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Letter

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1,1′-Carbonyldiimidazole (CDI) Mediated Coupling and Cyclization To Generate [1,2,4]Triazolo[4,3-*a*]pyridines

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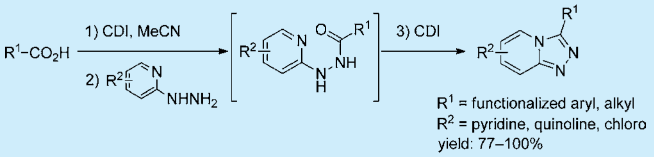
Ⓢ *Supporting Information*

ABSTRACT: An operationally efficient CDI mediated tandem coupling and cyclization reaction to generate [1,2,4]-triazolo[4,3-*a*]pyridines has been reported. The reaction conditions and scope were investigated, and the methodology was demonstrated in batch mode as well as in a continuous process.



R^1 = functionalized aryl, alkyl
R^2 = pyridine, quinoline, chloro
yield: 77–100%
15 examples

The [1,2,4]triazolo[4,3-*a*]pyridine structural motif is found in a variety of molecules of critical use in the pharmaceutical sciences, agricultural sciences, and material sciences. The literature reports the use of triazolopyridines as carbohydrate derivatives,[1] *C*-nucleoside analogs,[2] and as potential pharmaceuticals in the form of triazolobenzodiazepanes.[3] Herbicidal[4] as well as antimycobacterial[5] and -microbial[6] uses for triazolopyridines have also been reported. Within the pharmaceutical sciences, a wide range of biological activities have been reported for these moieties: (a) fibrinogen receptor (GPIIb/IIIa),[7] *β*-chemokine receptor CCR 5,[8] and histamine H_3 antagonist activity;[9] (b) farnesyl protein transferase (FPT),[10] P38*α* mitogen-activated (MAP) kinase,[11] receptor tyrosine kinase (c-Met),[12] serine/threonine Akt1/Akt2 kinase,[13] and human 11*β*-hydroxysteroid dehydrogenase type-1 (11*β*-HSD-1) inhibitor activity;[14] (c) antiviral activity,[15] and (d) anti-inflammatory activity.[16] Given the widespread application of the triazolopyridine motif, the development of efficient chemistries to access these structures is of great importance to the synthetic community.

The methods for the synthesis of triazolopyridines generally involve the dehydration of 2-pyridylhydrazides **3** or oxidative cyclization of 2-pyridylhydrozones **7** (Figure 1).[17] The requisite 2-pyridylhydrazines **1** are readily accessed by SnAr or palladium catalyzed couplings of hydrazine and 2-halopyridines. Coupling of 2-pyridylhydrazines **1** with carboxylic acids **2**[18] and/or the palladium mediated coupling of 2-chloropyridines **4** with aryl hydrazides **5**[19] has been reported to generate 2-pyridylhydrazides **3**, which are converted to the desired triazolopyridines **6** by dehydration/cyclization. The dehydration/cyclization has been reported with numerous reagents and conditions: Mitsunobu conditions,[20] Brønsted acids,[19,21] Burgess's reagent,[22] Lawesson's reagent,[18] phosphorus oxychloride,[23] and thermal[21] as well as microwave irradiation.[19] Alternatively, 2-pyridylhydrazones **7** generated either from palladium catalyzed coupling of 2-chloropyridines and an aldehyde-derived hydrazine[24] or from condensation of an aldehyde and 2-pyridylhydrazines[25] have been reported to generate triazolopyridines **6** after oxidative cyclization.

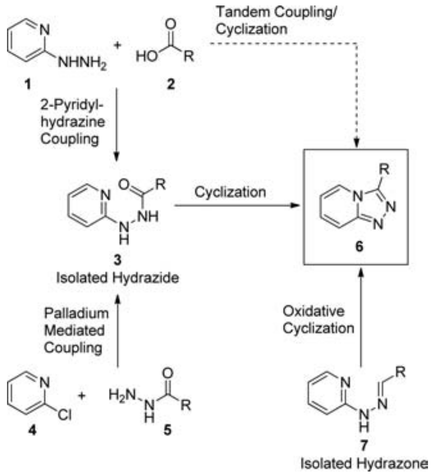


Figure 1. Synthetic approaches toward [1,2,4]triazolo[4,3-*a*]pyridines.

