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A mild synthesis of [1,2,4]triazolo[4,3-*a*]pyridines

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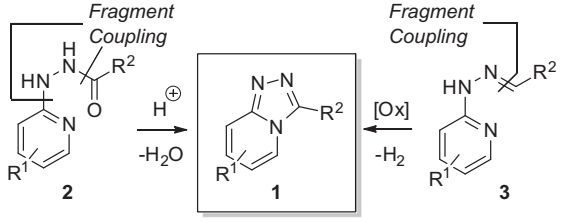
ABSTRACT

The reaction between 2-hydrazinopyridines and ethyl imidates was examined as a one-pot method for rapidly preparing [1,2,4]triazolo[4,3-*a*]pyridines. A diverse set of 2-hydrazinopyridines were cyclized with a variety of alkyl- and aryl-substituted ethyl imidates in good yields. The reaction proceeds optimally under mild conditions (50–70 °C) using 1.5 equiv of acetic acid. The electronic and steric properties of the hydrazine and imidate strongly impact the rate of the reaction. When highly electron deficient 2-hydrazinopyridines were used, the products rearranged to [1,2,4]triazolo[1,5-*a*]pyridines.

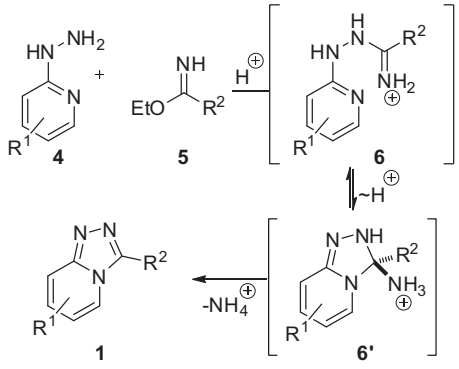
[1,2,4]Triazolopyridines **1** are an important class of heterocycles with broad utility in the pharmaceutical industry.[1–3] Common methods described in the literature for preparing the heterocycle involve a two-step approach (Scheme 1). The first step is a fragment coupling reaction to form acylhydrazide **2**, followed by an acid catalyzed cyclodehydration performed typically at high (>100 °C) temperatures,[1] or under microwave irradiation.[2] Alternatively, the later cyclodehydration can be carried out under milder conditions in the presence of dehydrating agents.[3] A notable alternative two-step synthesis of **1** involves a fragment coupling formation of hydrazone **3**, followed by oxidative cyclization to **1** (Scheme 1).[4]

The harsh conditions utilized in the aforementioned methods may be problematic with substrates that are sensitive to high temperatures or oxidants. While the addition of external dehydrating agents may lower the temperatures needed for the cyclodehydration, their presence can pose additional challenges. Depending on the agent, there could be further undesired reactivity with the substrates/products, or difficulties in removal of the stoichometric amount of waste byproducts. We desired a simpler synthesis that proceeds under mild (~50 °C), non-oxidative conditions to preserve functional group and substrate stability, and preferably without the use of external dehydrating agents.[5]

We decided to investigate the acid promoted cyclization of amidrazones (i.e., **6**)[6] as a mild route to **1** (Scheme 2). The requisite amidrazones themselves are easily formed by the reaction between 2-hydrazinopyridines **4** and imidates **5** under mild acidic conditions (Scheme 2),[6] which opens the door for the development of a one-pot process from **4** and **5** to **1**. Although the acid promoted



Scheme 1. Selected methods of forming [1,2,4]triazolopyridines **1**.[1–3]



Scheme 2. One-pot triazolopyridine synthesis from hydrazinopyridines and ethyl imidates.

reaction between hydrazines and imidates to form triazoles has been known for over a century,[7] its extension to form 1,2,4-triazolopyridines has received far less attention.[3g,8] Previous reports on

