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Ammonium Chloride-Promoted Four-Component Synthesis of Pyrrolo[3,4-*b*]pyridin-5-one

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Abstract: A novel multicomponent synthesis of 5-aminooxazole starting from simple and readily available inputs is described. Thus, simply heating a methanol solution of an aldehyde **3**, an amine **4**, and an α-isocyanoacetamide **5** provided the 5-aminooxazole (**1**) in good to excellent yield. The reaction of **1** with α,β-unsaturated acyl chloride **13** lead to the formation of pyrrolo[3,4-*b*]pyridin-5-one (**2**) in a single operation. A triple domino sequence, acylation/IMDA/retro-Michael cycloreversion, is involved in this new scaffold-generating reaction. After the observation that ammonium chloride can significantly accelerate the oxazole formation in toluene, a one-pot four-component synthesis of **2** is developed.

Introduction

Small polyfunctionalized heterocyclic compounds play important roles in the drug discovery process[1] and in isolation and structural identification of biological macromolecules.[2,3] Indeed, analysis of drugs in late development or on the market shows that 68% of them are heterocycles. With the progress achieved in the field of functional genomics and proteomics,[4] more information about the structures and functions of biologically active macromolecules is becoming available. To match such a formidable advance in biological research, the identification and optimization of new small molecular chemical substances that can specifically interact with therapeutical targets is of utmost importance[5] and constitute actually the bottleneck in medicinal chemistry.[6] It is therefore not surprising that researches in the field of combinatorial synthesis of heterocycles and natural product analogues have received special attention.[7]

Combinatorial chemistry is now firmly integrated in the drug discovery enterprise, for both lead identification and lead optimization.[8] Initially, the key elements in the design of libraries were considered to be library size.[9] However, the number game of the high-throughput synthesis has gradually been transformed into a quality and strategy game such that synthetic libraries were more and more oriented from oligomeric compounds to nonoligomeric heterocyclic structures.[10] Within this context, we initiated a research program aimed at the development of highly efficient synthesis of heterocyclic and macrocyclic compounds by combined use of multicomponent reaction (MCR)[11] and domino processes.[12] The guiding principle is to devise a novel

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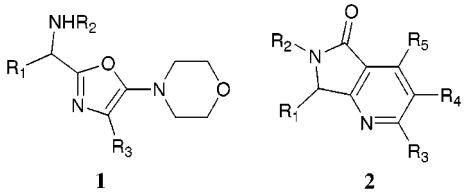


1 **2**

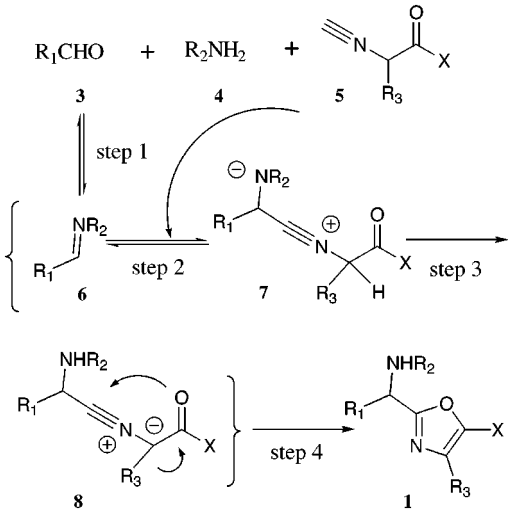
Figure 1.

multicomponent synthesis of a heterocycle[13] that is appropriately functionalized, allowing it to be engaged in the subsequent domino process. In an ideal case, the heterocycle obtained by MCR should be polyfunctionalized in such a way that different domino processes can be envisaged leading to completely different but biologically relevant cyclic scaffolds.[14] At the current stage of development in this field, although the sequence of MCR/postfunctionalization has been elegantly developed,[15] the multicomponent synthesis of heterocycles that is susceptible for further scaffold diversification and amplification is rare.[16] In this paper, we describe a novel three-component synthesis of 5-aminooxazole (**1**) and its subsequent one-pot triple domino transformation to pyrrolopyridine **2** (Figure 1).[17] A serendipitous discovery that ammonium chloride can promote the Ugi-type condensation in toluene allowed us to develop subsequently a one-pot four-component synthesis of pyrrolopyridine.

Results and Discussion

Three-Component Synthesis of 5-Aminooxazole. Synthesis of oxazole has attracted a renewed interest due to its presence in a number of bioactive marine natural products[18] and its application in the design of conformationally restricted pepti-

Scheme 1



domimetics.[19] Recently, polyfunctionalized oxazoles[20] and oxazole-containing macrocycles[21] have also been designed and used for multidirectional elaboration of combinatorial libraries and for selective molecular recognition of smaller molecular targets. However, none of the existing methods could satisfy our general goal aimed at using oxazole as a scaffold-generating template in a diversity-oriented synthetic program.[22,23] Consequently, an expeditious construction of oxazole via multicomponent reaction was sought. The sequence of event that we envisaged is shown in Scheme 1. Thus, condensation of an aldehyde **3** and an amine **4** should give the imine **6**, which would react with isonitrile **5** to produce the nitrilium intermediate **7**. This latter intermediate, after tautomerization would cyclized to produce the desired oxazole **1**. While the proposed sequence seemed logical, two uncertainties persisted. First, it has been reported that the reaction between imine and isonitrile occurred only in the presence of acid catalysis.[24] In Ugi 4CR, the role of carboxylic acid is not only to trap the nitrilium intermediate

