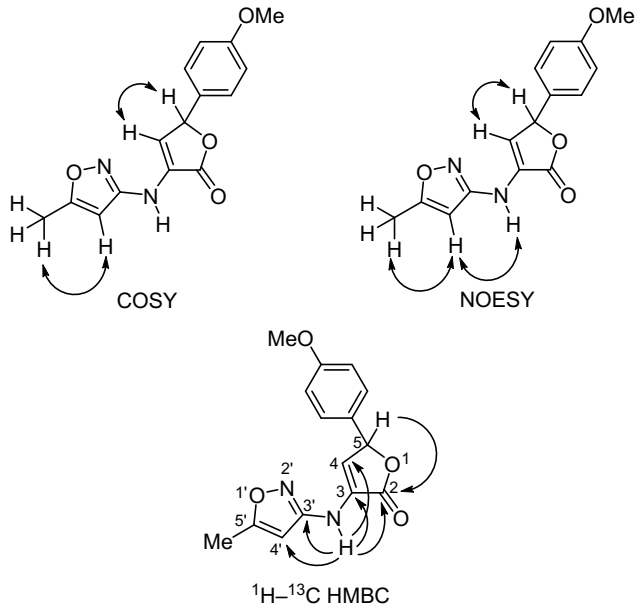


Figure 6. Some important 2D NMR correlations of compound **4c**.

The structures of compounds **5** and **11** were proved by IR and ^{1}H, ^{13}C NMR spectra together with their comparison with literature data. Thus, the NMR data for compounds **5** look very similar to data for compounds **4** excepting the presence of signals for the second isoxazole ring. The shifts in ^{1}H NMR spectra for the OH group (10.74–11.21 ppm) and the 5-CH group of pyrrolone ring (6.10–6.36 ppm) are in good accordance with chemical shifts described in the literature for similar compounds.[48] The IR data for heterocycles **5b** and **11g** contains peaks of lactone moiety C=O at 1693 cm^{-1} and NH at 3320 cm^{-1} and C=O at 1698 cm^{-1} and enol OH at 3240 cm^{-1}, respectively.

As it was expected, the chemical behavior of 3-amino-5-methylisoxazole in heterocyclizations with pyruvic acids significantly differs from chemical behavior of 5-amino-3-methylisoxazole: only one nucleophilic center of 3-amino-5-methylisoxazole (NH_2 group) takes part in the transformations while in the analogous reactions of 5-amino-3-methylisoxazole, two nucleophilic centers (NH_2 group and 4-CH center of isoxazole ring) are involved in the heterocyclizations in most cases. The multicomponent reactions of 3-amino-5-methylisoxazole with aromatic aldehyde and pyruvic acids under any studied conditions gave insufficient results from the viewpoint of purity and yields of the target compounds, therefore sequential procedures including preliminary synthesis of arylidene derivatives of pyruvic acid should be used instead. By the means of modification of starting pyruvic acids and reaction conditions several preparative procedures were developed that allowed synthesis of pure 5-aryl-3-[(5-methylisoxazol-3-yl)amino]-2(5*H*)-ones, 5-aryl-1-(5-methylisoxazol-3-yl)-3-[(5-methylisoxazol-3-yl)amino]-1,5-dihydro-2*H*-pyrrol-2-ones, and 4,5-diaryl-3-hydroxy-1-(5-methylisoxazol-3-yl)-1,5-dihydro-2*H*-pyrrol-2-ones. The differences in electronic structure of the above-mentioned aminoazoles were discussed both in crystalline state (X-ray analysis) and in solutions (^{13}C, ^{15}N NMR).

Experimental

^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance III 300 MHz (300 and 75 MHz, respectively; ^{1}H NMR – compounds **4b–f**, **5a–c**,**e**, **11a–c**,**h**,**k**,**l**, ^{13}C NMR – compounds **4a–g**, **5a–c**,**e**, **11a–c**,**e**,**f**,**h**,**j–l**) and Varian 400-MR (400 MHz; ^{1}H NMR – compounds **4a**,**g**, **11e**,**f**,**j**) spectrometers. COSY, NOESY, ^{1}H–^{13}C HSQC, and ^{1}H–^{13}C HMBC spectra of compound **4c** (400 and 100 MHz for ^{1}H and ^{13}C NMR spectra, respectively; ^{1}H and ^{13}C NMR – compounds **11d**,**g**,**i**) were acquired on a Bruker Avance III 400 MHz spectrometer. DMSO-d_6 was used as solvent and chemical shifts were reported relative to the residual solvent protons as internal standard (DMSO-d_6: ^{1}H NMR – 2.50 ppm, ^{13}C NMR – 39.52 ppm). Mass spectra were registered on an Advion Expression^L CMS mass spectrometer (direct input of sample) applying ESI (negative ion mode) for compounds **11a–c**,**e**,**f**,**l** and APCI (N_2, positive mode) for compounds **4a–g**, **5a–c**,**e**, **11d**,**g–k**. Elemental analyses were conducted on a EuroVector EA3000 instrument. Melting points were determined on a Kofler melting point apparatus. Ultrasonication was performed using standard ultrasonic bath (SELDI, Ukraine) with working frequency of 44.2 kHz or ultrasonic horn UZDN (Sumy, Ukraine) at 44.2 kHz (60% of the nominal power).

