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Synthesis of Polysubstituted 4,5,6,7-Tetrahydrofuro[2,3-*c*]pyridines by a Novel Multicomponent Reaction

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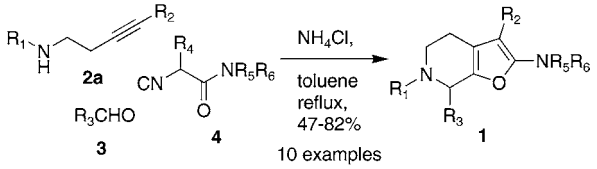
ABSTRACT



A novel three-component synthesis of tetrahydrofuro[2,3-*c*]pyridines (1) from readily accessible starting materials is described. Simply heating a toluene solution of an aminopentynoate (2a), an aldehyde (3), and an α-isocyanoacetamide (4) in the presence of ammonium chloride provided the 4,5,6,7-tetrahydrofuro[2,3-*c*]pyridines (1) in good to excellent yield. The fused ring system is produced in this one-pot process by the concomitant formation of five chemical bonds.

Furopyridines, although rarely isolated from nature,[1] are found in a number of medicinally relevant synthetic compounds.[2] For example, two potent HIV protease inhibitors PNU-142721 (**A**)[3] and L-754,394 (**B**)[4] (Figure 1) contain this structural unit. From a synthetic viewpoint, main two strategies have been developed for access to this bicyclic heterocycle.[5] One is the annulation of a furan ring onto a functionalized pyridine and the other is the elaboration of a pyridine ring from a preformed furan derivative.[6,7] Both routes suffer from the linearity and the ability to introduce significant molecular complexity in each step.

On the other hand, the reduced form of furopyridine such as 4,5,6,7-tetrahydrofuro[2,3-*c*]pyridines (**1**) were claimed

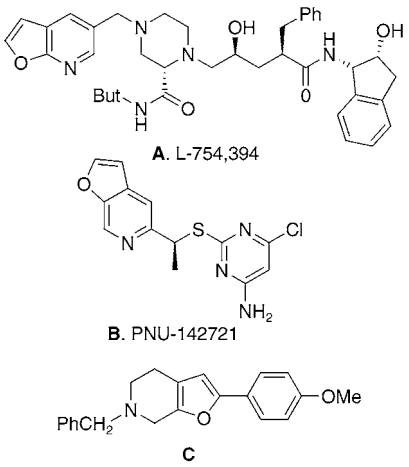


Figure 1. Bioactive furopyridine and tetrathydrofuropyridine.

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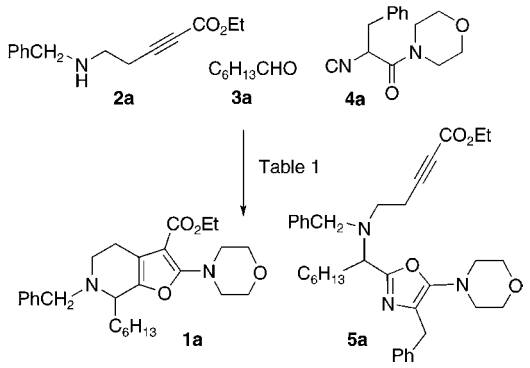
Scheme 1



to be useful as muscarinic agonists[88] and for the treatment of obesity.[99] Antianoxic activity has also been demonstrated, and 2-(4-methoxyphenyl)-6-benzyl-4,5,6,7-tetrahydrofuro-[2,3-*c*]pyridine (**C**, Figure 1) was found to be active against cerebral ischemia.[10] A few syntheses of fused heterocycle **1** have been reported, which include (a) reduction of the pyridium salt of the corresponding furopyridine,[11] (b) intramolecular Friedel−Crafts acylation of furan followed by reduction,[12] (c) intramolecular Friedel−Crafts alkylation,[13] (d) Pictet−Spengler cyclization,[14] and (e) furan annulation onto piperidone.[15] All these reported syntheses are linear and generally low yielding and do not allow the introduction of molecular diversity.

Based on the unique reactivity of α-isocyanoacetamide,[16] we have previously developed an efficient three-component synthesis of 5-aminooxazole.[17] Taking advantage of the potential chemical reactivity of 5-aminooxazole, we subsequently developed several new multicomponent syntheses of polyheterocycles[18] and macrocycles[19] by carefully designing appropriate substrates. As a continuation of our work in this field,[20] we report herein a new multicomponent synthesis of 4,5,6,7-tetrahydrofuro[2,3-*c*]pyridines from aminopentynoate (**2**), aldehyde (**3**), and α-isocyanoacetamide (**4**, Scheme 1). Besides being multicomponent, the salient feature of the present synthesis is the concomitant formation of the fused ring system of furopyridine from readily accessible substrates.

Table 1. Three-Component Synthesis of **1a** Using Various Reaction Conditions[a]

entry	solvent	T^b (°C)	additive	yield[c] (%)
1	toluene	80	NH_4Cl	31 (47[d])
2	toluene	reflux	NH_4Cl	82
3	xylene	reflux	NH_4Cl	39
4	toluene	reflux	LiBr	68
5	toluene	reflux		54
6	MeOH	reflux		0 (51[d])

[a] Concentration of substrate: 0.1 M. Reaction time: 15 h. Additive: 1.0 equiv. [b] Room temperature followed by heating. [c] Isolated yield. [d] Yield of oxazole **5a**.

