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Synthesis of α-substituted 2-(1*H*-1,2,4-triazol-3-yl)acetates and 5-amino-2,4-dihydro-3*H*-pyrazol-3-ones *via* the Pinner strategy

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ABSTRACT

A series of 2-(1*H*-1,2,4-triazol-3-yl)acetates, as well as 4-mono- and 4,4-disubstituted 5-amino-2,4-dihydro-3*H*-pyrazol-3-ones (including spirocyclic derivatives) have been synthesized using the Pinner reaction strategy. α-Mono- and α,α-disubstituted ethyl cyanoacetates were converted into the corresponding carboxyimidate salts that served as the key intermediates. Their further reaction with formylhydrazide or hydrazine hydrate provided triazolylacetates or aminopyrazolones (including spirocyclic derivatives), depending on the structure of the starting Pinner salt and the nature of the nucleophile. The scope and limitations of the developed synthetic method have been established.

Since 1877 when A. Pinner and Fr. Klein had discovered the synthesis of carboximidate hydrohalides (now referred to as the Pinner salts) [1,2], this class of substances became an important part of the synthetic toolbox for organic chemists. These carboxylic acid derivatives have attracted much attention due to their remarkable reactivity towards carbo- and hetero-nucleophiles that has been widely exploited for the synthesis of numerous organic compounds including nitrogen heterocycles [3–5]. Pyrazoles and 1,2,4-triazoles are examples of such heterocycles that have attracted much attention because of their remarkable applications in the pharmaceutical industry. In particular, these heterocycles have been incorporated into numerous marketed medicines such as diuretic Muzolimine for treatment of hypertension [6,7], antiviral agent Ribavirin for cure of chronic Hepatitis C virus (HCV) [8–10], or alpha blocker Dapiprazole used to reverse mydriasis after an eye examination [11–13].Fig 1.

As a part of our ongoing efforts towards the synthesis of triazole derivatives for drug discovery [14–19], we have turned our attention to non-fused (1,2,4-triazol-3-yl)acetates – promising synthetic intermediates for organic and medicinal chemistry. Several synthetic approaches to these compounds have been developed to date. Among them are EtONa-mediated cyclizations of ethyl malonyl-3-thiosemicarbazide followed by desulfurization with Raney Ni (Scheme 1, pathway ***A***) [20,21]; a reaction of ethyl 3-ethoxy-3-iminopropanoate with monosubstituted hydrazines and subsequent ring closure with $HC(OEt)_3$ or Ac_2O (pathway ***B***) [22,23]; or the two-step condensation of ethyl 3-alkoxy-3-iminopropanoates with hydrazides (pathways ***C***) [24,25]. Surprisingly, α-mono- [26] and α,α-disubstituted [27,28] non-fused (1,2,4-triazol-3-yl)acetates **1** appeared to be largely underrepresented in the literature and have never been obtained *via* the Pinner reaction strategy. Herein, we have turned our attention to α-mono- and α,α-disubstituted ethyl cyanoacetates (**2**) as the possible starting materials for the preparation of the title compounds. A possible complication of the selected strategy can include an alternative reaction pathway including nucleophilic attack of the intermediate carboxyimidates **3** at the ester moiety (Scheme 2). Such reactions leading to 3-amino-1*H*-pyrazol-5(4*H*)-ones **4** have been known in the literature [29–35]. This work is aimed at studying the scope and limitation of

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the aforementioned strategy for the synthesis of substituted triazolylacetates **1** or 3-amino-1*H*-pyrazol-5(4*H*)-ones **4**, as well as factors affecting the chemoselectivity of this transformation.

First of all, a series of appropriately substituted cyanoacetates **2a–f** was converted into the corresponding carboximidate hydrochlorides **3a–f** adopting the literature procedures [36–39]. The latter, in turn, were allowed to react with formylhydrazide under base-mediated conditions (Table 1).

Intriguingly, while the unsubstituted (**3a**·HCl) and 2-*i*-Pr-substituted (**3b**·HCl) derivatives were completely converted into triazolylacetates **1a,b**, the α,α-dimethylated counterpart **3c**·HCl was exclusively turned into the corresponding aminopyrazolone **4c** (Table 1, Entries 1–3). At the same time, the utilization of intermediates **3d–f**·HCl bearing an annulated (hetero)cyclic substituent afforded mixtures of appropriately substituted triazolylacetates **1d–f** and spirocyclic aminopyrazolones **4d–f** at different ratios (Table 1, Entries 4–6).