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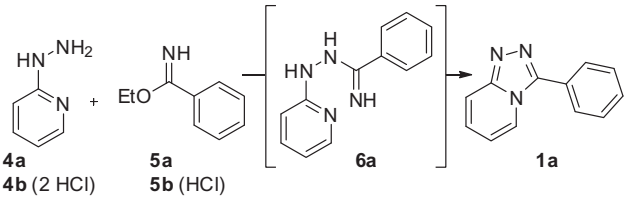
Table 1
Optimization of the reaction parameters



Entry	Solvent[a]	Additive (equiv)	Time (h)	Yield (conversion)[b] (%)
1	THF	AcOH (1.0)	24	(46)
2	PhMe	AcOH (1.0)	24	(52)
3	MeCN	AcOH (1.0)	24	(90)
4	EtOH	AcOH (1.0)	24	(99)
5	EtOH	None	24	(100 **6a**)
6	EtOH	BzOH (1.0)	24	(99)
7	EtOH	HCl (1.0)[c]	24	(84 **6a**)
8	EtOH	AcOH (1.5)	19	77
9[d]	EtOH	NaOAc (1.0)/AcOH (0.5)	19	78
10[e]	EtOH	NaOAc (3.0)	19	90

[a] Concentration 5 mL/g **5**.
[b] Isolated yields are an average of two runs, conversion measured by HPLC.
[c] Reaction between **4a** and **5b** with no additional additives.
[d] Reaction of **4a** and **5b**.
[e] Reaction of **4a** and **5b**.

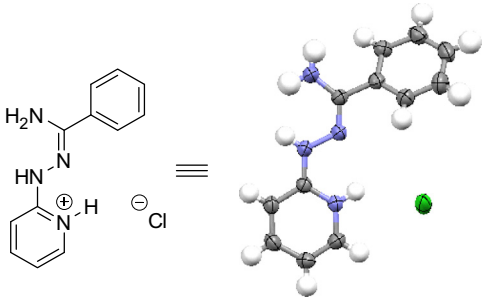


Figure 1. Amidrazone HCl salt **6a**·**HCl**.

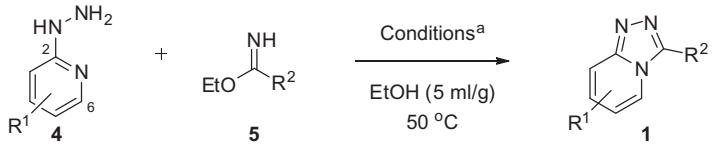
limited examples suffered from low yields due to incomplete conversions, or utilized pyridine as a solvent or co-solvent and/or thioimidates as reaction partners. In this study, we report our efforts in expanding the scope of this reaction and developing a mild, robust, high yielding protocol for the formation of [1,2,4]triazolopyridines **1**.

