Hydrazides in the reaction with hydroxypyrrolines: less nucleophilicity – more diversity

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Abstract

Expedient protocols for the synthesis of three types of highly functionalized azaheterocyclic scaffolds (dihydropyridazines, tetrahydropyridazines, and partially saturated tricyclic systems) from readily available hydroxypyrrolines and hydrazides are described. The directions of the transformation of a common initial intermediate, namely a Brønsted acid-activated hydroxypyrroline, depend on the reaction conditions and the structure of the hydrazides.

Introduction

Di- and tetrahydropyridazines are valuable heterocyclic motifs which are utilized as key fragments of influenza neuraminidase inhibitors [1], nonsteroidal progesterone receptor regulators [2,3], anti-inflammatory [4], antihypertensive and spasmylytic [5-7] agents (Figure 1). It is due to their prospects in drug design that a search for effective synthetic protocols to construct partially saturated pyridazine scaffolds is both highly topical and necessary.

Recently, we have developed a convenient approach to the 1,4-dihydropyridazine core based on the Brønsted acid-catalyzed regioselective recyclization of 5-hydroxypyrrolines (assembled in a one-pot manner from ketoximes and acetylene gas [8,9] or calcium carbide [10]) with hydrazines (Scheme 1) [11,12]. The reaction is operationally simple and tolerates a wide range of hydrazines including alkyl-, aryl-, and hetarylhydrazines [11] as well as semicarbazide and its derivatives [12].
However, the scope of this method with a special emphasis on the nature of hydrazine derivatives still remains obscure. Meeting this challenge becomes particularly important in view of the significance of the less nucleophilic hydrazides as N–N-bond containing starting materials in drug discovery [13-16].

Herein, we report how a lower nucleophilicity of the hydrazides diversifies the recyclization of 5-hydroxypyrrolines and results in the chemoselective formation of highly functionalized azaheterocyclic scaffolds. Such a short-cut to partially saturated azaheterocyclic scaffolds meets the interests of modern medicinal chemistry which today focuses on the study of partially saturated molecules because sp$^3$ carbon centers make the molecules potentially chiral and 3D structured, which improves the odds for drug discovery [17].

Results and Discussion

On the basis of our previous works [11,12] the reaction of 3,3-dimethyl-5-hydroxy-2-phenyl-$\Delta^1$-pyrroline (1a) with an equimolar amount of benzohydrazide (2a) was initially performed in the presence of trifluoroacetic acid (TFA, 10 mol %) in refluxing acetonitrile for 3 h. Unexpectedly, 6-(2'-benzoyl-hydrazinyl)-1,4,5,6-tetrahydropyridazine 3aa was isolated in a 46% yield, while the anticipated 1,4-dihydropyridazine 4aa was not detected at all (Table 1, entry 1). Although the increase of the reaction time up to 5 h slightly improved the yield of tetrahydropyridazine 3aa (53%, entry 2 in Table 1), more efficient appeared to be the use of a two-fold excess of benzohydrazide (2a) that provided 3aa in 93% isolated yield after reflux for 3 h (Table 1, entry 4). With these optimal conditions for the synthesis of tetrahydropyridazine 3aa in hand, we next turned our attention to its transformation to 1,4-dihydropyridazine 4aa. Both the prolonged reflux for 6 h (Table 1, entry 5) and the addition of 100 mol % of TFA (Table 1, entry 6) did not significantly promote the $3aa \rightarrow 4aa$ transformation, that was apparently caused by the deactivation of the acid catalyst by ammonia, released in the preceding step (vide infra for the mechanism discussion). To prevent this process, a stepwise addition of TFA was tested (Table 1, entries 7–11). Finally, the best isolated yield of 1,4-dihydropyridazine 4aa (74%) was achieved by a two-step, one-pot protocol, comprising the initial recyclization of hydroxypyrroline 1a with 2 equiv of benzohydrazide (2a) in refluxing acetonitrile for 3 h in the presence of 10 mol % of TFA followed by the introduction of 140 mol % of TFA and additional reflux for 3 h (Table 1, entry 11).

Next, the substrate scope and functional group tolerance of the protocols aimed to the chemoselective synthesis of di- and tetrahydropyridazines were investigated. Several features of the developed methods are noteworthy. It was found that all tested hydroxypyrrolines 1a–e and hydrazides 2a–g afforded the corresponding tetrahydropyridazines 3 (according to $^1$H NMR analysis of the crude reaction mixtures). However, due to the difficulties associated with their isolation and purification only few examples of analytically pure samples were obtained in 57–93% isolated yields (Scheme 2).