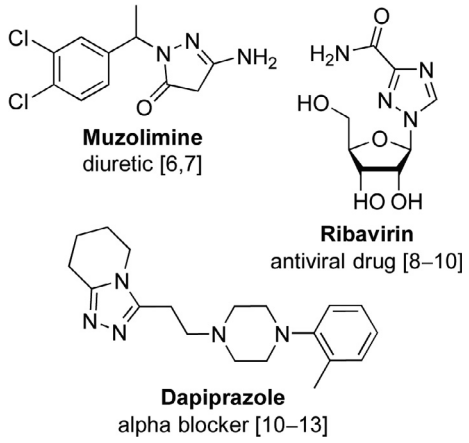


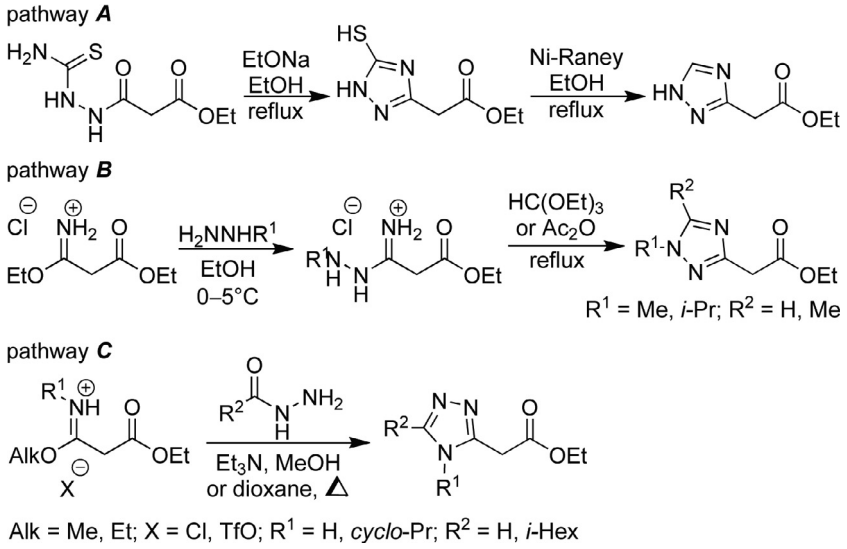
Fig. 1. 5-Aminopyrazolone and 1,2,4-triazole-containing marketed drugs.

These results might suggest that the nature of the α-substituent in **3** played a crucial role for the reaction direction with formylhydrazide. Apparently, a possibility of prototropy (or lack thereof) as well as conformational aspects of **3** could account for the selective formation of triazolylacetates **1a,b** and **1d–f** and aminopyrazolones **4c–f**.

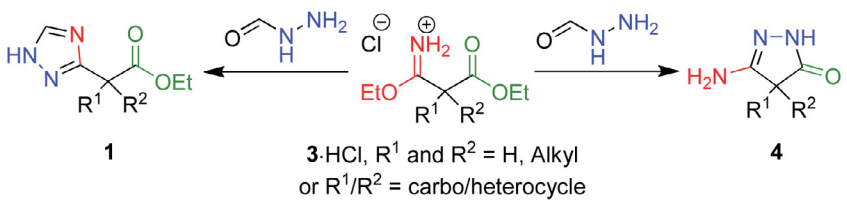
Thus, the deprotonation of carboximidate hydrochlorides (pK_a ~ 5 [40]) with a base might lead to either imino ethers or imino enoles depending on the substitution at the α-carbon atom. Specifically, the salts of unsubstituted (**3a**·HCl) as well as 2-*i*-Pr-substituted (**3b**·HCl) imidates were likely converted into the corresponding ethyl 3-ethoxy-3-hydroxyacrylimidates **3a** and **3b**, while hydrochloride of α,α-dimethylated imidate **3c**·HCl – into 3-ethoxy-3-iminopropanoate **3c** (Scheme 3). The close proximity as well as coplanar position of imino group and enol functionalities in **3** allowed for the hydrogen bonding that further reinforced the adopted conformation (Fig. 2).

Next, ethyl 3-ethoxy-3-hydroxyacrylimidates **3a** and **3b** reacted with formylhydrazide as the Michael acceptors providing the interim amidine **5**, that underwent the intramolecular condensation to give the corresponding triazolylacetates **4a,b** (Scheme 4).