The starting α,β-unsaturated acids **7**, salts **6**, esters **8** were synthesized according to known literature methods.[43,49] 3-Amino-5-methylisoxazole (**1**), aldehydes **2**, pyruvic acid (**3**) are commercially available. Arylpyruvic acids **10** were obtained according to the known procedure.[50]

Synthesis of 5-aryl-3-[(5-methylisoxazol-3-yl)amino]-furan-2(5*H*)-ones 4a–i (General method). Potassium 4-aryl-2-oxobut-3-enoate **6** (1 mmol) was completely dissolved in minimum amount of acetic acid at 25°C, and after that 3-amino-5-methylisoxazole (**1**) (0.098 g, 1 mmol) was added. The mixture was stirred at 25°C for 3 h. The precipitate was filtered off, washed with EtOH, and dried on air.

3-[(5-Methylisoxazol-3-yl)amino]-5-phenylfuran-2(5*H*)-one (4a). Yield 140 mg (53%), white solid, mp 189–191°C (HOAc). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.32 (3H, d, ^4J = 1.1, 3-CH_3 isoxazole); 6.03 (1H, d, ^4J = 1.1, H-4 isoxazole); 6.22 (1H, d, ^3J = 2.2, 5-CH furanone); 6.98 (1H, d, ^3J = 2.2, 4-CH furanone); 7.20–7.57 (5H, m, H Ph); 9.47 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 12.4; 81.8; 95.3; 123.4; 127.1 (2C); 127.6; 129.3 (2C); 129.4; 137.0; 160.6; 168.8; 169.8. Mass spectrum (APCI), *m*/*z* (I_{rel}, %): 257 $[M+H]^+$ (100). Found, %: C 65.46; H 4.75; N 11.01. $C_{14}H_{12}N_2O_3$. Calculated, %: C 65.62; H 4.72; N 10.93.

3-[(5-Methylisoxazol-3-yl)amino]-5-(*p*-tolyl)furan-2(5*H*)-one (4b). Yield 125 mg (46%), white solid, mp 184°C (HOAc). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.30 (3H, s, 4-C$\underline{H}_3$C$_6$H$_4$); 2.31 (3H, d, ^4J = 1.1, 3-CH_3 isoxazole); 6.03 (1H, d, ^4J = 1.1, H-4 isoxazole); 6.17 (1H, d, ^3J = 2.2, 5-CH furanone); 6.95 (1H, d, ^3J = 2.2, 4-CH furanone); 7.22 (4H, s, H Ar); 9.45 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 12.3; 21.2; 81.8; 95.3; 123.4; 127.2 (2C); 127.6; 129.8 (2C); 133.9; 138.8; 160.7; 168.8; 169.9. Mass spectrum (APCI), *m*/*z* (I_{rel}, %): 271 $[M+H]^+$ (100). Found, %:

C 66.59; H 5.21; N 10.48. $C_{15}H_{14}N_2O_3$. Calculated, %: C 66.66; H 5.22; N 10.36.

5-(4-Methoxyphenyl)-3-[(5-methylisoxazol-3-yl)amino]-furan-2(5*H*)-one (4c). Yield 186 mg (66%), white solid, mp 192–194°C (HOAc). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.32 (3H, d, ^4J = 1.1, 3-CH_3 isoxazole); 3.76 (3H, s, 4-C$\underline{H}_3$OC$_6$H$_4$); 6.03 (1H, d, ^4J = 1.1, H-4 isoxazole); 6.16 (1H, d, ^3J = 2.2, 5-CH furanone); 6.93 (1H, d, ^3J = 2.2, 4-CH furanone); 6.94–7.32 (4H, m, H Ar); 9.45 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 12.4 (3-CH_3); 55.6 (4-$\underline{C}$H$_3$OC$_6$H$_4$); 81.7 (C-5 furanone); 95.3 (C-4 isoxazole); 114.6 (2C Ar); 123.2 (C-4 furanone); 127.7 (C-3 furanone); 128.6 (C Ar); 128.9 (2C Ar); 160.2 (C Ar); 160.7 (C-1 isoxazole); 168.8 (C-3 isoxazole); 169.9 (C=O). Mass spectrum (APCI), *m*/*z* (I_{rel}, %): 287 $[M+H]^+$ (100). Found, %: C 63.07; H 4.95; N 9.73. $C_{15}H_{14}N_2O_4$. Calculated, %: C 62.93; H 4.93; N 9.79.