The survey of reaction conditions is summarized in Table 1 using benzylaminopentynoate (**2a**), heptanal (**3a**), and α-isocyanoacetamide (**4a**) as model starting materials. When the reaction was carried out in toluene at 80 °C in the presence of 1 equiv of ammonium chloride,[17b,21] the desired furo[2,3-*c*]pyridine **1a** was effectively isolated in 31% yield together with oxazole **5a** (47%). Since **5a** was suspected of being the precursor of **1a**, the same reaction was performed at higher temperature. As can be observed, at the refluxing temperature of toluene, the yield of **1a** was raised to 82% (entry 2). However, a further increase in the reaction temperature had an adverse effect (entry 3). Lithium bromide[22] can also efficiently promote this transformation (entry 4). Interestingly, even in the absence of additive, **1a** was still produced in 54% yield (entry 5). On the other hand, a reaction carried out in methanol failed to produce the expected furopyridine, presumably due to the lower reaction temperature. In this case, only oxazole **5a** was isolated (entry 6).

A possible reaction sequence that accounts for the formation of tetrahydrofuropyridine **1** is depicted in Scheme 2. A three-component reaction between amine, aldehyde, and isocyanide is expected to provide the oxazole **5** via an imininum (**6**) and then a nitrilium (**7**) intermediate. Intramolecular Diels−Alder (D−A) cycloaddition between the in

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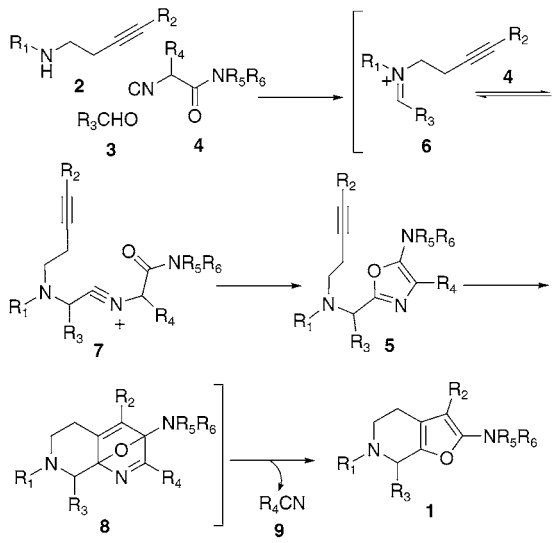
Scheme 2



situ generated oxazole and the tethered acetylene function should then afford the oxa-bridged intermediate, which can undergo fragmentation by a retro D−A process to furnish the furo[2,3-*c*]pyridine (**1**) and benzylnitrile.[23] Two irreversible steps, the formation of oxazole and retro-Diels−Alder reaction, might provide driving forces for this experimentally simple, yet mechanistically complex, reaction. It is interesting to note that five different functionalities participate in this one-pot process, leading to the formation of a bicyclic ring system with the creation of five chemical bonds. The efficient conversion of isolated oxazole **5a** (Scheme 2, $R_1 = R_4 =$ Bn, $R_2 =$ COOEt, $R_3 = C_6H_{13}$, $NR_4R_5 =$ morpholinyl) into the furopyridine **1a** under standard conditions (NH_4Cl, toluene, reflux) supported the proposed reaction sequence.

To probe the generality of this multicomponent reaction, a variety of starting materials including two aminoalkynes,[24] seven aldehydes, and five α-isocyanoacetamides were next examined (Figure 2). By applying the standard conditions (NH_4Cl, toluene, reflux), good to excellent yields of tetrasubstituted furopyridines were obtained from both aliphatic and aromatic aldehydes having different steric and electronic properties. The amino function can be varied by simply changing the structure of isocyanoacetamide. Indeed, morpholinyl, piperidinyl, pyrrolidinyl, and diethylamino substituents were successfully introduced into the C-2 position of the furopyridine skeleton (Figure 3).[25]

The incorporation of an electronically poor dienophile into the amine seems to be a prerequisite in order to realize the entire sequence. In fact, when aminoalkynyl **2b** (Figure 2)

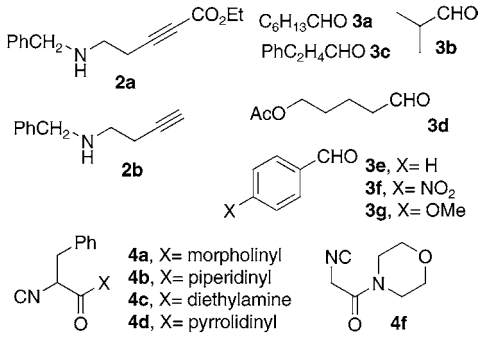


Figure 2. Structure of starting materials.

was reacted with aldehyde **3b** and isocyanide **4a** under standard conditions, only oxazole **5b** was isolated in 87% yield (Scheme 2, $R_1 = R_4 =$ Bn, $R_2 =$ H, $R_3 =$ isopropyl, $NR_4R_5 =$ morpholinyl). Performing the reaction at higher temperature (xylene, reflux) did not lead to the formation of the desired compound. Attempts to activate the terminal acetylene by introducing $PtCl_2$[26] or CuI[27] into the reaction mixture only led to the degradation of the oxazole **5b**.