Contrary to the above, **3c** reacted with formylhydrazide at the carbonyl moiety first. There might be two possible reasons for this. On the one hand, a lone pair of electrons of the imine moiety precluded the formylhydrazide attack at the imidate fragment. On the other hand, hydrogen bonding increased the electrophilicity of the

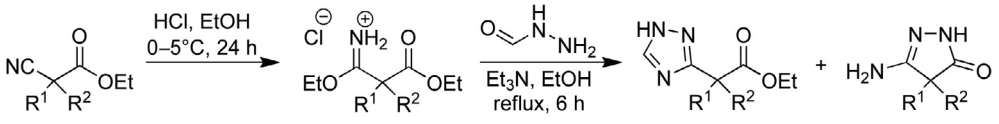


Scheme 1. Known approaches to 2-(1,2,4-triazol-3-yl) acetates.



Scheme 2. Reaction of carboxyimidate hydrochlorides with formylhydrazide.

Table 1
The reaction of 3·HCl with formylhydrazide.



2 **3**·HCl **1** **4**

Entry	Starting compound **2**	Intermediate **3** (isolated yield, %)	Product **1** (yield by ^{1}H NMR / isolated, %)	Product **4** (yield by ^{1}H NMR / isolated, %)	R^1/R^2
1	**2a**	**3a**·HCl (81)	**1a** (100/78)	**4a** (0/0)	H/H
2	**2b**	**3b**·HCl (75)	**1b** (100/73)	**4b** (0/0)	*i*-Pr/H
3	**2c**	**3c**·HCl (67)	**1c** (0/0)	**4c** (100/72)	Me/Me
4	**2d**	**3d**·HCl (40)	**1d** (85/32)	**4d** (15/5)	$(CH_2)_2$
5	**2e**	**3e**·HCl (82)	**1e** (40/31)	**4e** (60/46)	$(CH_2)_3$
6	**2f**	**3f**·HCl (77)	**1f** (50/19)[a]	**4f** (50/30)[a]	$(CH_2)_2O$ $(CH_2)_2$

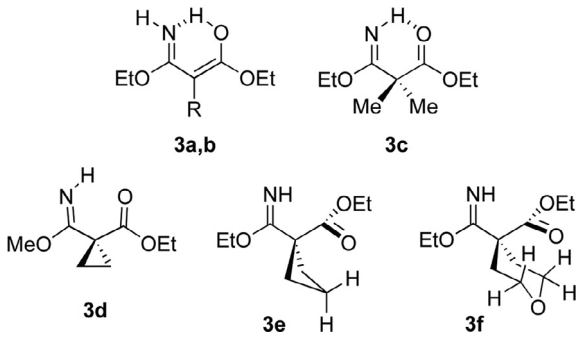
[a] Compound **4f** partially precipitated from the reaction mixture. The ratio is given for liquid reaction phase and overall yields are presented.

carbonyl group. The concerted impact of these factors resulted in the formation of intermediate **6** followed by intramolecular cyclization leading to aminopyrazolone **4c** (Scheme 5).

At the same time, the annular atoms of the attached (hetero)-cyclic substituent in **3e** and **3f** pushed both the imidate and carbonyl groups out of the plane due to the repulsive 1,3-interactions, thus disrupting the hydrogen bonding (Fig. 2). This

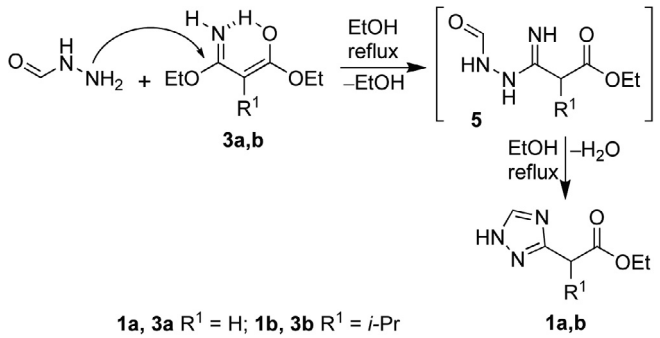
3a,b **3a–f**·HCl **3c–f**

Scheme 3. Reaction of carboxyimidate hydrochlorides with formylhydrazine.



3a,b **3c** **3d** **3e** **3f**

Fig. 2. Proposed tautomeric forms and conformations of **3a–f**.



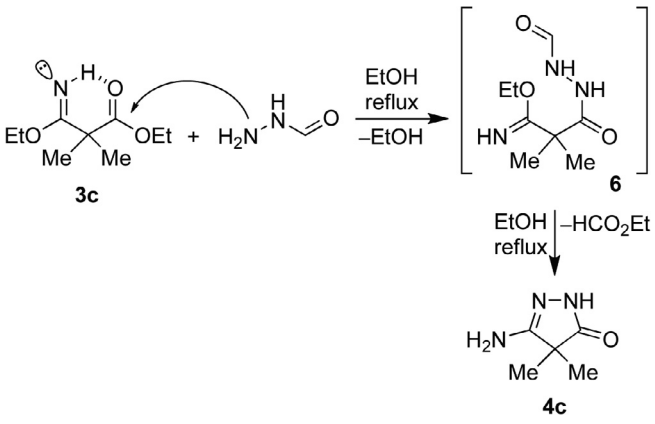
3a,b **5** **1a,b**

1a, 3a R^1 = H; **1b, 3b** R^1 = *i*-Pr

Scheme 4. A proposed mechanism for the formation of **1a,b**.