5-(4-Ethoxyphenyl)-3-[(5-methylisoxazol-3-yl)amino]-furan-2(5*H*)-one (4d). Yield 183 mg (61%), white solid, mp 158–159°C (HOAc). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.31 (3H, t, ^3J = 7.0, 4-C$\underline{H}_3$CH$_2$OC$_6$H$_4$); 2.32 (3H, s, 3-CH_3 isoxazole); 4.02 (2H, q, ^3J = 7.0, 4-CH$_3$C$\underline{H}_2$OC$_6$H$_4$); 6.03 (1H, s, H-4 isoxazole); 6.16 (1H, s, 5-CH furanone); 6.87–7.33 (5H, m, H Ar, 4-CH furanone); 9.44 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 12.4; 15.0; 63.6; 81.7; 95.3; 115.1 (2C); 123.2; 127.7; 128.5; 128.9 (2C); 159.5; 160.7; 168.8; 169.9. Mass spectrum (APCI), *m*/*z* (I_{rel}, %): 301 $[M+H]^+$ (100). Found, %: C 64.10; H 5.31; N 9.31. $C_{16}H_{16}N_2O_4$. Calculated, %: C 63.99; H 5.37; N 9.33.

5-(4-Fluorophenyl)-3-[(5-methylisoxazol-3-yl)amino]-furan-2(5*H*)-one (4e). Yield 136 mg (50%), white solid, mp 181°C (HOAc). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.32 (3H, d, ^4J = 1.1, 3-CH_3 isoxazole); 6.03 (1H, d, ^4J = 1.1, H-4 isoxazole); 6.23 (1H, d, ^3J = 2.2, 5-CH furanone); 6.98 (1H, d, ^3J = 2.2, 4-CH furanone); 7.19–7.46 (4H, m, H Ar); 9.48 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 12.3; 81.1; 95.3; 116.1 (2C, d, J_{CF} = 21.7); 123.1; 127.7; 129.5 (2C, d, J_{CF} = 8.6); 133.2; 160.6; 162.7; 168.8; 169.7. Mass spectrum (APCI), *m*/*z* (I_{rel}, %): 275 $[M+H]^+$ (100). Found, %: C 61.24; H 3.98; F 7.02; N 10.09. $C_{14}H_{11}FN_2O_3$. Calculated, %: C 61.31; H 4.04; F 6.93; N 10.21.

5-(4-Chlorophenyl)-3-[(5-methylisoxazol-3-yl)amino]-furan-2(5*H*)-one (4f). Yield 183 mg (63%), white solid, mp 194–196°C (HOAc). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.32 (3H, d, ^4J = 1.0, 3-CH_3 isoxazole); 6.02 (1H d, ^4J = 1.0, H-4 isoxazole); 6.24 (1H, d, ^3J = 2.2, 5-CH furanone); 6.97 (1H, d, ^3J = 2.2, 4-CH furanone); 7.23–7.60 (4H, m, H Ar); 9.49 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 12.4; 80.9; 95.3; 123.0; 127.7; 129.1 (2C); 129.3 (2C); 133.9; 136.0; 160.6; 168.8; 169.7. Mass spectrum (APCI), *m*/*z* (I_{rel}, %): 291 $[M+H]^+$ (100). Found, %: C 57.90; H 3.75; Cl 12.11; N 9.77. $C_{14}H_{11}ClN_2O_3$. Calculated, %: C 57.84; H 3.81; Cl 12.19; N 9.64.

5-(4-Bromophenyl)-3-[(5-methylisoxazol-3-yl)amino]-furan-2(5*H*)-one (4g). Yield 195 mg (57%), white solid, mp 198–200°C (HOAc). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.32 (3H, d, ^4J = 1.1, 3-CH_3 isoxazole); 6.02 (1H, d, ^4J = 1.1, H-4 isoxazole); 6.22 (1H, d, ^3J = 2.2, 5-CH furanone); 6.97 (1H, d, ^3J = 2.2, 4-CH furanone); 7.22–7.71 (4H, m, H Ar); 9.50 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 12.4; 81.0; 95.3; 122.5; 122.9; 127.7; 129.4 (2C); 132.2 (2C); 136.5; 160.6; 168.8; 169.7. Mass spectrum (APCI), *m*/*z* (I_{rel}, %): 336 $[M+H]^+$ (100). Found, %: C 50.32; H 3.29; Br 23.70; N 8.45. $C_{14}H_{11}BrN_2O_3$. Calculated, %: C 50.17; H 3.31; Br 23.84; N 8.36.

5-Aryl-1-(5-methylisoxazol-3-yl)-3-[(5-methylisoxazol-3-yl)amino]-1,5-dihydro-2*H*-pyrrol-2-ones 5a–c,e. Method A (for compounds **5a**–**c**). A mixture of ethyl 4-aryl-2-oxobut-3-enoate **8a**–**c** (0.5 mmol), 3-amino-5-methylisoxazole (**1**) (0.098 g, 1 mmol), and acetonitrile (0.5 ml) was cooled to –15°C. After that, $Sc(OTf)_3$ (0.050 g, 0.1 mmol, 20 mol %) was added. The mixture was stirred at –15°C until all ester was dissolved. After that, the reacting mixture was left for 7 days at –15°C. The precipitate was filtered off, washed with acetonitrile, and dried on air.

Method B (for compound **5e**). 4-[4-(Methoxycarbonyl)-phenyl]-2-oxobut-3-enoic acid (**7h**) (0.234 g, 1 mmol) was dissolved in minimum amount of refluxing methanol, and 3-amino-5-methylisoxazole (**1**) (0.196 g, 2 mmol, 2 equiv) was added. The mixture was heated under reflux for 45 min. After cooling of the reaction mixture, the solid precipitate was filtered off and dried on air.

