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A simple and efficient automatable one step synthesis of triazolopyridines from carboxylic acids

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Abstract—Triazolopyridines can be rapidly and efficiently synthesized from a variety of carboxylic acids with 2-hydrazinopyridines in one simple step. The use of commercially available PS-PPh_3 resin combined with microwave heating delivered the product triazolopyridines in good yields and purities.

Lead optimization is one of the most critical phases within the drug discovery paradigm. Frequently, a critical part of the lead molecular skeleton has been studied and shown to be crucial for a particular biological activity, while other parts of the molecular skeleton need chemical modifications so as to achieve the desired properties of a development candidate.[1] Thus, an ongoing goal in the pharmaceutical industry has been to maximize the structural complexity and skeletal diversity of lead compounds whilst still maintaining critical pharmacophores in order to increase the chance of finding an optimal drug candidate.

To this end, we have been actively involved in the preparation of diverse biologically relevant heterocycles from precursors containing common chemical functionalities and readily available building blocks. In recent Letters, we have reported general and efficient reaction protocols for the preparation of 1,2,4-oxadiazoles **1**,[2] 1,3,4-oxadiazoles **2**,[3] benzoxazoles **3** and benzimidazoles **4**.[4] Notably, all of these synthetic methods start from readily accessible carboxylic acids as the common precursor and utilize the same reagent combinations, namely, PS-PPh_3/CCl_3CN under microwave heating conditions.[5] A key advantage of this approach is that starting from a common carboxylic acid scaffold, by simply using common reagents and a common operation, distinct structures can be easily accessed by utilizing a matrix of distinct building blocks (Fig. 1). In this

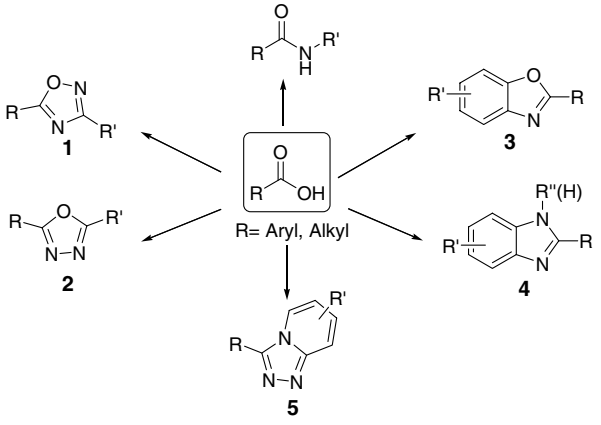

Figure 1. Syntheses of diverse structural motifs from carboxylic acid with PS-PPh_3/CCl_3CN and microwave heating.

Letter, we report the further extension of our strategy to synthesize triazolopyridines **5** from carboxylic acids and 2-hydrazinopyridines.

Triazolopyridines are an important class of heterocyclic compounds that have a wide range of pharmaceutical and biological activities including herbicibal, antifungal, anticonvulsant and anxiolytic activities.[6] Although several methods have been reported in the literature for the synthesis of triazolopyridines, many either require harsh reaction conditions or are multi-step in nature. Few very reliable and operationally facile examples have been reported for the efficient synthesis of triazolopyridines from readily available carboxylic acids in one step.[7]

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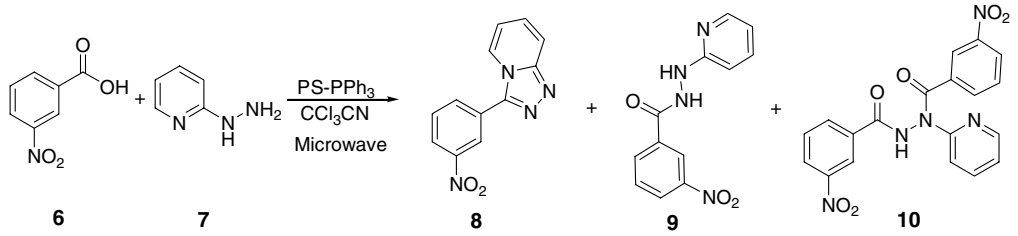
Table 1. Optimization of reaction conditions for the synthesis of representative triazolopyridines **8**

