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Convenient two-step preparation of [1,2,4]triazolo[4,3-*a*]pyridines from 2-hydrazinopyridine and carboxylic acids

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Abstract—Triazolopyridines are an important class of biologically active heterocyclic compounds. In this letter, we describe a new method for the synthesis of [1,2,4]triazolo[4,3-*a*]pyridines starting from 2-hydrazinopyridine and carboxylic acids. The resulting acetohydrazides are cyclized in a key step using the Lawesson's reagent. The reaction conditions were explored, as well as the scope of this reaction concerning the substituent in position 3 of the triazolopyridine ring. We also demonstrated that this heterocyclization is racemization free in the presence of a chiral carbon in position α to the heterocycle.

Triazolopyridines are an important class of heterocyclic compounds. They express bactericidal,[1,2] anxiolitic,[3] herbicidal[4] or diuretic and renal vasodilating[5] activities and can act as inhibitors of mitogen-activated protein (MAP) kinases[6,7] or as growth hormone secretagogues.[8] They also can be used for the treatment of gastrointestinal disorders[9] or as antithrombotic agents.[10]

Therefore, versatile and widely applicable methods for the synthesis of these heterocycles are of considerable interest. Most methods for the preparation of these compounds are based on heterocyclic hydrazones or hydrazides as precursors. However, these methods have some restrictions concerning their applicability and the use of toxic reagents like lead tetra acetate or phosphorus oxychloride.[11] In order to overcome these limitations, the oxidants chloramine T[12] and (diacetoxy)iodobenzene[2] as well as an electrochemical method[13] or copper-mediated oxidative heterocyclization[14] have been introduced.

As part of our continuing effort to target new bioactive heterocyclic scaffolds, we describe a new two-step method leading to [1,2,4]triazolo[4,3-*a*]pyridines from 2-hydrazinopyridine and carboxylic acids in good to high yield.

The synthetic route to the targeted molecules is outlined in Scheme 1. Carboxylic acid **1** is coupled with BOP reagent[15] to commercially available 2-hydrazinopyridine to give the corresponding acetohydrazide **2**. By reaction with Lawesson's reagent,[16] **2** is converted into the corresponding substituted [1,2,4]triazolo[4,3-*a*]pyridine **3** in one pot. A possible mechanism for this reaction is the formation of the thioacetohydrazide, which is not isolated, immediately followed by the nucleophilic attack of the nitrogen atom of the pyridyl moiety on the thiocarbonyl function. A rearomatization in two steps, as showed in Scheme 1, gives the final bicycle.

Various conditions were tested on a model compound to explore the influence of solvent, reaction temperature, reaction time and number of equivalents of Lawesson's reagent on the conversion rate of the acetohydrazide **2a** to the 3-phenethyl-[1,2,4]triazolo[4,3-*a*]pyridine **3a** (Scheme 2). The results are summarized in Table 1.

We can see in Table 1 that 0.5 equiv of Lawesson's reagent is sufficient. In some cases, more equivalents do not improve the conversion rate and lead to degradation (see entries 5 and 6). Best conversion rates were obtained with acetonitrile or toluene as a solvent performing the reaction at 80 °C for 2 h (entry 3 or entry

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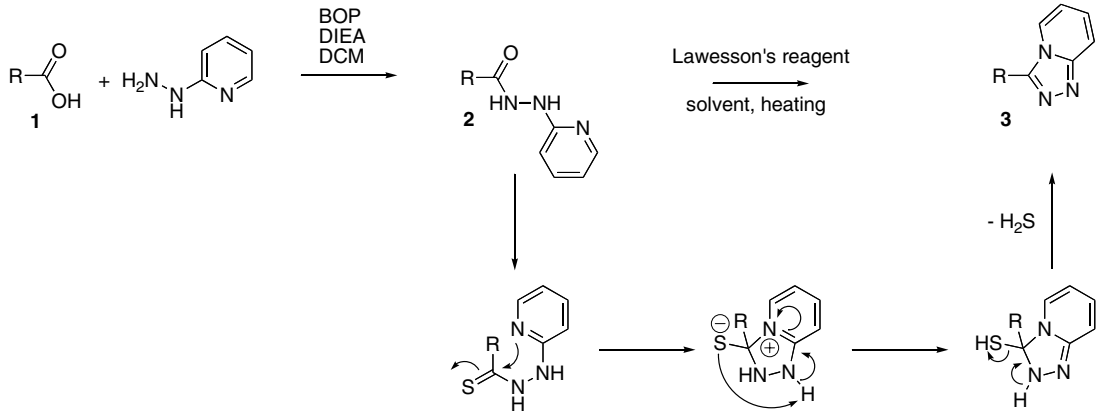
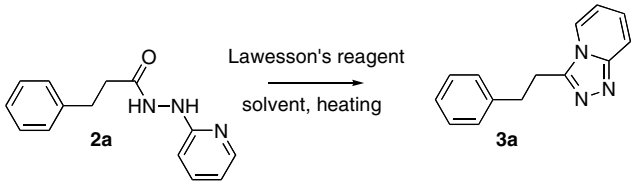


Scheme 1. General synthetic route to [1,2,4]triazolo[4,3-*a*]pyridines.