1-(5-Methylisoxazol-3-yl)-3-[(5-methylisoxazol-3-yl)-amino]-5-phenyl-1,5-dihydro-2*H*-pyrrol-2-one (5a). Yield 39 mg (23%), white solid, mp 243–245°C (MeCN). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.30 (3H, d, ^4J = 1.1, 3-CH_3 isoxazole); 2.36 (3H, d, ^4J = 1.1, 3-CH_3 isoxazole); 5.79 (1H, d, ^3J = 2.6, 5-CH pyrrolone); 6.05 (1H, d, ^4J = 1.1, H-4 isoxazole); 6.65 (1H, d, ^3J = 2.6, 4-CH pyrrolone); 6.83 (1H, d, ^4J = 1.1, H-4 isoxazole); 7.15–7.41 (5H, m, H Ar); 9.38 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 12.3; 12.6; 62.4; 95.3; 95.6; 119.4; 126.9 (2C); 128.3; 129.1 (2C); 130.3; 137.6; 156.5; 160.7; 166.1; 168.5; 170.6. Mass spectrum (APCI), *m*/*z* (I_{rel}, %): 337 $[M+H]^+$ (100). Found, %: C 64.33; H 4.83; N 16.54. $C_{18}H_{16}N_4O_3$. Calculated, %: C 64.28; H 4.79; N 16.66.

1-(5-Methylisoxazol-3-yl)-3-[(5-methylisoxazol-3-yl)-amino]-5-(*p*-tolyl)-1,5-dihydro-2*H*-pyrrol-2-one (5b). Yield 50 mg (29%), white solid, mp 253–255°C (MeCN). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.25 (3H, s, 4-C$\underline{H}_3$C$_6$H$_4$); 2.30 (3H, d, ^4J = 1.0, 3-CH_3 isoxazole); 2.35 (3H, d, ^4J = 1.0, 3-CH_3 isoxazole); 5.74 (1H, d, ^3J = 2.6, 5-CH pyrrolone); 6.05 (1H, d, ^4J = 1.0, H-4 isoxazole); 6.63 (1H, d, ^3J = 2.6, 4-CH pyrrolone); 6.81 (1H, d, ^4J = 1.0, H-4 isoxazole); 7.11 (4H, s, H Ar), 9.36 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 12.3; 12.5; 21.1; 62.2; 95.3; 95.6; 119.5; 126.9 (2C); 129.7 (2C); 130.3; 134.5; 137.6; 156.5; 160.7; 166.1; 168.5; 170.6. Mass spectrum (APCI), *m*/*z* (I_{rel}, %): 351 $[M+H]^+$ (100). Found, %: C 65.19; H 5.14; N 16.04. $C_{19}H_{18}N_4O_3$. Calculated, %: C 65.13; H 5.18; N 15.99.

5-(4-Chlorophenyl)-1-(5-methylisoxazol-3-yl)-3-[(5-methylisoxazol-3-yl)amino]-1,5-dihydro-2*H*-pyrrol-2-one (5c). Yield 94 mg (51%), white solid, mp 250–251°C (MeCN). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.30 (3H, d, ^4J = 1.1, 3-CH_3 isoxazole); 2.36 (3H, d, ^4J = 1.1, 3-CH_3 isoxazole); 5.80 (1H, d, ^3J = 2.6, 5-CH pyrrolone); 6.05 (1H, d, ^4J = 1.1,

H-4 isoxazole); 6.64 (1H, d, ^3J = 2.6, 4-CH pyrrolone); 6.83 (1H, d, ^4J = 1.1, H-4 isoxazole); 7.15–7.52 (4H, m, H Ar); 9.41 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 12.3; 12.6; 61.7; 95.3; 95.5; 118.8; 129.0 (2C); 129.1 (2C); 130.6; 132.8; 136.7; 156.5; 160.7; 166.0; 168.5; 170.7. Mass spectrum (APCI), *m*/*z* (I_{rel}, %): 371 $[M+H]^+$ (100). Found, %: C 58.41; H 4.05; Cl 9.63; N 15.03. $C_{18}H_{15}ClN_4O_3$. Calculated, %: C 58.31; H 4.08; Cl 9.56; N 15.11.

Methyl 4-{1-(5-methylisoxazol-3-yl)-4-[(5-methylisoxazol-3-yl)amino]-5-oxo-2,5-dihydro-1*H*-pyrrol-2-yl}benzoate (5e). Yield 140 mg (36%), white solid, mp 232–234°C (MeOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.30 (3H, d, ^4J = 1.1, 3-CH_3 isoxazole); 2.36 (3H, d, ^4J = 1.0, 3-CH_3 isoxazole); 3.83 (3H, s, 4-C$\underline{H}_3$OOCC$_6$H$_4$); 5.88 (1H, d, ^3J = 2.6, 5-CH pyrrolone), 6.05 (1H, d, ^4J = 1.1, H-4 isoxazole); 6.65 (1H, d, ^3J = 2.6, 4-CH pyrrolone); 6.85 (1H, d, ^4J = 1.0, H-4 isoxazole); 7.35–7.95 (4H, m, H Ar); 9.45 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 12.3; 12.6; 52.6; 62.0; 95.3; 95.4; 118.5; 127.3 (2C); 129.6; 130.1 (2C); 130.7; 143.3; 156.5; 160.7; 166.0; 166.3; 168.6; 170.8. Mass spectrum (APCI), *m*/*z* (I_{rel}, %): 395 $[M+H]^+$ (100). Found, %: C 60.84; H 4.68; N 14.11. $C_{20}H_{18}N_4O_5$. Calculated, %: C 60.91; H 4.60; N 14.21.