When the same set of hydroxypyrrolines 1a–e and hydrazides 2a–g was subjected to the two-step, one-pot protocol, the desired 1,4-dihydropyridazines 4 were formed in 20–74% isolated yields (Scheme 3). Electron-rich hydrazides appeared to be good recyclization agents as was exemplified by the assembly of 1,4-dihydropyridazines 4ab and 4ag from 4-methylbenzohydrazide (2b) and acetohydrazide (2g) in 69% and 54% isolated yields, respectively. In contrast, the recyclization of hydroxypyrroline 1a with electron-deficient 4-nitrobenzohydrazide (2c) proceeded somewhat less efficiently to afford the corresponding 1,4-dihydropyridazine 4ac in 44% isolated yield. The structural fragment of the well-known antibiot-
Table 1: A study of the model reaction between hydroxypyrroline 1a and benzohydrazide (2a)\(^a\).

| entry | TFA loading (x mol %) | time (h) | yield of 3aa\(^b\) | yield of 4aa\(^b\) |
|-------|-----------------------|----------|---------------------|---------------------|
| 1     | 10                    | 3        | 46                  | 0                   |
| 2     | 10                    | 5        | 53                  | 0                   |
| 3     | 10                    | 1        | 33                  | 0                   |
| 4     | 10                    | 3        | 93                  | 0                   |
| 5     | 10                    | 6        | 92                  | 0                   |
| 6     | 100                   | 6        | 3aa:4aa = 78:22\(^c\) |                     |
| 7     | 10 + 40               | 3 + 3    | 3aa:4aa = 55:45\(^c\) |                     |
| 8     | 10 + 90               | 3 + 3    | 3aa:4aa = 28:72\(^c\) |                     |
| 9     | 10 + 90               | 3 + 4    | 3aa:4aa = 22:78\(^c\) |                     |
| 10    | 10 + 90               | 3 + 5    | 3aa:4aa = 22:78\(^c\) |                     |
| 11    | 10 + 140              | 3 + 3    | 3aa:4aa = 3.97 (74%)\(^b,c\) |               |

\(^a\)Reaction conditions: hydroxypyrroline 1a (95 mg, 0.5 mmol), benzohydrazide (2a, 0.5 mmol for entries 1 and 2, 1.0 mmol for entries 3–11), TFA (x mol %), acetonitrile (3 mL), reflux; \(^b\)if not stated otherwise, isolated yields are given; \(^c\)according to \(^1\)H NMR of the crude reaction mixture.

Scheme 2: Synthesis of tetrahydropyridazines 3.

ic isoniazid (2f) was successfully incorporated in the tetrahydropyridazine core (the yield of 3af was 60\%, Scheme 2), but only traces of the 1,4-dihydropyridazine 4af were detected following the two-step, one-pot protocol (Scheme 3). Apparently, the basic pyridine nitrogen atoms of intermediate 3af deactivate the acid catalyst, whilst the use of 3.4 equiv of TFA causes the full protonation of the pyridine rings thus making them strongly electron-deficient substituents that finally prevent an acid-cata-
Scheme 3: Synthesis of dihydropyridazines 4.

Scheme 4: Recyclization of hydroxypyrroline 1a with hydrazides 2d and 2e.
Conclusion
In summary, an acid-catalyzed recyclization of hydroxypyrrolines (easily synthesized from ketoximes and acetylene) with hydrazides was studied. The reduced nucleophilicity of the hydrazides in comparison with other hydrazine derivatives constitutes the basis for the convenient chemoselective syntheses of highly functionalized azaheterocyclic scaffolds (di- and tetrahydropyridazines) with an acyl function at the nitrogen atom, thus having a substituent pattern similar to that of the known biologically active compounds of the pyridazine family. Moreover, the presence of other nucleophilic functions in the hydrazide component creates diversification points and enables more complex molecular architectures to be assembled that was demonstrated by the synthesis of partially saturated azatricyclic systems.

Supporting Information
Supporting Information File 1
Experimental methods, compound characterization data, and copies of $^1$H and $^{13}$C NMR spectra.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-17-29-S1.pdf]

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