The reaction between 2-hydrazinopyridine (**4a**) and ethyl benzimidate (**5a**) with 1.0 equiv of acetic acid was examined as a model system in a variety of solvents at 50 °C (Table 1, entries 1–4).[9] In all the solvents examined, the corresponding amidrazone **6a** was formed cleanly in less than 30 min. The subsequent cyclization of the amidrazone to product **1a**, was clean and complete in ethanol after 24 h, however it was incomplete in THF, MeCN and toluene. A brief survey of acids was conducted (Table 1, entries 5–7). The control experiment confirmed that in the absence of acid, the amidrazone **6a** was the sole product, and no further cyclization took place. Benzoic acid was as effective as acetic acid, however stronger acids such as HCl (introduced by using ethyl benzimidate hydrochloride (**5b**)) immediately formed the amidrazone HCl salt (**6a**·**HCl**), without further cyclization to **1a** due to substrate deactivation (Fig. 1). Based on these results, we chose acetic acid for our study. Increasing the amount of acetic acid to 1.5 equiv reduced the reaction time to 19 h; additional amounts had no effect on reaction profile or rate. These conditions led to a 77% isolated yield of **1a** (Table 1, entry 8). A greater than stoichiometric amount of acetic acid was necessary since 1 equiv was needed to neutralize the ammonia byproduct of the reaction. For example, if ammonium acetate is used instead of acetic acid, allowing the ammonia to build up, the reaction proceeds slowly (67% conversion after 24 h). Since a common method for the formation of imidates **5** is through a Pinner reaction, which often yields imidate hydrochloride salts,[10] we investigated the use of ethyl benzimidate hydrochloride (**5b**) (Table 1, entry 9). Since the presence of HCl is detrimental (entry 7) and 1.5 equiv of acetic acid is the optimum quantity (entry 8), we added 1.0 equiv of sodium acetate to buffer the HCl in situ, and added an additional 0.5 equiv of acetic acid. This resulted in an identical reaction profile to entry 8, affording **1a** in 78% yield. The reaction of 2-hydrazinopyridine dihydrogen chloride (**4b**) and **5b** in the presence of 3.0 equiv of sodium acetate gave an identical reaction profile; but **1a** was isolated in 90% yield (Table 1, entry 10). The ~12% increase in yield was not attributed to the excess 3.0 equiv of acetic acid or the presence of 3.0 equiv of sodium chloride byproduct, as control experiments with **4a** and **5a** gave **1a** in 77% and 78% isolated yield, respectively. We cautiously suggest that the reagents are more stable when stored and used as salts, therefore we chose to use the salt forms of the 2-pyridylhydrazine whenever possible. We next applied these conditions to a range of electronically and structurally diverse substrates to examine the scope and functional group tolerance of the reaction.

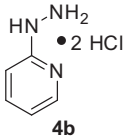
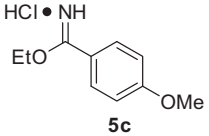
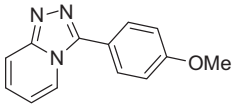
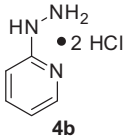
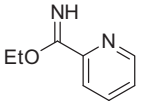
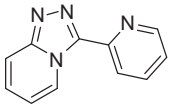
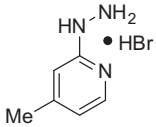
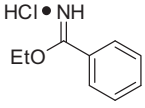
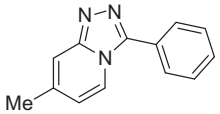
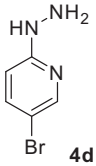
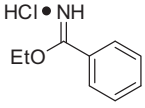
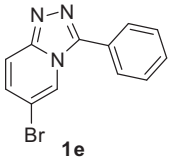
We found that both electron rich and electron deficient imidates are acceptable substrates in the reaction. The reaction between **4b** and the electron rich *p*-methoxybenzimidate hydrochloride (**5c**) proceeded cleanly to afford **1b** in 90% yield (Table 2, entry 1). Likewise, the reaction of **4b** and electron deficient ethyl picolinimidate (**5d**) afforded the desired product **1c** in 80% (Table 2, entry 2). While the electronic nature of the imidate only subtly affected the reaction rate, the electronic properties of the hydrazinopyridine had a stronger effect on the reaction. The comparatively more electron rich 4-methyl substituted hydrazine **4c** reacted with **5b** to afford the amidrazone rapidly, however it cyclized to **1d** much slower than the parent reaction (Table 1, entry 8) at 50 °C presumably due to the greater basicity of the pyridine ring, leading to more $N_{Pyridine}$ protonation and hence deactivation. At 70 °C however, the reaction was rapid, giving the product **1d** in 87% yield in 4 h (Table 2, entry 3). The addition of an electron withdrawing group on the 5-position of the hydrazinopyridine ring greatly reduced the reaction rate with **5b**. The reaction between **4d** and **5b** required heating to 70 °C for 24 h to form the product **1e** in 87% yield (Table 2, entry 4).