Synthesis of 4,5-diaryl-3-hydroxy-1-(5-methylisoxazol-3-yl)-1,5-dihydro-2*H*-pyrrol-2-ones 11a–l (General method). 3-Amino-5-methylisoxazole (**1**) (0.068 g, 0.75 mmol) and arylpyruvic acid **10a**–**c** (1.5 mmol) were added to a solution of aldehyde **2** (0.75 mmol) in *i*-PrOH (1.5 ml). The mixture was stirred on the water bath at 70°C for 3 h. After that, the mixture was filtered and washed with *i*-PrOH. The precipitate was heated in *i*-PrOH (5 ml) for 10 min, filtered off, washed with *i*-PrOH, hexane, and dried.

4-(4-Chlorophenyl)-3-hydroxy-1-(5-methylisoxazol-3-yl)-5-phenyl-1,5-dihydro-2*H*-pyrrol-2-one (11a). Yield 202 mg (72%), brick-red solid, mp 238–240°C (*i*-PrOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.33 (3H, d, ^4J = 1.1, 3-CH_3 isoxazole); 6.21 (1H, s, 5-CH pyrrolone); 6.76 (1H, d, ^4J = 1.1, H-4 isoxazole); 7.10–7.80 (9H, m, H 2Ar); 11.09 (1H, s, 3-OH pyrrolone). ^{13}C NMR spectrum, δ, ppm: 12.5; 60.7; 95.7; 123.8; 128.4 (2C); 128.6; 128.8 (2C); 128.8 (2C); 129.7 (2C); 130.4; 132.6; 137.3; 143.2; 156.3; 165.5; 170.5. Mass spectrum (ESI), *m*/*z* (I_{rel}, %): 367 $[M(^{37}Cl)–H]^-$ (48), 366 $[M]^-$ (20), 365 $[M(^{35}Cl)–H]^-$ (100). Found, %: C 65.60; H 4.18; Cl 9.54; N 7.75. $C_{20}H_{15}ClN_2O_3$. Calculated, %: C 65.49; H 4.12; Cl 9.66; N 7.64.

4-(4-Chlorophenyl)-3-hydroxy-1-(5-methylisoxazol-3-yl)-5-(*p*-tolyl)-1,5-dihydro-2*H*-pyrrol-2-one (11b). Yield 185 mg (64%), brick-red solid, mp 244°C (*i*-PrOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.17 (3H, s, 4-C$\underline{H}_3$C$_6$H$_4$); 2.33 (3H, d, ^4J = 1.1, 3-CH_3 isoxazole); 6.16 (1H, s, 5-CH pyrrolone); 6.75 (1H, d, ^4J = 1.1, H-4 isoxazole); 6.99–7.29 (4H, m, H Ar); 7.31–7.75 (4H, m, H Ar); 11.06 (1H, s, 3-OH pyrrolone). ^{13}C NMR spectrum, δ, ppm: 12.5; 21.1; 60.4; 95.8; 123.8; 128.3 (2C); 128.8 (2C); 129.4 (2C); 129.7 (2C); 130.5; 132.6; 134.2; 137.9; 143.1; 156.2; 165.5; 170.4. Mass spectrum (ESI), *m*/*z* (I_{rel}, %): 379 $[M(^{35}Cl)–H]^-$ (100), 380 $[M]^-$ (22), 381 $[M(^{37}Cl)–H]^-$ (38). Found, %: C 66.18; H 4.52; Cl 9.41; N 7.44. $C_{21}H_{17}ClN_2O_3$. Calculated, %: C 66.23; H 4.50; Cl 9.31; N 7.36.

4-(4-Chlorophenyl)-3-hydroxy-5-(4-methoxyphenyl)-1-(5-methylisoxazol-3-yl)-1,5-dihydro-2*H*-pyrrol-2-one (11c). Yield 170 mg (56%), brick-red solid, mp 241–243°C (*i*-PrOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.33 (3H, d, ^4J = 1.1, 3-CH_3 isoxazole); 3.66 (3H, s, 4-C$\underline{H}_3$OC$_6$H$_4$); 6.15 (1H, s, 5-CH pyrrolone); 6.75 (1H, d, ^4J = 1.1, H-4 isoxazole); 6.76–7.33 (4H, m, H Ar); 7.33–7.83 (4H, m, H Ar); 11.05 (1H, s, 3-OH pyrrolone). ^{13}C NMR spectrum, δ, ppm: 12.5; 55.4; 60.2; 95.8; 114.2; 123.6; 128.8 (2C); 128.9 (2C); 129.7 (4C); 130.6; 132.5; 143.1; 156.3; 159.4; 165.4; 170.4. Mass spectrum (ESI), *m*/*z* (I_{rel}, %): 395 $[M(^{35}Cl)–H]^-$ (100), 397 $[M(^{37}Cl)–H]^-$ (31). Found, %: C 63.64; H 4.27; Cl 8.82; N 7.08. $C_{21}H_{17}ClN_2O_4$. Calculated, %: C 63.56; H 4.32; Cl 8.93; N 7.06.