There are multiple drawbacks to the cyclization strategies presented above: (a) all strategies require the isolation of either 2-pyridylhydrazide **3** or 2-pyridylhydrazone **7** cyclization precursors, (b) the reported acidic and/or thermal cyclization conditions are generally not compatible with diverse functionality, and (c) while the use of Burgess's reagent, Lawesson's reagent, or Mitsunobu conditions provide mild cyclization conditions, these strategies inherently suffer from atom inefficiencies. Thus, we became interested in the development of a mild and operationally efficient synthesis of triazolopyridines using a single dehydration reagent for both coupling and cyclization events.[26] Herein, we describe the use of 1,1′-carbonyldiimidazole (CDI) as a mild and efficient reagent in the synthesis of triazolopyridines. This research focused on identifying a single-flask coupling/cyclization reagent, developing mild conditions that tolerated diverse functionality, and assessing this methodology as a continuous manufacturing (CM) process.

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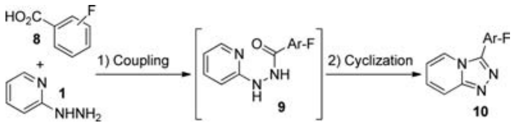
Our investigations into the single-flask acylation of 2-pyridylhydrazines and subsequent dehydration to generate triazolpyridines began by screening typical amide coupling reagents and monitoring by liquid chromatography−mass spectrometry (LCMS, Table 1). The screening reactions were performed by (1) charging 1.0−1.5 equiv of the coupling reagent to a solution containing the carboxylic acid **8**, (2) charging 1.0 equiv of the 2-pyridylhydrazine (neat), and (3) charging an additional 1.0−2.0 equiv of coupling reagent. The carbodiimide reagents DCC/oxyma and DIC/oxyma primarily generated linear intermediate **9**, with only minor conversion to triazolopyridine **10** observed (entries 1−2). Activation of carboxylic acid **9** with thionyl chloride, coupling, and attempted cyclization promoted by an additional charge of thionyl chloride generated a complicated reaction (entry 3). While phosphonium reagent BOP generated only linear product **9**, HATU successfully converted **1** and **8** to the desired product **10** (entries 4−5). Additionally, both propylphosphonic anhydride (T3P) and CDI were also competent in the single-flask conversion of hydrazine and acid to product **10** in high conversion and purity (entries 6−7). Due to the relatively low cost, commercial availability, and demonstrated utility on large scale,[27] CDI was selected for further development.

Table 1. Coupling and Dehydration Reagent Investigations



entry	conditions[a]	results
1	DCC, oxyma, DMF, ambient temp	cyclic product **10** observed poor purity profile
2	DIC, oxyma, DMF, ambient temp	low conversion to cyclic product **10**
3	$SOCl_2$, DIEA, DMF, ambient temp	cyclic product **10** observed poor purity profile
4	BOP, DIEA, DMF, ambient to 50 °C	linear product **9** only
5	HATU, DIEA, DMF, ambient to 50 °C	high conversion to cyclic product **10**
6	T3P, DIEA, DMA, ambient to 40 °C	high conversion to cyclic product **10**
7	CDI, DMF, ambient to 40 °C	high conversion to cyclic product **10**

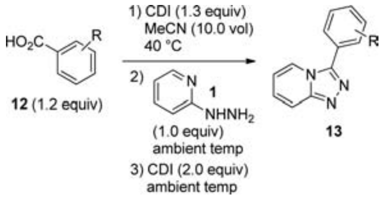
[a] Both 2-fluorobenzoic and 4-fluorobenzoic acid were utilized for the initial screening experiments.

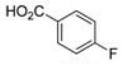
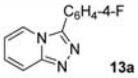
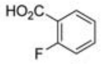
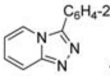
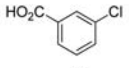
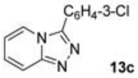
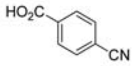
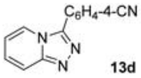
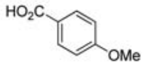
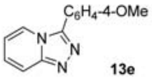
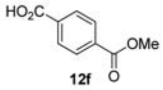
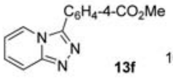
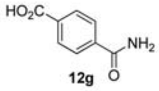
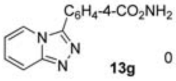
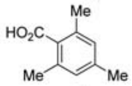
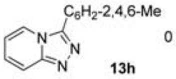
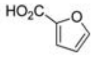
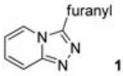
The reaction was performed by utilizing two separate CDI charges. In order to design a robust process to accommodate a diverse substrate scope, 1.2 equiv of the carboxylic acid was activated with 1.3 equiv of CDI at 40 °C (age time ≥30 min),[28] followed by charging 1.0 equiv of the 2-pyridylhydrazine (neat) and aging at ambient temperature for ≥30 min to generate hydrazide **9**. The dehydration was accomplished by charging an additional 2.0 equiv of CDI (neat) and aging ≥30 min at ambient temp.[29] Elevated temperature (40 °C) was implemented to ensure that the acid activation went to completion. If CDI was still present when **1** was added, then CDI and the 2-pyridylhydrazine provided the [1,2,4]triazolo[4,3-*a*]pyridin-3-ol impurity.

