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Synthesis of novel 1-[(1-ethoxymethylene)amino]imidazol-5(4*H*)-ones and 1,2,4-triazin-6(5*H*)-ones from optically active α-aminocarboxylic acid hydrazides

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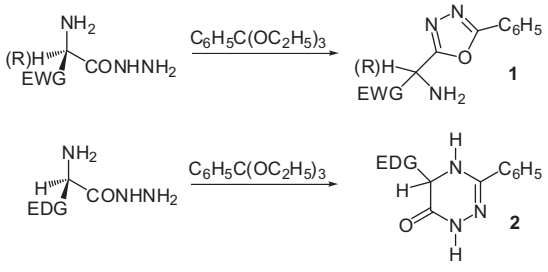
ABSTRACT

New derivatives of 1-[(1-ethoxymethylene)amino]imidazol-5(4*H*)-one and 1,2,4-triazin-6(5*H*)-one were synthesized via reactions of optically active α-aminocarboxylic acid hydrazides and triethyl orthoesters in xylene. The factors influencing the formation of the unexpected five-membered products and attempts to elucidate the mechanism are discussed.

Heterocyclic compounds containing five-membered azole or six-membered azine scaffolds have attracted the attention of many scientists due to their broad spectrum of biological activity. In addition, these scaffolds find various industrial applications. One subgroup of the azole family is imidazole and its derivatives,[1] with many of these attracting interest in medicinal chemistry mainly for their antifungal, antiprotozoal and antihypertensive activities.[2] They have also been utilized as corrosion inhibitors, ionic liquids, and for the production of thermally stable polymers.[3] The first imidazole synthesis was successfully performed in 1858 by Debus.[4] The three-component reaction involving dicarbonyl compounds, aldehydes, ammonia, or its salts is still employed for the formation of this particular group of heterocycles.[5,6] The most popular methods for the preparation of imidazoles make use of α-halocarbonyl compounds and guanidines,[7] 1,2-diaminoalkanes, and carboxylic acids[8] or comprise transformations of other heterocycles such as azirines,[9] 4-aminoisoxazoles,[10] 1,2,4-oxadiazoles,[11] and pyrazines.[12]

1,2,4-Triazine and its derivatives constitute another interesting azine subgroup.[13] These are applied in medicine as potential antibacterial and antifungal agents, in the agrochemical industry as plant protecting materials, and as components of commercial dyes.[14–18] A wide range of synthetic procedures have been reported for 1,2,4-triazin-6-one derivatives. They are commonly prepared from acid hydrazides,[19] amides,[20] iminoesters,[21,22] or from azirines.[23]

Our earlier research on the application of free α-aminocarboxylic acid hydrazides and triethyl orthoesters demonstrated the possibility of the synthesis of both six-membered 1,2,4-triazines and five-membered 1,3,4-oxadiazoles.[24] We found that the product formed depended strongly on the structure of the starting hydrazide, in particular on the electronic nature and steric hindrance of substituents adjacent to the α carbon. In cases where the reactions were conducted with the use of equimolar amounts of triethyl orthobenzoate and hydrazides containing electron-withdrawing groups (EWG) or bulky substituents at the α position, we observed the formation of mainly 1,3,4-oxadiazoles (**1**) possessing a free aminomethyl group at position 2 (Scheme 1).



Scheme 1. General relationship between the structures of the α-aminocarboxylic acid hydrazides and the products resulting from the reaction with equimolar amounts of triethyl orthobenzoate.

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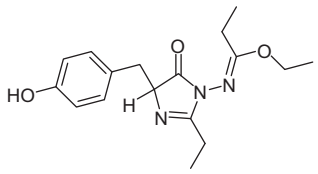
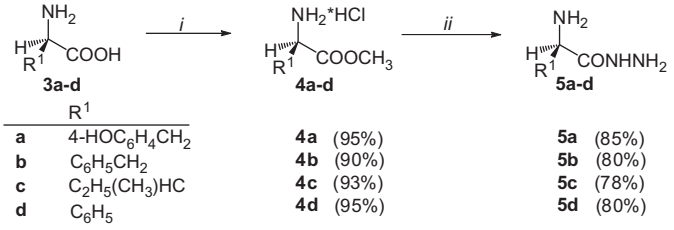


Figure 1. The structure of 1-[(1-ethoxypropylene)amino]-2-ethyl-4-(4-hydroxybenzyl)imidazol-5(4*H*)-one.