4,5-Bis(4-chlorophenyl)-3-hydroxy-1-(5-methylisoxazol-3-yl)-1,5-dihydro-2*H*-pyrrol-2-one (11d). Yield 200 mg (65%), brick-red solid, mp 242–244°C (*i*-PrOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.34 (3H, s, 3-CH_3 isoxazole); 6.25 (1H, s, 5-CH pyrrolone); 6.78 (1H, s, H-4 isoxazole); 7.19–7.79 (8H, m, H 2Ar); 11.14 (1H, s, 3-OH pyrrolone). ^{13}C NMR spectrum, δ, ppm: 12.5; 59.9; 95.7; 123.5; 128.9 (4C); 129.6; 130.3 (2C); 130.4 (2C); 132.8; 133.2; 136.5; 143.4; 156.3; 165.4; 170.6. Mass spectrum (APCI), *m*/*z* (I_{rel}, %): 400 $[M(^{35}Cl,\ ^{35}Cl)]^+$ (100), 401 $[M(^{35}Cl,\ ^{37}Cl)]^+$ (22). Found, %: C 60.02; H 3.56; Cl 17.51; N 7.04. $C_{20}H_{14}Cl_2N_2O_3$. Calculated, %: C 59.87; H 3.52; Cl 17.67; N 6.98.

Methyl 4-[3-(4-chlorophenyl)-4-hydroxy-1-(5-methylisoxazol-3-yl)-5-oxo-2,5-dihydro-1*H*-pyrrol-2-yl]benzoate (11e). Yield 263 mg (81%), brick-red solid, mp 225°C (MeOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.33 (3H, d, ^4J = 1.1, 3-CH_3 isoxazole); 3.78 (3H, s, 4-C$\underline{H}_3$OOCC$_6$H$_4$); 6.33 (1H, s, 5-CH pyrrolone); 6.78 (1H, d, ^4J = 1.1, H-4 isoxazole); 7.27–7.95 (8H, m, H 2Ar); 11.21 (1H, s, 3-OH pyrrolone). ^{13}C NMR spectrum, δ, ppm: 12.5; 52.6; 60.2; 95.6; 123.5; 128.8 (2C); 128.9 (2C); 129.6 (2C); 129.7 (2C); 129.9; 130.2; 132.8; 142.9; 143.4; 156.2; 165.4; 166.2; 170.6. Mass spectrum (ESI), *m*/*z* (I_{rel}, %): 423 $[M(^{35}Cl)–H]^-$ (100), 424 $[M]^-$ (23), 425 $[M(^{37}Cl)–H]^-$ (48). Found, %: C 62.22; H 4.08; Cl 8.40; N 6.57. $C_{22}H_{17}ClN_2O_5$. Calculated, %: C 62.20; H 4.03; Cl 8.34; N 6.59.

4-[3-(4-Chlorophenyl)-4-hydroxy-1-(5-methylisoxazol-3-yl)-5-oxo-2,5-dihydro-1*H*-pyrrol-2-yl]benzonitrile (11f). Yield 272 mg (91%), brick-red solid, mp 226°C (MeOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.34 (3H, d, ^4J = 1.1, 3-CH_3 isoxazole); 6.36 (1H, s, 5-CH pyrrolone); 6.79 (1H, d, ^4J = 1.1, H-4 isoxazole); 7.23–7.88 (8H, m, H Ar); 11.25 (1H, s, 3-OH pyrrolone). ^{13}C NMR spectrum, δ, ppm: 12.5; 60.0; 95.5; 111.5; 118.8; 123.2; 128.9 (2C); 129.5 (2C); 129.6 (2C); 130.0; 132.8 (3C); 143.3; 143.6; 156.2; 165.4; 170.8. Mass spectrum (ESI), *m*/*z* (I_{rel}, %): 390 $[M(^{35}Cl)–H]^-$ (100), 391 $[M]^-$ (24), 392 $[M(^{37}Cl)–H]^-$ (33). Found, %: C 64.43; H 3.58; Cl 8.92; N 10.67. $C_{21}H_{14}ClN_3O_3$. Calculated, %: C 64.38; H 3.60; Cl 9.05; N 10.72.