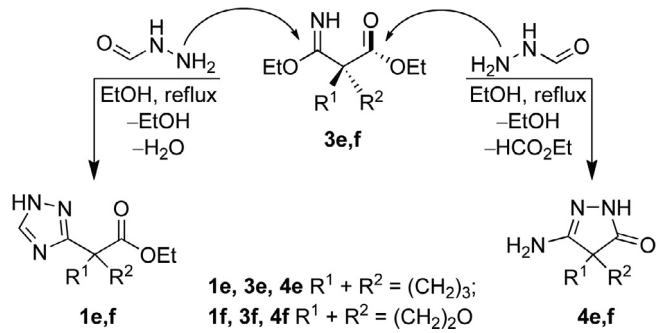
drived the imidate and carboxylate groups to possess comparable electrophilicity that led to the formation of both possible products (Scheme 6).

Based on this, the interaction between cyclopropyl derivative **3d** and formylhydrazide looks odd at the first glance since it should demonstrate the reactivity similar to that of **3c**. A possible reason behind this might be the larger plane angle value between the carboximidate and the carboxylate moieties caused by the cyclopropane moiety, which hampered the formation of the intramolecular hydrogen bond in the structure of **3d** and defined the somewhat preferred initial attack of the nucleophile at the carboximidate group. This assumption was confirmed by DFT calculations. In particular, the predicted Gibbs free energy value for the



3c **6** **4c**

Scheme 5. The proposed mechanism for formation of **4c**.



3e,f **1e,f** **4e,f**

1e, 3e, 4e $R^1 + R^2 = (CH_2)_3$;
1f, 3f, 4f $R^1 + R^2 = (CH_2)_2O$

Scheme 6. The synthesis of **1e,f** and **4e,f**.

following hypothetic isodesmic reaction involving the conformers of **3c** and **3d** having intramolecular hydrogen bonds (Figure 3)

3c + *cyclo*-C_3H_6 = **3d** + C_3H_8

was $\Delta G = -3.6$ kcal/mol, which reflected noticeable strain energy in the conformer of **3d** (comparable to the stabilization gain typically provided by hydrogen bonding).

Since the above method appeared to be unsuitable for obtaining **4a**, **4b** and **4d**, as well as **1c**, we have considered other synthetic approaches to obtain these compounds. In this way, a series of pyrazolones **4a–f** was synthesized by reaction of **3a–f**·HCl with hydrazine hydrate (Table 2).

The inability of direct synthesis of **1c** from **3c**·HCl was also circumvented by an alternative synthetic pathway. Thus, ethyl triazolylacetate **1a** was treated with BnCl and K_2CO_3 in DMF in order to install the protecting group at the heterocyclic core and prevent the methylation of the NH group at the later step. The obtained mixture of *N*-protected regioisomers **7** was exhaustively methylated at the active methylene group by using an excess of MeI and NaH as a base to give a mixture of regioisomeric α,α-dimethylated products **8**. Eventually, Pd-catalyzed hydrogen-mediated cleavage of the benzyl protecting group afforded the target methyl

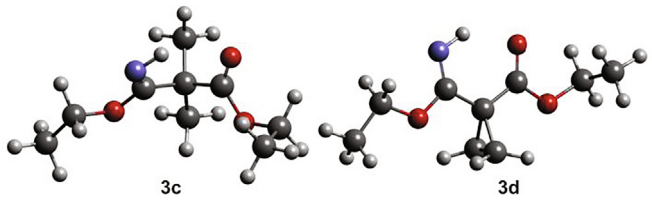
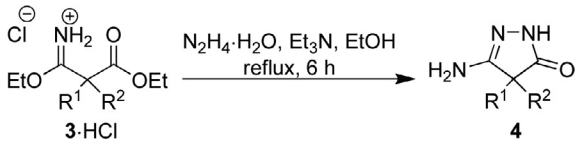


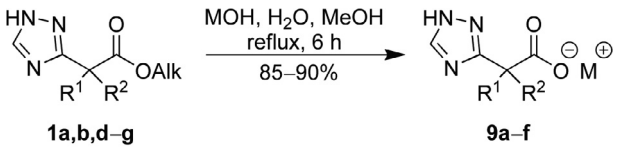
Fig. 3. Conformers of 3c and 3d having an intramolecular hydrogen bond according to DFT calculations.