Derivatives of 1,2,4-triazine (**2**) were obtained in satisfactory yields from the reactions of hydrazides bearing an electron-donating group (EDG) at the α position (Scheme 1). These substituents increase both the nucleophilicity and basicity of the amino group. In this way, the amino center responsible for the formation of the six-membered ring becomes more reactive than the competing carbonyl. Heating L-(−)-tyrosine hydrazide in the presence of an excess of the orthoester, we obtained another five-membered heterocycle identified as 1-[(1-ethoxypropylene)amino]-2-ethyl-4-(4-hydroxybenzyl)imidazol-5(4*H*)-one (Fig. 1).[25]

Inspired by this unexpected result, we decided to investigate the reactions of selected α-aminocarboxylic acid hydrazides in order to obtain this interesting class of heterocycles. The starting hydrazides were obtained from commercially available α-aminocarboxylic acids according to well known procedures. Thus, L-(−)-tyrosine, L-(−)-phenylalanine, L-(+)-isoleucine, and D-(−)-α-phenylglycine (**3a–d**) were transformed into the corresponding methyl ester hydrochlorides **4a–d** with methanol and thionyl chloride. The resulting compounds **4a–d** were then converted into the final hydrazides **5a–d** by reaction with hydrazine hydrate under mild conditions (Scheme 2).

Acid hydrazides **5a–c** were heated with excess amounts of triethyl orthoesters: orthoacetate, orthopropionate, and orthobenzoate ($R^2 = CH_3$, C_2H_5, C_6H_5, Scheme 3) yielding the derivatives of imidazol-5(4*H*)-one **7** (method A). The optimization of the reaction conditions revealed that the formation of the desired imidazol-5(4*H*)-ones **7** proceeded smoothly in a non-polar solvent (xylene)



Scheme 2. Synthesis of the starting α-aminocarboxylic acid hydrazides **5**. Reagents and conditions: (i) MeOH, $SOCl_2$, 0 °C, 6 h; (ii) $N_2H_4{\cdot}H_2O$, MeOH, rt, 24 h.

Table 1
Optimization of the reaction conditions for the preparation of 1-[(1-ethoxyethylene)amino]-2-methyl-4-(4-hydroxybenzyl)imidazol-5(4*H*)-one (**7a**)

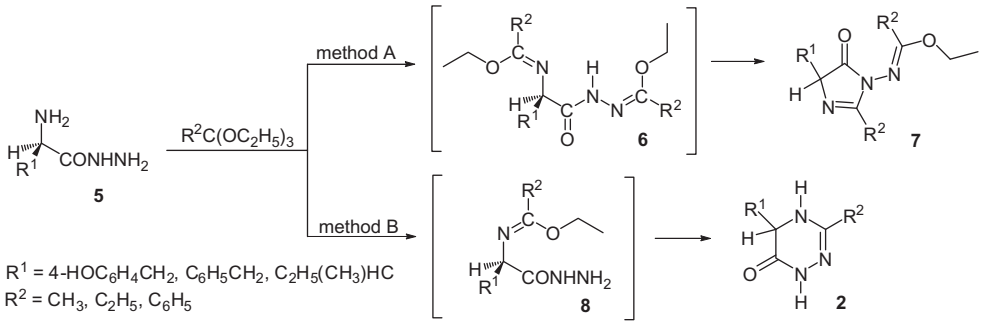
Entry	Molar ratio			Solvent	**7a** Yield[a] (%)	**2a** Yield[a] (%)
	Hydrazide **5a**	$CH_3C(OC_2H_5)_3$	*p*-TsOH			
1	1	5	—	—	48	0
2	1	5	0.07	—	68	0
3	1	3	0.07	CH_3CN	55	10
4	1	3	0.07	Xylene	75	7
5	1	1	0.07	Xylene	5	66

[a] Yield with respect to the starting hydrazide **5a**.

and in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH) (Table 1, entry 4). Decreasing the molar ratio of hydrazide **5a** and $CH_3C(OC_2H_5)_3$ to an equimolar amount changed the reaction course and resulted in the formation of the six-membered 1,2,4-triazin-6(5*H*)-one **2** (method B) (Table 1, entry 5).