3-Hydroxy-1-(5-methylisoxazol-3-yl)-4,5-diphenyl-1,5-dihydro-2*H*-pyrrol-2-one (11g). Yield 235 mg (93%), white solid, mp 258°C (*i*-PrOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.34 (3H, s, 3-CH_3 isoxazole); 6.20 (1H, s,

5-CH pyrrolone); 6.77 (1H, s, H-4 isoxazole); 7.08–7.81 (10H, m, H Ph); 10.82 (1H, s, 3-OH pyrrolone). ^{13}C NMR spectrum, δ, ppm: 12.5; 60.8; 95.8; 125.2; 128.1 (2C); 128.2; 128.4 (2C); 128.5; 128.7 (2C); 128.8 (2C); 137.6; 131.6; 142.7; 156.4; 165.7; 170.4. Mass spectrum (APCI), *m*/*z* (I_{rel}, %): 333 $[M+H]^+$ (100). Found, %: C 72.33; H 4.77; N 8.50. $C_{20}H_{16}N_2O_3$. Calculated, %: C 72.28; H 4.85; N 8.43.

3-Hydroxy-5-(4-methoxyphenyl)-1-(5-methylisoxazol-3-yl)-4-phenyl-1,5-dihydro-2*H*-pyrrol-2-one (11h). Yield 240 mg (87%), white solid, mp 248°C (*i*-PrOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.33 (3H, d, ^4J = 1.1, 3-CH_3 isoxazole); 3.65 (3H, s, 4-C$\underline{H}_3$OC$_6$H$_4$); 6.15 (1H, s, 5-CH pyrrolone); 6.75 (1H, d, ^4J = 1.1, H-4 isoxazole); 6.76–7.79 (9H, m, H Ar); 10.80 (1H, s, 3-OH pyrrolone). ^{13}C NMR spectrum, δ, ppm: 12.5; 55.4; 60.3; 95.8; 114.1 (2C); 125.0; 128.1 (2C); 128.1; 128.7 (2C); 129.1; 129.7 (2C); 131.7; 142.6; 156.3; 159.3; 165.6; 170.3. Mass spectrum (APCI), *m*/*z* (I_{rel}, %): 363 $[M+H]^+$ (100). Found, %: C 69.68; H 5.08; N 7.71. $C_{21}H_{18}N_2O_4$. Calculated, %: C 69.60; H 5.01; N 7.73.

5-(4-Chlorophenyl)-3-hydroxy-1-(5-methylisoxazol-3-yl)-4-(*p*-tolyl)-1,5-dihydro-2*H*-pyrrol-2-one (11i). Yield 200 mg (70%), brick-red solid, mp 254–256°C (*i*-PrOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.23 (3H, s, 4-C$\underline{H}_3$C$_6$H$_4$); 2.34 (3H, s, 3-CH_3 isoxazole); 6.20 (1H, s, 5-CH pyrrolone); 6.78 (1H, s, H-4 isoxazole); 7.03–7.71 (8H, m, H Ar); 10.76 (1H, s, 3-OH pyrrolone). ^{13}C NMR spectrum, δ, ppm: 12.5; 21.3; 60.0; 95.6; 125.1; 128.0 (2C); 128.5; 128.8 (2C); 129.4 (2C); 130.3 (2C); 133.0; 136.9; 137.9; 142.2; 156.3; 165.7; 170.5. Mass spectrum (APCI), *m*/*z* (I_{rel}, %): 381 $[M+H]^+$ (100). Found, %: C 66.18; H 4.52; Cl 9.22; N 7.40. $C_{21}H_{17}ClN_2O_3$. Calculated, %: C 66.23; H 4.50; Cl 9.31; N 7.36.

Methyl 4-[4-hydroxy-1-(5-methylisoxazol-3-yl)-5-oxo-3-phenyl-2,5-dihydro-1*H*-pyrrol-2-yl]benzoate (11j). Yield 274 mg (92%), white solid, mp 260–262°C (*i*-PrOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.33 (3H, d, ^4J = 1.0, 3-CH_3 isoxazole); 3.77 (3H, s, 4-C$\underline{H}_3$OOCC$_6$H$_4$); 6.32 (1H, s, 5-CH pyrrolone); 6.79 (1H, d, ^4J = 1.0, H-4 isoxazole); 7.17–7.86 (9H, m, H Ar); 10.99 (1H, br. s, 3-OH pyrrolone). ^{13}C NMR spectrum, δ, ppm: 12.5; 52.6; 60.3; 95.6; 124.9; 128.0 (2C); 128.3; 128.8 (4C); 129.7 (2C); 129.8; 131.3; 142.9; 143.2; 156.3; 165.7; 166.2; 170.6. Mass spectrum (APCI), *m*/*z* (I_{rel}, %): 391 $[M+H]^+$ (100). Found, %: C 67.74; H 4.71; N 7.12. $C_{22}H_{18}N_2O_5$. Calculated, %: C 67.69; H 4.65; N 7.18.