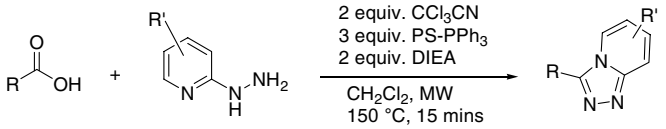


6 **7** **8** **9** **10**

Entry	Solvent	Method[8]	Base	Product **8**[a]	Product **9**[a]	Product **10**[a]
1	CH_3CN	A	None	Trace[b]	14%	35%
2	CH_3CN	A	DIEA	Trace[b]	10%	40%
3	CH_3CN	B	DIEA	30%	40%	10%
4	THF	B	DIEA	20%	70%	Trace[b]
5	CH_2Cl_2	B	DIEA	95%	None	Trace
6	CH_2Cl_2	A	DIEA	97%	None	Trace
7	CH_2Cl_2	B	None	15%	30%	Trace[b]
8	CH_2Cl_2	C	None	60%	15%	Trace[b]

[a] Conversion based on crude LC/MS analysis.
[b] Other unidentified peaks were also observed.

Table 2. Synthesis of triazolopyridines from carboxylic acids and 2-hydrazinopyridines with PS-PPh_3/CCl_3CN



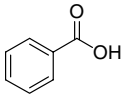
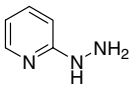
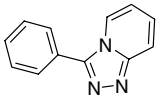
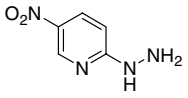
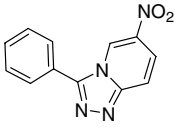
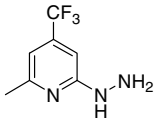
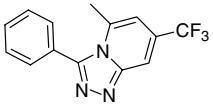
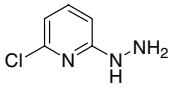
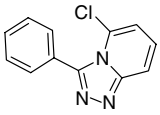
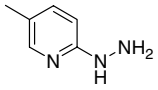
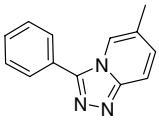
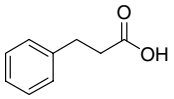
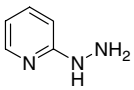
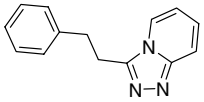
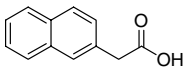
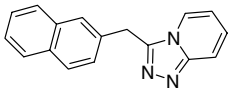
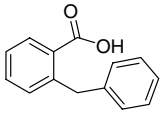
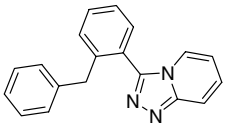
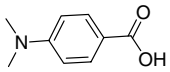
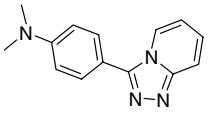
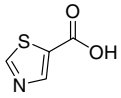
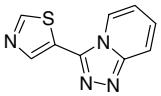
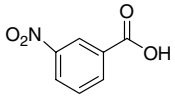
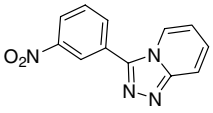
Entry	Acid	2-Hydrazinopyridine	Product	Isolated yield (%)
1				92
2				61
3				85
4				75
5				80
6				65
7				68

Table 2 (*continued*)

Entry	Acid	2-Hydrazinopyridine	Product	Isolated yield (%)
8				72
9				67
10				82
11				78

As mentioned previously, we have shown that the reagent combination of PS-PPh_3 and CCl_3CN is particularly effective in enabling the transformation of carboxylic acids into their heterocycle derivatives in a facile manner. It was thought that triazolopyridines **5** could be synthesized from carboxylic acids using analogous procedures. In practice, when 1 equiv of carboxylic acid **6** and 1 equiv of 2-hydrazinopyridine **7** were heated in the presence of 3 equiv PS-PPh_3 and 2 equiv CCl_3CN in CH_3CN under microwave conditions, bisacylated product **10** was observed as the major product along with acylated product **9** (Table 1, entries 1 and 2). Interestingly, the desired product **8** was observed when the reaction was carried out in a one-pot two step process (method B) in CH_3CN although side products **9** and **10** were also observed (Table 1, entry 3) in significant amounts. In order to identify optimal conditions for conversion to the desired triazolopyridine **8**, various solvents were studied using this one-pot two step process (Table 1, entries 3–5) in the presence of DIEA as the base. Encouragingly, we quickly discovered that when CH_2Cl_2 was used as the solvent, **8** was obtained with almost complete conversion as judged by crude LC/MS analysis (Table 1, entry 5). Subsequently, we were delighted to discover that near quantitative conversion to **8** was observed when the reaction was carried out in one step in CH_2Cl_2 (Table 1, entry 6).