Isopropyl acetate (IPAc), dichloromethane (DCM), *N*,*N*-dimethylacetamide (DMA), 2-methyltetrahydrofuran (MeTHF), and acetonitrile (MeCN) were all proven compatible with the reaction conditions.[30] Acetonitrile (10.0 mL/g) was selected for the substrate scope investigations since the addition of water (10.0 mL/g) to the crude reaction mixture quenched the remaining CDI and specifically precipitated the desired product in high yield and purity. It was hypothesized that this MeCN/water crystallization would be a general and convenient isolation for the subsequent substrate scope investigations.

Aromatic acid derivatives with a range of different functional groups were tolerated under the reaction conditions (Table 2).

Table 2. Scope of Tandem Coupling/Cyclization Reactions with Functionalized Benzoic Acids



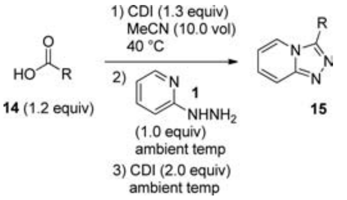
entry	acid substrate	product	yield [%][a]
1	 **12a**	 **13a**	89
2	 **12b**	 **13b**	80
3	 **12c**	 **13c**	90
4	 **12d**	 **13d**	96
5	 **12e**	 **13e**	93
6	 **12f**	 **13f**	100
7	 **12g**	 **13g**	0
8	 **12h**	 **13h**	0
9	 **12i**	 **13i**	88

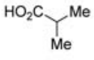
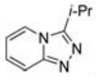
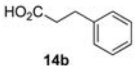
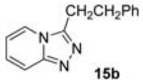
[a] Isolated yield after direct crystallization of product from the reaction mixture.

In general, halogenated benzoic acids provided triazolopyridines in high isolated yield (80−90%, entries 1−3). Benzoic acids containing nitrile, methyl ether, and methyl ester functionality also provided triazolopyridines in high yield (93−100%, entries 4−6). Only in the case of potentially reactive amide functionality (4-carbamoylbenzoic acid, entry 7) or sterically challenging functionality (2,4,6-trimethylbenzoic acid, entry 8) did the reaction fail.[31] The furan-2-carboxylic acid provided the desired triazolopyridine in high yield (88%, entry 9).

Alkyl substituted carboxylic acids were also well tolerated under the reaction conditions (Table 3). The branched isobutyric acid and linear 3-phenylpropanoic acid both provided the desired products in high isolated yield (entries 1−2). Attempts to crystallize the alkyl substituted triazolopyridines under the typical conditions were not successful. Thus, products were purified by column chromatography following aqueous workup.

Table 3. Scope of the Tandem Coupling/Cyclization Reactions with Alkyl Substituted Carboxylic Acids

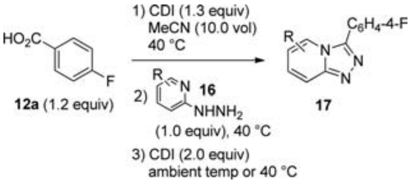


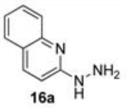
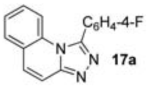
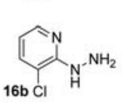
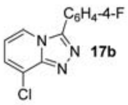
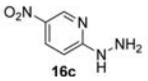
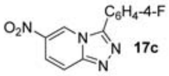
entry	acid substrate	product	yield [%][a]
1	 **14a**	 **15a**	77
2	 **14b**	 **15b**	89

[a] Isolated yield after column chromatography.

The scope of the hydrazine component was also examined (Table 4). 2-Hydrazinylquinoline and 3-chloro-2-hydrazinylpyridine provided the desired triazolopyridines in excellent isolated yield (93−99%, entries 1−2). However, 5-nitropyridine failed to perform the final cyclization (entry 3). A higher temperature (40 °C) was required for the hydrazide coupling for all entries, while chloro-substituted hydrazine **16b** required 40 °C to perform the final cyclization to generate triazolopyridine **17b**.

Table 4. Scope of the Tandem Coupling/Cyclization Reaction with Functionalized 2-Pyridylhydrazines



entry	hydrazide substrate	product	yield [%][a]
1	 **16a**	 **17a**	99
2	 **16b**	 **17b**	93
3	 **16c**	 **17c**	0

[a] Isolated yield after direct crystallization of product from the reaction mixture.