Scheme 2. Model compound used for the study of the reaction conditions.

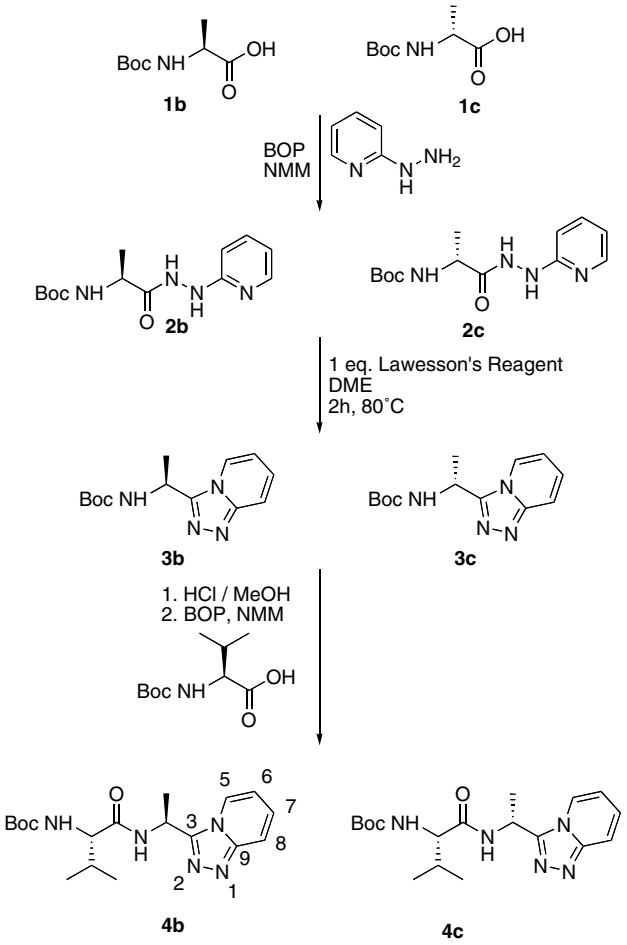
9 with, respectively, 80% and 84%), or with ethylene glycol dimethyl ether at 60 °C for 2 h (entry 16 with 86%).

We then attempted to introduce a chiral carbon atom in α position to the triazolopyridine to explore epimerization during the cyclization reaction.

For this purpose, we synthesized two diastereoisomers following Scheme 3, starting from (L) and (D) alanine to obtain the corresponding acetohydrazides **2b** and **2c**, respectively. After heterocyclization, the triazolopyridines **3b** and **3c** were, respectively, Boc deprotected, and Boc (L) valine was coupled to afford the corresponding diastereoisomers **4b** and **4c**.

Table 1. Influence of the reaction conditions on the conversion rate determined by RP-HPLC analysis at 214 nm

Entry	Time (h)	Temperature (°C)	Solvent	Lawesson's reagent (equiv)	Conversion (%)
1	0.5	80	CH_3CN	0.5	64
2	1.0	80	CH_3CN	0.5	73
3	2.0	80	CH_3CN	0.5	80
4	0.5	80	CH_3CN	1.0	72
5	2.0	80	CH_3CN	1.0	62
6	2.0	80	CH_3CN	2.0	54
7	0.5	80	PhMe	0.5	85
8	1.0	80	PhMe	0.5	81
9	2.0	80	PhMe	0.5	84
10	0.5	80	PhMe	1.0	73
11	0.5	80	DME	0.5	74
12	0.5	80	DME	1.0	55
13	1.0	80	DME	2.0	68
14	0.5	60	PhMe	0.5	53
15	0.5	60	DME	0.5	62
16	2.0	60	DME	0.5	86
17	2.0	60	DME	1.0	52



Scheme 3. Synthesis of L,L- and L,D-triazolopyridine diastereoisomers.

The optical purity of these two diastereoisomers was checked by ^{1}H NMR. For this purpose, three experiments were achieved: compounds **4b**, **4c** and also a 50/50 (w/w) mixture of compounds **4b** and **4c** were analyzed in DMSO-d_6.