One drawback of this powerful MCR in the present state of development is the lack of atom economy.[28] Indeed, benzylnitrile was a side product when phenylalanine-derived isocyanoacetamides (**4a**−**d**) were used. To overcome this, isocyanoacetamide **4f** was synthesized from isocyanoacetate[29]

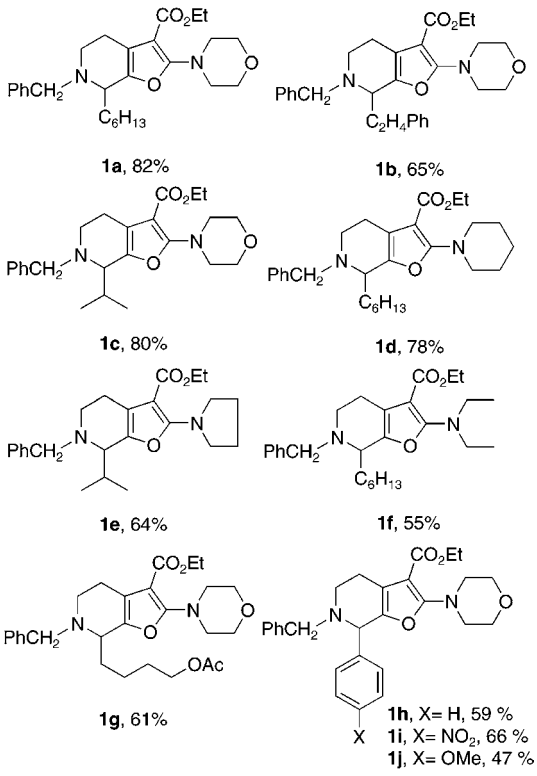


Figure 3. Isolated yields of analytically pure compounds.

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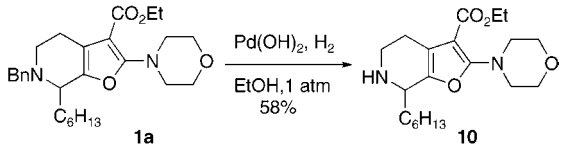
(24) **2a** and **2b** were synthesized following literature procedure; see: Hirai, Y.; Terada, T.; Yamasaki, T.; Momose, T. *J. Chem. Soc., Perkin Trans. 1* **1992**, 509.

by transamidation.[30,31] Gratifyingly, reaction of **4f** with **2a** and **3a** under standard conditions (toluene, NH_4Cl, reflux) provided the desired furopyridine **1a** in about 65% yield. Only one molecule of H_2O and a molecule of HCN were lost in this transformation that leads to the creation of five chemical bonds.

Compound **1**, containing an ester and a furan function, should be susceptible to further structural elaborations.[32] Additionally, the *N*-benzyl group can be removed from **1a** under hydrogenolytic conditions [H_2, $Pd(OH)_2$, EtOH, 1 atm, 58%] to provide the furopyridine **10** with a secondary amine function allowing further chemical transformation (Scheme 3).

Scheme 3



In conclusion, we have developed a first multicomponent synthesis of polysubstituted 4,5,6,7-tetrahydro[2,3-*c*]furopyridines **1** starting from simple and readily available precursors. The key to this reaction is the choice of appropriately polyfunctionalized substrates that undergo reactions in a highly ordered fashion. Indeed, two of the three inputs engaged in the present MCR reacted twice, consequently creating significant molecular complexity. The reaction is easy to perform and allows the introduction of at least three diversity points into the final bicyclic scaffold. We are further pursuing this substrate design approach for the development of novel multicomponent reactions.

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Supporting Information Available: Physical data for compounds **1a**−**j**, **5a**,**b**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) **Representative Procedure.** A solution of amine **2a** (1 equiv) and aldehyde **3** (1.2 equiv) in dry toluene (0.1 M) was stirred at room temperature in the presence of 1 equiv of NH_4Cl for 1 h. α-Isocyanoacetamide (**4**) (1.2 equiv) was added, and the reaction mixture was heated to reflux. The reaction was monitored by TLC (typically 15 h). The reaction mixture was cooled to room temperature, and toluene was removed under reduce pressure. After dilution with water, the product was extracted with dichloromethane. The combined organic extracts were washed with brine and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified by either preparative TLC (silica gel) or flash chromatography (silica gel). Eluent heptane/AcOEt (typically 2/1−1/1).

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(29) Commercially available or can be synthesized from glycine by a three-step sequence: (a) MeOH, H^+; (b) HCOOH, EDC, CH_2Cl_2; (b) $POCl_3$, Et_3N, CH_2Cl_2.

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