The substitution patterns of the hydrazinopyridine ring had a drastic effect on the reaction rate. Interestingly, if a functional group is located at the 3-position, the reaction is significantly faster. The reaction of 3-bromo-2-hydrazinopyridine (**4f**) with **5b** afforded product **1f** in 90% yield in 3.5 h (Table 3, entry 1, compared to Table 2, entry 4). We attribute this rate enhancement to a conformational bias that would not be available to the 5-bromo containing amidrazone. We hypothesize that the 3-position substitution in the pyridine ring will increase the population of productive conformers by restricting the rotation of the amidrazone around the N–$C2_{Pyridine}$ ring bond (Fig. 2).[11] This rate enhancement could effectively compensate for substrates with otherwise diminished reactivity. Even the electron deficient hydrazinopyridine **4g** reacted at 50 °C to give the product **1g** (Table 3, entry 2). An electron rich hydrazinopyridines with 3-substitution such as **4h** reacted the fastest out of all the hydrazinopyridines studied (compare Table 3, entry 3 with Table 2, entry 1). This enhancement, coupled with the mildness of the conditions allowed for the rapid formation of products with sensitive functional groups

Table 2
Electronic effects of the substrates in the reaction

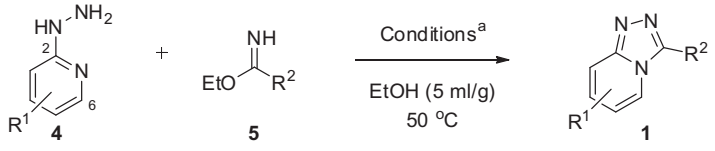


4 5 1

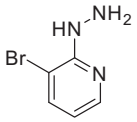
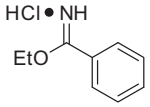
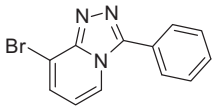
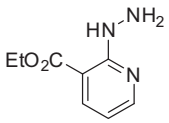
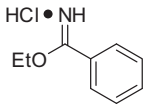
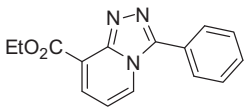
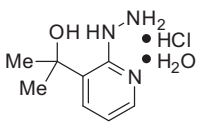
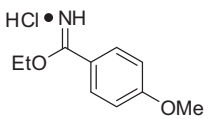
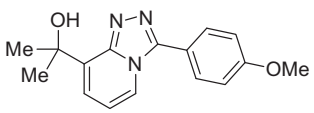
Entry	Hydrazinopyridine	Imidate	Conditions	Time (h)	Product	Yield[a] (%)
1	 **4b**	 **5c**	3.0 equiv NaOAc	24	 **1b**	90
2	 **4b**	 **5d**	2.0 equiv NaOAc	22	 **1c**	80
3	 **4c**	 **5b**	2.0 equiv NaOAc, 70 °C	4	 **1d**	87
4	 **4d**	 **5b**	1.0 equiv NaOAc, 0.5 equiv HOAc, 70 °C	2	 **1e**	87

[a] Isolated yields are an average of two runs.

Table 3
3- and 6-Substituted hydrazinopyridines as substrates

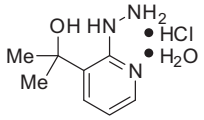
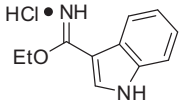
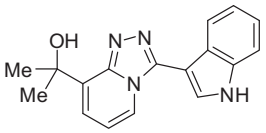
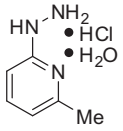
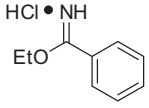
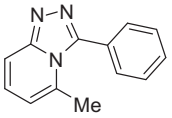


4 5 1

Entry	Hydrazinopyridine	Imidate	Conditions	Time (h)	Product	Yield[a] (%)
1	 **4f**	 **5b**	1.0 equiv NaOAc, 0.5 equiv HOAc	3.5	 **1f**	90
2	 **4g**	 **5b**	1.0 equiv NaOAc, 0.5 equiv HOAc	24	 **1g**	72
3	 **4h**	 **5c**	2.0 equiv NaOAc	1	 **1h**	92

(*continued on next page*)

Table 3 (*continued*)

Entry	Hydrazinopyridine	Imidate	Conditions	Time (h)	Product	Yield[a] (%)
4	 **4h**	 **5e**	2.0 equiv NaOAc	1.25	 **1i**	88
5	 **4i**	 **5b**	2.0 equiv NaOAc, 70 °C	72	 **1j**	72

[a] Isolated yields are an average of two runs.