Addition of DIEA as the base was found to be crucial for the observed high conversion to **8** (Table 1, entry 7). However, when PS-DIEA was used as the base, **10** was the major product observed in the crude LC/MS analysis. Also of note was the observation that 2 equiv CCl_3CN was necessary to achieve optimal conversion to **8**. With 1.2 equiv of CCl_3CN, acylated product **9** was the major product along with small amount of triazolopyridine **8** as observed by LC/MS analysis of the crude reaction mixture (Table 1, entry 8). As observed previously, the PS-PPh_3/CCl_3CN reagent combination appeared to play a dual role as the acylating reagent and dehydrating reagent.

The conditions identified above were next used to study the scope of the transformation.[9] Gratifyingly, this paradigm was found to be quite general and worked well for both alkyl and aryl carboxylic acids to afford the desired triazolopyridines in fair to excellent yields (Table 2), although in some cases, small amounts of acylated and bisacylated side products were also observed. The reaction proved to be facile to workup by simple filtration of the resin and evaporation of the solvent.

In summary, we have developed an efficient and general one step reaction protocol for the synthesis of triazolopyridines starting from carboxylic acids. The use of solid-phase reagents in combination with microwave heating greatly simplified reaction optimization and purification processes. The method we have developed fits into our overall strategy where starting from a common precursor, in this case a carboxylic acid, using a combination of the same reagents and a common operation, multiple heterocyclic scaffolds with distinct structural complexity and diversity can be easily accessed. We believe that this approach provides the advantages for both focused library synthesis and diversity-oriented synthesis. Thus diverse structure skeletons can be obtained within one library to greatly facilitate either a hit to lead or the lead optimization process. Efforts towards this goal are currently in process and will be reported in due course.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.02.004.

References and notes

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7. For some recent examples, see: (a) Moulin, A.; Martinez, J.; Fehrentz, J. *Tetrahedron Lett.* **2006**, 7591–7594; (b) Ciesielski, M.; Pufky, D.; Doring, M. *Tetrahedron* **2005**, *61*, 5942–5947; (c) Cucek, K.; Vercek, B. *Synlett* **1994**, 667–668; (d) Ramalingam, T.; Murty, M. S. R.; Nageswar, Y. V. D.; Sattur, P. B. *J. Heterocycl. Chem.* **1990**, *27*, 981; (e) Bourgeois, P.; Cantegril, R.; Chene, A.; Gelin, J.; Mortier, J.; Moyroud, J. *Synth. Commun.* **1993**, *23*, 3195–3199.
8. Method A: 0.1 mmol of acid **6** and 0.1 mmol of **7** were added to a microwave tube containing 0.3 mmol of PS-PPh_3 in 1 ml solvent. 0.2 mmol DIEA was also added for entries 2 and 6. Finally 0.2 mmol CCl_3CN was added. The mixture was heated in microwave at 150 °C for 15 min; Method B: 0.1 mmol of acid **6** was added to a microwave tube containing 0.3 mmol of PS-PPh_3 in 1 ml solvent followed by 0.2 mmol CCl_3CN. The mixture was heated in microwave at 100 °C for 5 min. The microwave tube was uncapped and 0.1 mmol **7** was added to the above mixture followed by 0.2 mmol DIEA (entries 3–5). The mixture was recapped and was heated again in microwave at 150 °C for 15 min; Method C: same as method B except 0.12 mmol of CCl_3CN was added.
9. General procedure: A Smith process vial (0.5–2 ml) was charged with a stir bar. To the vessel were added 0.2 mmol of the carboxylic acid and 0.2 mmol of the 2-hydrazinopyridine in 1.5 ml dry CH_2Cl_2. 0.6 mmol PS-PPh_3 (3 mmol/g) was added to the reaction mixture followed by 0.4 mmol DIEA and 0.4 mmol CCl_3CN. The reaction vessel was sealed and heated in a microwave oven to 150 °C for 15 min. After cooling, the reaction vessel was uncapped and the resin was filtered and washed by additional CH_2Cl_2 and MeOH. The desired product triazolopyridine was isolated by reverse-phase HPLC. All products thus obtained were greater than 95% pure as determined by LC/MS and NMR analysis.