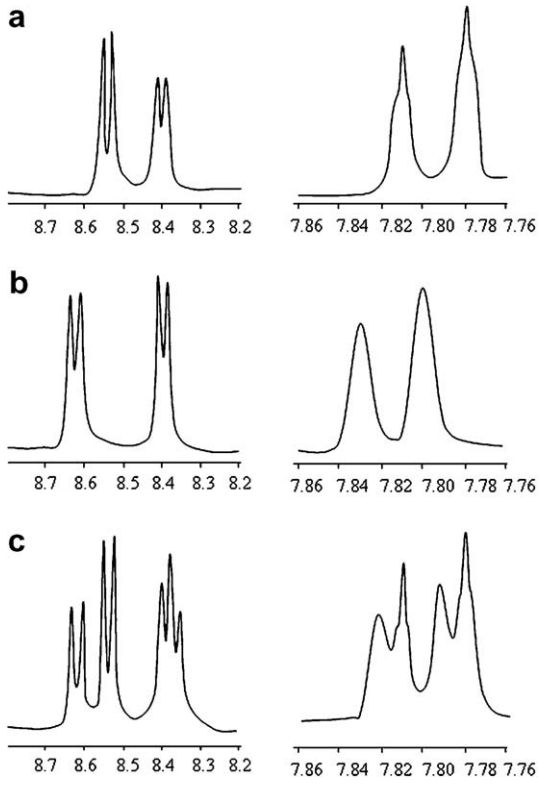


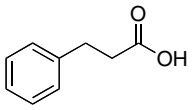
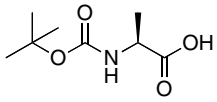
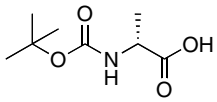
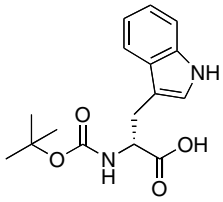
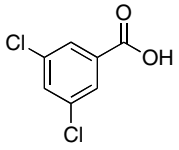
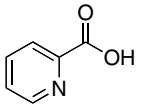
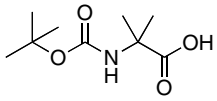
Figure 1. (a) ^{1}H NMR spectral data for compound **4b**; (b) ^{1}H NMR spectral data for compound **4c**; (c) ^{1}H NMR spectral data for a 50/50 (w/w) mixture of compounds **4b** and **4c**.

These experiments revealed a different chemical shift for the two diastereoisomers in two distinct regions of the spectrum (Fig. 1): in the region 7.76–7.86 ppm, corresponding to the H_8 proton of the triazolopyridine ring, and also in the region 8.20–8.80 ppm, corresponding to the NH of the Boc group and the H_5 proton of the triazolopyridine.

In both cases, compounds **4b** and **4c** revealed a single signal, whereas the mixture of the two diastereoisomers showed the superposition of two distinct signals, which corresponded to compounds **4b** and **4c** (Fig. 1). We can conclude that the heterocyclization to triazolopyridine using the Lawesson's reagent is racemization free for the carbon in position α to the heterocycle, in the limit of the detection by ^{1}H NMR.

To further investigate the scope of this reaction, several substituents were introduced at the R position (Scheme 4), as shown in Table 2.

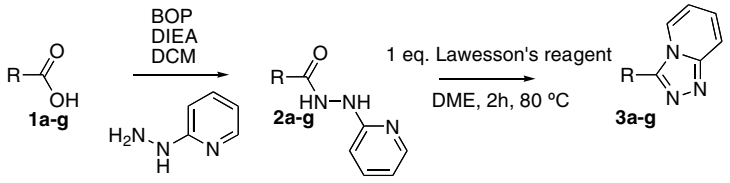
Table 2. Variation of the R substituent

Compound	Formula	Yield (%)	
		2	**3**
1a		85	80
1b		94	70
1c		94	70
1d		76	70
1e		98	98
1f		88	60
1g		100	0

All synthesized products were fully characterized by RP-HPLC, LC/MS spectrometry, ^{1}H and ^{13}C NMR (see Supplementary data).

Heterocyclization tolerates a wide range of functionalities: aromatic and alkyl groups, as well as heterocyclic groups, allowing to form biaryl compounds in some cases (compounds **3e** and **3f** in Table 2). Relatively bulky groups are well accepted (compounds **3d** and **3e** in Table 2) but in some cases, steric hindrance seems to be prohibitive for the ring formation (compound **3g** was not detected).

In conclusion, we propose a new convenient two-step synthesis of [1,2,4]triazolo[4,3-*a*]pyridines allowing the



Scheme 4. Introduction of several substituents at the R-position.

introduction of various substituents at the R-position, including the substituents bearing a chiral atom at the α position to the cycle. In this case, the optical integrity of the carbon is conserved, in the limit of ^{1}H NMR detection.

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Supplementary data

Synthetic procedures for all intermediates, MS, ^{1}H and ^{13}C NMR and RP-HPLC. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tetlet.2006.08.075.

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