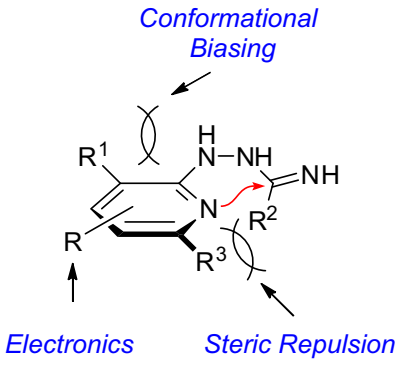
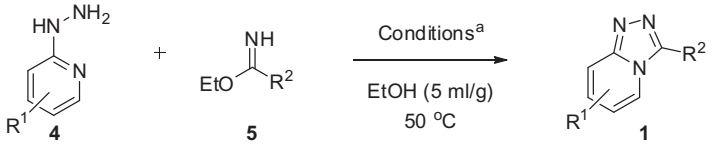


Figure 2. Factors affecting the cyclization.

such as indoyl product **1i** (Table 3, entry 4). Of note, the equivalent of water brought in by substrate **4h** did not appear to interfere with these rapid reactions. In contrast to 3-substitution, a 6-substituted hydrazinopyridine reacted far slower (Fig. 2). 6-Methyl-2-hydrazinopyridine (**4i**) required more forcing conditions and a greatly extended reaction time form the product **1j** (Table 3, entry 5). Monitoring the reaction by LCMS indicated that the major byproducts were consistent with the corresponding benzamide and the hydrazone (e.g., **2**) which resulted from the slow hydrolysis of the amidrazone due to the presence of water in the starting material **4i**.

When *alkyl* imidates were utilized, we noticed a facile reaction with a variety of 2-hydrazinopyridines (Table 4). Both electron deficient (Table 4, entries 1 and 2) and electron rich 2-hydrazinopyridines (Table 4, entry 3) reacted smoothly to afford the

Table 4
Heterocycle formation with alkyl imidates



4 **5** **1**

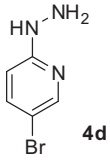
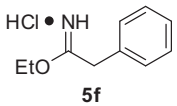
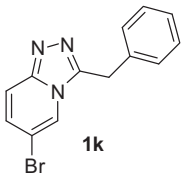
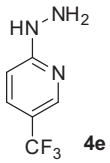
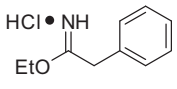
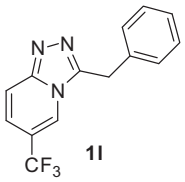
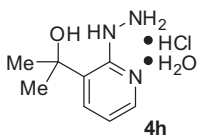
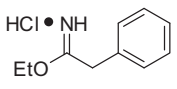
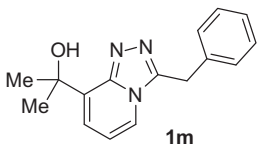
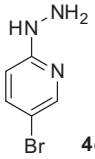
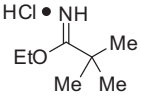
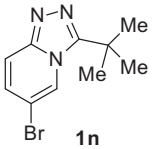
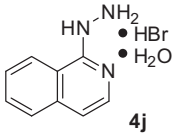
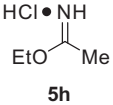
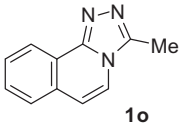
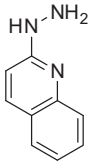
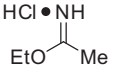
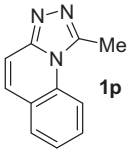
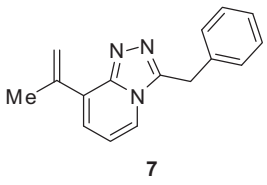
Entry	Hydrazinopyridine	Imidate	Conditions	Time (h)	Product	Yield[a] (%)
1	 **4d**	 **5f**	1.0 equiv NaOAc, 0.5 equiv HOAc	2.5	 **1k**	81
2	 **4e**	 **5f**	1.0 equiv NaOAc, 0.5 equiv HOAc	1.5	 **1l**	74
3	 **4h**	 **5f**	2.0 equiv NaOAc	0.67	 **1m**	88