3-Hydroxy-5-(4-methoxyphenyl)-1-(5-methylisoxazol-3-yl)-4-(*p*-tolyl)-1,5-dihydro-2*H*-pyrrol-2-one (11k). Yield 240 mg (83%), white solid, mp 225–226°C (*i*-PrOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.22 (3H, s, 4-C$\underline{H}_3$C$_6$H$_4$); 2.33 (3H, d, ^4J = 1.1, 3-CH_3 isoxazole); 3.65 (3H, s, 4-C$\underline{H}_3$OC$_6$H$_4$); 6.10 (1H, s, 5-CH pyrrolone); 6.75 (1H d, ^4J = 1.1, H-4 isoxazole); 6.75–7.67 (8H, m, H Ar); 10.74 (1H, br. s, 3-OH pyrrolone). ^{13}C NMR spectrum, δ, ppm: 12.5; 21.3; 55.4; 60.3; 95.8; 114.1 (2C); 125.3; 128.0 (2C); 128.8; 129.3; 129.3 (2C); 129.7 (2C); 137.7; 141.9; 156.3; 159.3; 165.7; 170.3. Mass spectrum (APCI), *m*/*z* (I_{rel}, %): 377 $[M+H]^+$ (100). Found, %: C 70.22; H 5.32; N 7.37. $C_{22}H_{20}N_2O_4$. Calculated, %: C 70.20; H 5.36; N 7.44.

Methyl 4-[4-hydroxy-1-(5-methylisoxazol-3-yl)-5-oxo-3-(*p*-tolyl)-2,5-dihydro-1*H*-pyrrol-2-yl]benzoate (11l). Yield 260 mg (84%), white solid, mp 240–242°C (*i*-PrOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.21 (3H, s, 4-C$\underline{H}_3$C$_6$H$_4$); 2.32 (3H, d, ^4J = 1.1, 3-CH_3 isoxazole); 3.77 (3H, s, 4-C$\underline{H}_3$OOCC$_6$H$_4$); 6.28 (1H, s, 5-CH pyrrolone); 6.78 (1H, d, ^4J = 1.1, H-4 isoxazole); 7.05–7.88 (8H, m, H Ar); 10.84 (1H, s, 3-OH pyrrolone). ^{13}C NMR spectrum, δ, ppm: 12.5; 21.3; 52.5; 60.3; 95.6; 125.2; 127.9 (2C); 128.4; 128.8 (2C); 129.4 (2C); 129.6 (2C); 137.9; 129.8; 142.3; 143.4; 156.3; 165.7; 166.2; 170.5. Mass spectrum (ESI), *m*/*z* (I_{rel}, %): 403 $[M–H]^-$ (100), 404 $[M]^-$ (44). Found, %: C 68.24; H 5.04; N 6.98. $C_{23}H_{20}N_2O_5$. Calculated, %: C 68.31; H 4.98; N 6.93.

X-ray structural investigation of 3-amino-5-methylisoxazole (1) and 5-amino-3-methylisoxazole. The crystals of 3-amino-5-methylisoxazole ($C_4H_6N_2O$) are triclinic. At 293 K: *a* 5.3016(8), *b* 7.257(1), *c* 7.4066(9) Å; α 68.56(1), β 83.83(1), γ 71.19(1)°; *V* 251.04(6) Å^3, M_r 98.11, *Z* 2, space group $P\bar{1}$, d_{calc} 1.298 g/cm^3, μ(MoKα) 0.097 mm^{-1}, *F*(000) 104. Intensities of 1594 reflections (876 independent, R_{int} 0.009) were measured on a Xcalibur-3 diffractometer (graphite monochromated MoKα radiation, CCD detector, ω-scaning, $2\Theta_{max}$ 50°).

The crystals of 5-amino-3-methylisoxazole ($C_4H_6N_2O$) are orthorhombic. At 293 K: *a* 7.4663(6), *b* 8.8879(7), c 7.8373(7) Å; *V* 520.08(7) Å^3; M_r 98.11; *Z* 4; space group *Pna*2$_1$; d_{calc} 1.253 g/cm^3, μ(MoKα) 0.093 mm^{-1}; *F*(000) 208. Intensities of 4663 reflections (1179 independent, R_{int} 0.030) were measured on a Xcalibur-3 diffractometer (graphite monochromated MoKα radiation, CCD detector, ω-scaning, $2\Theta_{max}$ 60°).

The structures were solved by direct method using the SHELXTL package.[51] Position of the hydrogen atoms were located from electron density difference maps and refined by "riding" model with U_{iso} = nU_{eq} of the carrier atom (n = 1.5 for methyl group and n = 1.2 for other hydrogen atoms). The hydrogen atoms of amino groups were refined using isotropic approximation. Full-matrix least-squares refinement of the structures against F^2 in anisotropic approximation for non-hydrogen atoms using 876 (3-amino-5-methylisoxazole (**1**)), 1078 (5-amino-3-methylisoxazole) reflections was converged to: wR_2 0.097 (R_1 0.035 for 789 reflections with $F > 4\sigma(F)$, *S* 1.100) for structure of 3-amino-5-methylisoxazole (**1**) and wR_2 0.056 (R_1 0.027 for 700 reflections with $F > 4\sigma(F)$, *S* 0.891) for structure of 5-amino-3-methylisoxazole. The final atomic coordinates and crystallographic data for molecules of 3-amino-5-methylisoxazole (**1**) and 5-amino-3-methylisoxazole have been deposited at the Cambridge Crystallographic Data Center (deposits CCDC 1865795 for 3-amino-5-methylisoxazole (**1**) and CCDC 1865794 for 5-amino-3-methylisoxazole).

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