The yields of the reactions leading to the five-membered imidazol-5(4*H*)-ones **7a–i** were high and varied from 51% to 78% (Table 2). It was found that compounds possessing alkyl groups ($R^2 = CH_3$, C_2H_5) at position 2 were formed more easily than their counterparts substituted with a phenyl group. In addition, the steric hindrance caused by the R^1 substituent in the starting hydrazide also played an important role. The yields of imidazol-5(4*H*)-ones **7g–i** obtained from L-(+)-isoleucine hydrazide (**5c**) were relatively lower than those prepared from the hydrazides of L-(−)-tyrosine (**5a**) and L-(−)-phenylalanine (**5b**). The six-membered 1,2,4-triazin-6(5*H*)-ones **2a–i**, produced in the reactions with equimolar amounts of orthoester, were also obtained in high yields of 56–80% (Table 2). The structure of the products both from the family of imidazol-5(4*H*)-one **7** and 1,2,4-triazin-6(5*H*)-one **2** was confirmed by X-ray analysis,[25,26] elemental analysis, and typical spectroscopic methods.

However, regardless of the presence or absence of a catalyst, we did not obtain any acyclic intermediates **6** or **8**, which accompanied the reactions starting from α-hydroxy- and *N*-protected α-aminocarboxylic acids and orthoesters.[27,28] Thus, the compounds possessing a free amino group at the α position, were more reactive than their α-hydroxy or *N*-protected α-amino counterparts and underwent cyclization immediately after their formation. Hydrazides of α-aminocarboxylic acids constitute materials possessing at least two nucleophilic sites susceptible to attack by orthoesters: the free amino group adjacent to the α carbon and the hydrazine group. Generally, the amino group is more reactive than the hydrazine that neighbors the carbonyl functionality. The reaction of D-(−)-α-phenylglycine methyl ester (**9**) with triethyl orthoacetate leading to *N*-(1-ethoxyethylene) derivative (**10**) proceeded smoothly with heating for about 30 min, while the transformation of phenylacetic acid hydrazide **5e** into the

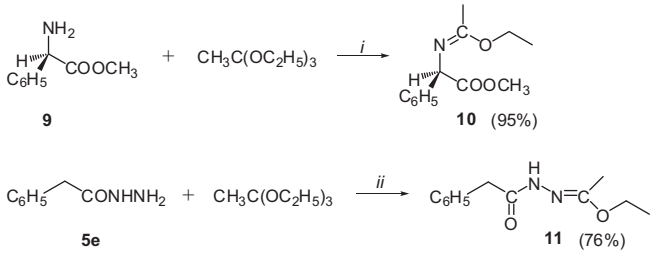


Scheme 3. Reactions of α-aminocarboxylic acid hydrazides **5** with triethyl orthoesters: method A – conducted with excess orthoester (3 equiv), xylene, *p*-TsOH (0.07 equiv), reflux 2–20 h; method B—conducted with equimolar amounts of orthoester (1 equiv), xylene, *p*-TsOH (0.07 equiv), reflux 2–6 h.

Table 2
Imidazol-5(4*H*)-ones **7** and 1,2,4-triazin-6(5*H*)-ones **2** obtained from the reactions of α-aminocarboxylic acid hydrazides **5** with triethyl orthoesters[29]

Entry	R^1	R^2	Product **7** method A			Product **2** method B		
			Time (h)	Yield[a] (%)	Mp (°C)	Time (h)	Yield[a] (%)	Mp (°C)
a	4−$HOC_6H_4CH_2$	CH_3	20	75	164–165[24]	6	66	58-60
b	4−$HOC_6H_4CH_2$	C_2H_5	20	78	173–175	6	74	63–65
c	4−$HOC_6H_4CH_2$	C_6H_5	8	51	79–81	3	68	106–107[23]
d	$C_6H_5CH_2$	CH_3	4	78	—	4	80	118–120
e	$C_6H_5CH_2$	C_2H_5	4	74	—	4	78	176–178
f	$C_6H_5CH_2$	C_6H_5	2	62	95–96	2	56	208–210
g	$C_2H_5(CH_3)HC$	CH_3	8	59	—	6	70	142–144
h	$C_2H_5(CH_3)HC$	C_2H_5	6	65	—	6	66	81–83
i	$C_2H_5(CH_3)HC$	C_6H_5	2	57	—	4	63	158–161

[a] Yield with respect to the starting hydrazide **5**.