An assessment of this methodology as a continuous manufacturing process was investigated (Figure 2). The poor solubility of CDI in MeCN necessitated the use of DMA (CDI solubility approximately 100 mg/mL) to ensure homogeneous streams. The 4-fluorobenzoic acid (1.2 equiv), first CDI charge (1.3 equiv), and 2-pyridyl hydrazine (1.0 equiv) were each dissolved in 10.0 mL/g of DMA. The second CDI charge (2.0 equiv) was dissolved in 20.0 mL/g DMA. This CM design resulted in a 5× net dilution compared to the batch process. While the acid activation step is fast at ambient temperature, the coupling and cyclization reactions were performed at 90 °C to achieve the desired residence time of 17 min for the coupling and 10 min for the final cyclization.[32]

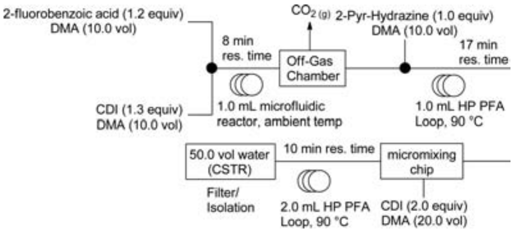


Figure 2. Schematic of [1,2,4]triazolo[4,3-*a*]pyridine CM process.

The CM system was successfully demonstrated producing 2 mg/min, delivering product with high isolated purity. The first reaction, 4-fluorobenzoic acid (1.2 equiv, 10.0 mL/g DMA) and CDI (1.3 equiv, 10.0 mL/g DMA), was performed using a 1 mL quartz microreactor at ambient temperature (8 min residence time) to achieve rapid mixing. The second reaction, reaction of the acyl imidazole with 2-pyridylhydrazine (1.0 equiv, 10.0 mL/g DMA), was performed using a static micromixing tee and a 1.0 mL capacity HP PFA reactor at 90 °C (17 min residence time). The third reaction, dehydration of the hydrazide, was performed using a quartz micromixing chip and 2.0 mL capacity HP PFA reactor at 90 °C (10 min residence time). The triazolopyridine product was precipitated by addition to a continuous stirred-tank reactor (CSTR) containing deionized (DI) water (50.0 mL/g) at ambient temperature.[33]

The carbon dioxide ($CO_{2(g)}$) generated from the initial CDI activation created segmented flow and impacted the mixing and conversion of downstream chemistry. Thus, a degassing cell was implemented whereas the segmented flow was pumped into a vial (under nitrogen), and the gas was released into the headspace. The $CO_{2(g)}$ evolution from the CDI mediated cyclization also created segmented flow and impacted conversion to the final product due to the decrease in residence time. This was overcome by subjecting the reaction stream to a quartz mixing chip before heating to 90 °C and utilizing a longer residence time (2.0 mL capacity HP PFA reactor, 10 min residence time). These modifications improved the crude reaction mixture purity at steady state to 84 liquid chromatography area percent (LCAP_{254}).[34] The final purity profile of the isolated solids was improved to 100 LCAP_{254} after continuous precipitation. While high dilution of a category 1B (toxic for reproduction)[35] solvent was utilized for this preliminary assessment, this feasibility study successfully established a CM process that generated isolated solids in high purity.

In conclusion, an operationally efficient CDI mediated tandem coupling and cyclization reaction to generate [1,2,4]triazolo[4,3-*a*]pyridines has been reported. This reaction tolerated various functional groups and was demonstrated in batch mode as well as in a continuous process.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03589.

> Experimental procedures; and characterization data for new compounds (^{1}H and ^{13}C NMR spectra) (PDF)

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Notes

The authors declare no competing financial interest.

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(31) The intermediate hydrazide was not observed for entries 7−8. Imidazole·HCl was also examined without success; see: Woodman, E. K.; Chaffey, J. G. K.; Hopes, P. A.; Hose, D. R. J.; Gilday, J. P. *Org. Process Res. Dev.* **2009**, *13*, 106.

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(34) (a) Impurities observed at steady state included the linear hyrdrazide and unreacted acid and hydrazine. (b) Attempts to solubilize the $CO_{2(g)}$ at high pressure was not investigated.

(35) *Committee for Risk Assessment (RAC) Opinion Proposing Harmonized Classification and Labelling at EU level of N,N-Dimethylacetamide (DMAC)*; European Chemicals Agency (ECHA), Annankatu: Helsinki, Finland, 2014.