Table 2
The reaction of 3·HCl with hydrazide hydrate.



3·HCl 4

Entry	Intermediate **3**	Product **4** (isolated yield, %)	R^1/R^2
1	**3a**·HCl	**4a** (82)	H/H
2	**3b**·HCl	**4b** (66)	*i*-Pr/H
3	**3c**·HCl	**4c** (81)	Me/Me
4	**3d**·HCl	**4d** (70)	$(CH_2)_2$
5	**3e**·HCl	**4e** (73)	$(CH_2)_3$
6	**3f**·HCl	**4f** (74)	$(CH_2)_2O(CH_2)_2$



1a,b,d–g **9a–f**

for R^1 and R^2 refer Table 1 and Scheme 7
1a,b,d–f Alk = Et; **1g** Alk = Me
9a,b M = Na; **9c–f** M = Li

Scheme 8. The synthesis of **9a–f**.

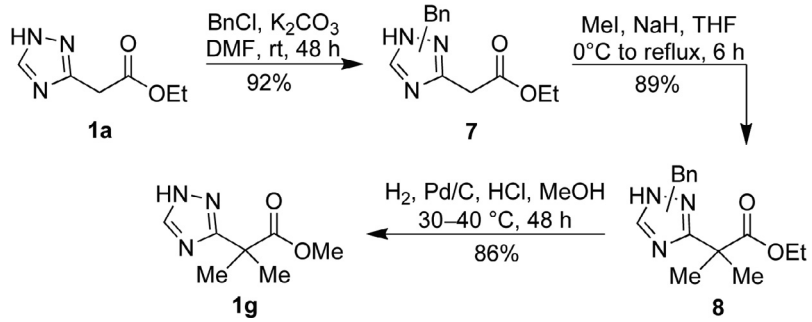
2-methyl 2-(1*H*-1,2,4-triazol-3-yl)acetate (**1 g**) in 70% overall yield (Scheme 7).

Since the last step was carried out in methanolic media, transesterification took place. The use of ethanolic media was not fruitful and resulted in recovery of the starting material (possibly due to the suppressive effect of water in 96% EtOH on the catalyst efficiency).

Saponification of esters **1a,b,d–g** proceeded smoothly; however, further isolation of the corresponding carboxylic acids was complicated because of partial decarboxylation. Therefore, the products were isolated as stable sodium (**9a,b**) or lithium (**9c–f**) salts (Scheme 8).

The structure of all products obtained was proven by standard spectroscopic methods. The solid state structure of **4a** was additionally investigated by single crystal X-ray diffraction method (see the supporting information), which proved the tautomeric form given above. The analysis of the packing motif has shown that all the possibilities for hydrogen bonding were completely realized in the crystal. As the result, the crystal structure is described as a parallel packing of discrete 2D supramolecular networks.

In conclusion, an efficient approach to gram-scale synthesis of α-mono- and α,α-disubstituted 2-(1*H*-1,2,4-triazol-3-yl)acetates as well as 4-mono- and 4,4-disubstituted 5-amino-2,4-dihydro-3*H*-pyrazol-3-ones via the Pinner reaction strategy has been developed. It was found that 2-monosubstituted as well as cyclopropane-annulated 3-imino-3-alkoxy-2-methylpropanoates reacted with formylhydrazide affording the corresponding (1,2,4-triazol-3-yl)acetates. At the same time, 3-imino-3-alkoxy-2-methylpropanoates bearing an annulated carbo/heterocyclic ring (larger than cyclopropane) turned into approximately equimolar mixtures of the appropriately substituted triazolylacetates and spirocyclic aminopyrazolones. An analogous reaction with hydrazine hydrate gave the corresponding 5-amino-2,4-dihydro-3*H*-pyrazol-3-ones in all cases. An alternative approach to α,α-disubstituted 2-(1*H*-1,2,4-triazol-3-yl)acetates was also proposed based on the double alkylation of the methylene unit in the parent *N*-protected 2-(1*H*-1,2,4-triazol-3-yl)acetate. The saponification of (1,2,4-triazol-3-yl)acetates allowed for the preparation of the



Scheme 7. The synthesis of **1g**.

corresponding lithium or sodium salts; isolation of free carboxylic acids was accompanied with partial decarboxylation. The developed procedure provides access to promising building blocks and scaffolds that have a great potential for early drug discovery [41].

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.152956.

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