Scheme 4. Synthesis of *N*-(1-ethoxyethylene)-α-phenylglycine methyl ester (**10**) and *N*′-(1-ethoxyethylene)-phenylacetic acid hydrazide (**11**) in the reaction with triethyl orthoacetate. Reagents and conditions: (i) $CH_3C(OC_2H_5)_3$, xylene, 30 min, reflux; (ii) $CH_3C(OC_2H_5)_3$, xylene, reflux, 6 h.

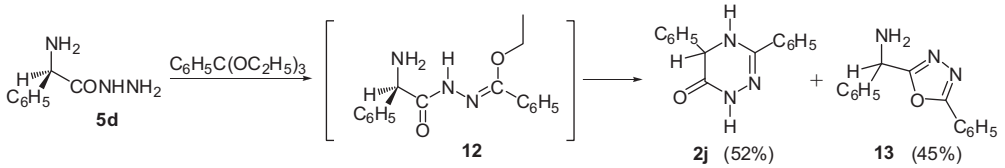
corresponding *N*′-(1-ethoxyethylene) hydrazide (**11**) required heating for a few hours with the orthoester (Scheme 4). Such behavior is probably caused by the difference in basicity of the two nucleophilic sites. The pK_a ionization constants of D-(−)-α-phenylglycine hydrazide (**5d**) determined by the potentiometric method in aqueous-methanol solution being equal to: pK_{a1} = 6.53 ± 0.08 for the amino group adjacent to the α carbon and pK_{a2} = 2.45 ± 0.10 for the terminal hydrazine group, remain in accordance with observed trends.

Different results were obtained when D-(−)-α-phenylglycine hydrazide (**5d**) was heated with an equimolar amount of triethyl orthobenzoate. This time no traces of the imidazol-5(4*H*)-one **7** were found in the post-reaction mixture, but another five-membered product: 2-(1-amino-1-phenylmethyl)-5-phenyl-1,3,4-oxadiazole (**13**) (Scheme 5).[24] It was concluded that this outcome was caused not only by the decrease in the nucleophilicity of the amino group, but mainly due to the steric hindrance of the phenyl groups both from hydrazide **5d** and orthobenzoate. In this way, the competing hydrazine site reacted readily yielding *N*′-ethoxybenzylidenehydrazide **12**, which underwent cyclization with the formation of two different products: the six-membered 1,2,4-triazine **2j** and the five-membered 1,3,4-oxadiazole **13**.

Analyzing the mechanism of the reaction between orthoesters and α-aminocarboxylic acid hydrazides, possessing a methylene linker at the α position (**5a**–**c**), we assumed that the amino group adjacent to the α carbon in hydrazides **5a**–**c** attacked the electrophilic carbon atom of the orthoester yielding iminoether **8** (Scheme 3). When the transformation was conducted with equimolar amounts of reagents, the resulting iminoether **8** underwent further cyclization to form 1,2,4-triazin-6(5*H*)-one derivatives **2**. However, in excess orthoester, the less reactive hydrazine group of intermediate **8** reacted with another molecule of the orthoester giving the appropriate diiminoether **6**. This acyclic compound cyclized to form imidazol-5(4*H*)-ones **7** (Scheme 3) in the presence of a catalytic amount of *p*-TsOH. The bulky phenyl group at the α position of the starting D-(−)-α-phenylglycine hydrazide (**5d**) prevented the reaction with sterically crowded triethyl orthoester at the reactive α-amino site. Thus, the hydrazine group attacked the electrophilic carbon atom of the orthobenzoate to form the intermediate **12** (Scheme 5). This underwent cyclization in the presence of the catalyst yielding both 1,3,4-oxadiazole **13** and 1,2,4-triazine **2**.