Table 4 (*continued*)

Entry	Hydrazinopyridine	Imidate	Conditions	Time (h)	Product	Yield[a] (%)
4	 **4d**	 **5g**	1.0 equiv NaOAc, 0.5 equiv HOAc, 70 °C	17	 **1n**	81
5	 **4j**	 **5h**	2.0 equiv NaOAc[b]	2	 **1o**	85
6	 **4k**	 **5h**	1.0 equiv NaOAc, 0.5 equiv HOAc	1	 **1p**	82

[a] Isolated yields are an average of two runs.
[b] An additional 1.0 equiv of **5h** and sodium acetate were added after 1 h.



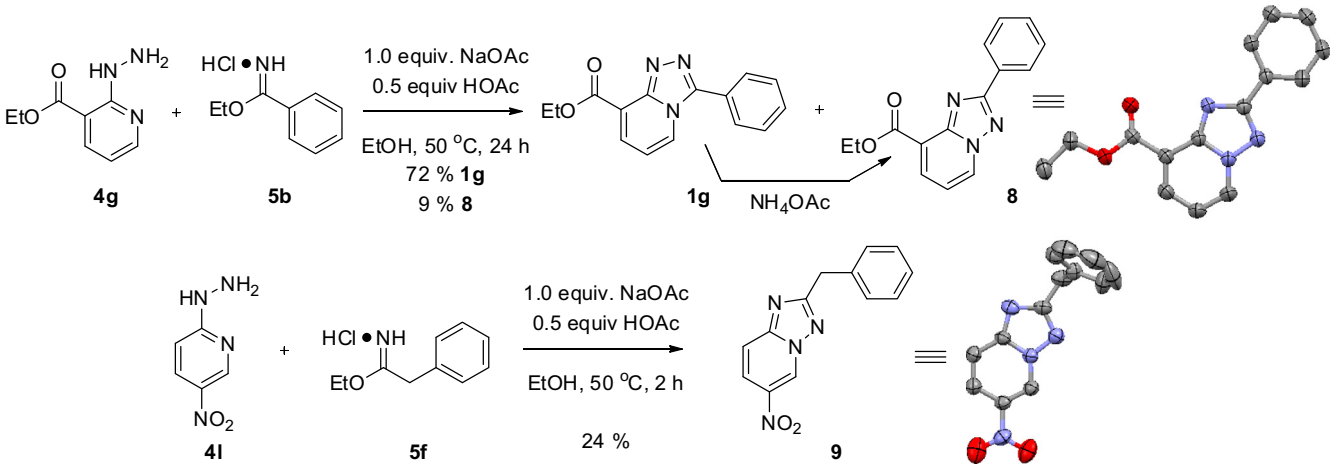
7

Figure 3. Olefin byproduct **7**.

heterocycle. The mildness of these conditions is highlighted by entry 3, where the acid catalyzed dehydration of the tertiary alcohol to the olefin byproduct **7** was isolated in only 0.8% yield (Fig. 3).[9] Using the sterically encumbered ethyl pivalimidate hydrochloride (**5g**), the reaction with **4d** was slower, however proceeded cleanly to the product **1n** (Table 4, entry 4).