The optical rotations of imidazol-5(4*H*)-ones **7** (method A) and 1,2,4-triazin-6(5*H*)-ones **2** (method B), derived from optically active hydrazides of: L-(+)-tyrosine (**5a**, $[\alpha]_D^{20}$ +80.5), L-(+)-phenylalanine (**5b**, $[\alpha]_D^{20}$ +33.0), and L-(+)-isoleucine (**5c**, $[\alpha]_D^{20}$ +27.8), showed that in the reactions with triethyl orthoacetate, orthopropionate, and orthobenzoate, racemization at the asymmetric carbon occurred although this atom was not directly involved in the formation of the products. We believe that this phenomenon can be explained by tautomerism, where the mobile hydrogen atom situated on the stereogenic carbon atom at the α position of the intermediate iminoethers **6** or **8** could be envisioned to migrate to the imino or carbonyl groups with a simultaneous shift of the double bond and loss of the optical activity.

In summary, the hydrazides of free α-aminocarboxylic acids are valuable starting materials in the direct synthesis of five-membered imidazol-5(4*H*)-ones, 1,3,4-oxadiazoles, and six-membered 1,2,4-triazin-6(5*H*)-ones. The electronic effects of the substituents adjacent to the α carbon in the starting hydrazide, the steric hindrance of both the orthoester and hydrazide, and finally the molar ratio of the reagents were the most important factors impacting on the reaction course and the products. Electron-donating substituents and stoichiometric amounts of orthoester promoted the formation of 1,2,4-triazin-6(5*H*)-ones, while the use of excess



Scheme 5. Formation of 1,2,4-triazin-6(5*H*)-one **2j** and 2-aminomethyl-1,3,4-oxadiazole **13** from D-(−)-α-phenylglycine hydrazide (**5d**) and triethyl orthobenzoate.

orthoester gave mainly new imidazol-5(4*H*)-ones. Electron-withdrawing and bulky groups favoured the reaction at the opposite hydrazine group. In this case, the transformations were carried out with the use of equimolar amounts of reagents resulting in the formation of derivatives of 1,3,4-oxadiazole.

Supplementary data

Supplementary data (experimental procedures and characterization data for all new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.06.052.

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29. *Representative procedure*—(method A): L-(−)-Phenylalanine hydrazide (**5b**, 1.79 g, 10 mmol) was added to a mixture of triethyl orthobenzoate (6.87 g, 30 mmol, 7.0 mL), dry xylene (40 mL) and *p*-TsOH (0.12 g) and heated at reflux temperature for 2 h (TLC). After cooling, the mixture was washed with H_2O (30 mL), dried over $MgSO_4$ and then concentrated under reduced pressure. The crude solid was subjected to column chromatography (silica gel, eluent: benzene/AcOEt 1:3 v/v) to give 2.46 g (62%) of 1-[(1-ethoxybenzylidene)amino]-2-phenyl-4-benzylimidazol-5(4*H*)-one (**7f**) as yellow crystals with a melting point of 95–96 °C; R_f (benzene/AcOEt 1:3 v/v) 0.62; [Found: C, 75.52; H, 5.87; N, 10.62. $C_{25}H_{23}N_3O_2$ requires C, 75.54; H, 5.83; N, 10.57%]. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.32 (3H, t, *J* 6.8 Hz, $Ph(OCH_2CH_3)C{=}N$–N1), 2.61 (1H, dd, *J* 4.0 and 13.6 Hz, CH-C4), 2.92 (1H, dd, *J* 4.0 and 13.6 Hz, CH-C4), 4.30 (1H, t, *J* 4.0 Hz, H-C4), 4.37 (2H, q, *J* 6.8 Hz, $Ph(OCH_2CH_3)C{=}N$–N1), 7.17–7.25 (7H, m, H_{Ar}), 7.40–7.51 (6H, m, H_{Ar}), 7.82 (2H, d, *J* 8.0 Hz, H_{Ar}). ^{13}C NMR (DMSO-d_6): δ 13.9, 36.7, 64.4, 66.4, 126.3, 126.8, 127.9, 128.1, 128.2, 128.4, 128.5, 128.7, 129.3, 130.3, 130.8, 131.3, 159.8, 170.2, 176.2. UV–vis: λ_{max} (MeOH) 201.0 nm ($\varepsilon{\cdot}10^{-3}$ 14.42 cm^{-1} LM^{-1}), 242.0 (8.58); IR (ATR) ν: 3058, 1731, 1611, 1595, 1514, 1446, 1370, 1323, 1263, 1227, 1122, 1075, 936, 815, 779, 736, 711, 694 cm^{-1}.