2-Hydrazinoheteroaryl substrates other than hydrazinopyridines could also be successfully used (Table 4, entries 5 and 6). Interestingly, when 1-hydrazinoisoquinoline hydrobromide hydrate (**4j**) was used with the highly reactive imidate **5h**, the reaction halted at approximately 50% product **1o** and 50% starting material **4j** with no amidrazone intermediate observed. An additional charge of **5h** drove the reaction to completion (Table 4, entry 5). It was apparent that in this specific case, the highly reactive imidate **5h** was being degraded by the water brought in by the substrate **4j**, since the reaction of **4k** with **5h** proceeded cleanly without any additional reagent charges (Table 4, entry 6).

During the course of our study of the reaction of ethyl 2-hydrazinonicotinate (**4g**) and **5b** (Table 3, entry 2), we observed a byproduct in 9% yield. Unexpectedly, there was no evidence of the nucleophilic attack at the ester group under the reaction conditions. The structure of the byproduct was unequivocally verified by X-ray diffraction as a [1,2,4]triazolo[1,5-*a*]pyridine (**8**, Fig. 4). It is plausible that this heterocycle may arise from the product **1g** via a Dimroth-like rearrangement.[1a,12] Control experiments[9] revealed that ammonium acetate, which is likely generated in the reaction, is capable of promoting this rearrangement. The reverse reaction, the conversion of **8** to **1g**, was not observed under these conditions. This rearrangement is a dominant pathway when very electron poor hydrazinopyridines are used in the cyclization.[12c] The reaction between **5f** and the highly electron deficient 2-hydrazino-5-nitropyridine (**4l**, Fig. 4) afforded the [1,2,4]



4g **5b** **1g** **8** **4l** **5f** **9**

Figure 4. Thermal ellipsoid (50%) representation of [1,2,4]triazolo[1,5-*a*]pyridine products. Hydrogen atoms have been removed for clarity.

triazolo[1,5-*a*]pyridine **9** as the sole product in 24% yield with the mass balance being multiple unidentified decomposition products (Fig. 4).

In summary, we have developed mild conditions[13] for a one-pot synthesis of [1,2,4]triazolo[4,3-*a*]pyridines without the use of oxidation chemistry or external dehydration reagents. By utilizing ethyl imidates in ethanol, this method overcomes the noxious thioimidates and pyridine solvent used in the earlier work. This simple methodology leads to the preparation of the triazolopyridine heterocycles directly from hydrozinopryridines and imidates, which can be advantageous over the traditional two-step routes using acyl hydrazides (Scheme 1) as intermediates. The reaction can be conducted under mild conditions, which preserves acid sensitive functionality such as tertiary alcohols and indole heterocycles. We observed that the reaction rate was subtly influenced by the electronic properties of the imidates, but moderately by the steric properties. Both the electronic and steric properties of the hydrazinopyridine greatly impacted the reaction rate. We believe this method offers a practical alternative in the preparation of these heterocycles.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.08.024.

References and notes

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13. *Representative procedure, synthesis of* ***1a*** *(*Table 1*, entry 8):* To a mixture of ethyl benzimidate (**5a**, 1.00 g, 6.70 mmol, 1.00 equiv) and 2-hydrazinopyridine (**4a**, 754 mg, 6.70 mmol, 1.00 equiv) was added absolute ethanol (5.00 mL) followed by acetic acid (576 μL, 10.05 mmol, 1.50 equiv). The mixture was heated to 50 °C for 19 h. The slurry was cooled to room temperature and concentrated in vacuo to afford an orange residue which was partitioned between dichloromethane (50 mL) and an aqueous saturated solution of sodium bicarbonate (25 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (25 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to afford an orange solid. The solid was purified by flash column chromatography over silica gel (50% ethyl acetate in dichloromethane to remove impurities, then 5% methanol in dichloromethane to elute the product) to afford **1a** as a white solid (1.03 g, 79%). For characterization data, see Supplementary data.