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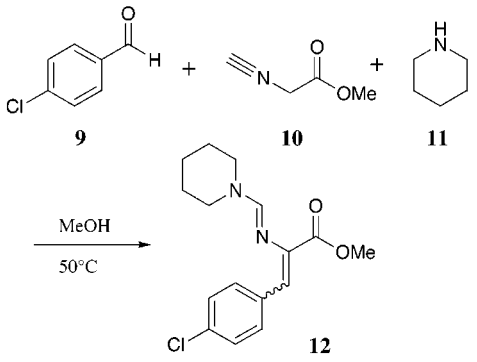
Scheme 2

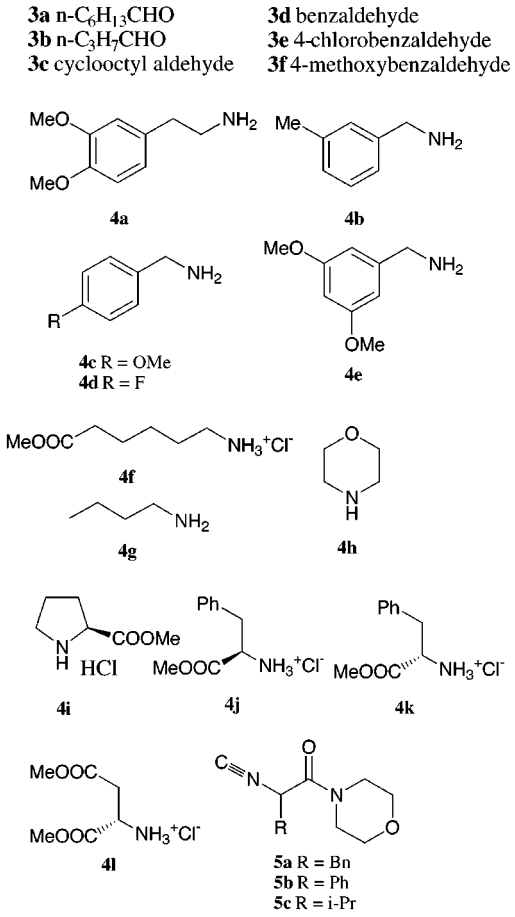


9 **10** **11** **12**

but also to activate the imine toward nucleophilic attack via salt formation. However, aminooxazole is very unstable under acidic consitions.[25] Second, both the divalent isonitrile carbon and the α- methylene carbon are nucleophilic in nature; hence, their relative reactivity needed to be carefully controlled if one wanted to favor one particular reaction manifold. The rich chemistry of α-isocyanoacetate and TOSMIC developed by Schöllkopf[26] and Van Leusen,[27] respectively, is based on the nucleophilicity of the α-methylene carbon.[28]

Matsumoto and co-workers reported in 1978 that simply heating a solution of 4-chlorobenzaldehyde (**9**), methyl α-isocyanoacetate (**10**), and piperidine (**11**) in MeOH led to the formation of amidine **12** in ∼50% yield (Scheme 2).[29] The reaction is suggested to be initiated by the Knoevenagel condensation followed by a formal α-addition of the secondary amine onto the isocyano group. It is thus evident that the relative nucleophilicity of the α-methylene carbon and that of the divalent isonitrile carbon needed to be counterbalanced in order to orient the three-component reaction toward the direction we expected.

Toward this end, we thought to use the α-isocyanoacetamide instead of the α-isocyanoacetate for the following reasons. First, The $pK_{a(\alpha CH)}$ of an amide is 2−4 units higher than that of an ester. Consequently, the α-methylene proton of amide should be less easily deprotonated. The fact that the amide function is less electron-withdrawing than the ester function should also render the isonitrile carbon slightly more nucleophilic. Second, the higher Lewis basicity of amide oxygen than the ester counterpart should kinetically favor the ring-forming process. Since oxazole formation is nonreversible, the increased reaction rate of this step should provide the overall driving force to the desired sequence. Experimentally, it was found that simply heating a methanol solution of heptaldehyde (**3a**), 2-(3′,4′-dimethoxy)phenethylamine (**4a**), and an isocyanoacetamide **5a** led to the formation of 5-aminooxazole (**1a,** $R_1 = nC_6H_{13}$, R_2 = 2-(3′,4′-dimethoxy)phenethyl, R_3 = Bn, X = morpholinyl; Scheme 1) in good yield.[30] Neither imidazoline nor amidine resulting from the competitive aldol- (Knoevenagel) and Mannich-type condensation was observed.[31] The desired sequence dominated over the Pictet−Spengler condensation since no tetrahydroisoquinoline was isolable.[32] Apparently, the intermolecular reaction between isonitrile and the imine intermediate was faster than the intramolecular trapping of the imine by a properly positioned electron-rich aromatic ring under these conditions. From 6 aldehydes, 12 amines, and 3 isonitriles (Figure 2), some representative oxazoles synthesized are listed in Figure 3. The condensation can be performed with approximately equimolar quantities of three components, simplifying the purification step. Under these mild conditions, ring-chain tautomerization of isonitrile to 2-unsubstituted oxazole via a nitrilium intermediate was not observed.[33] With secondary amine as input, higher than 90% yield of pure oxazole was obtained (**1g**, **1h**). As expected for an Ugi-type reaction, racemic



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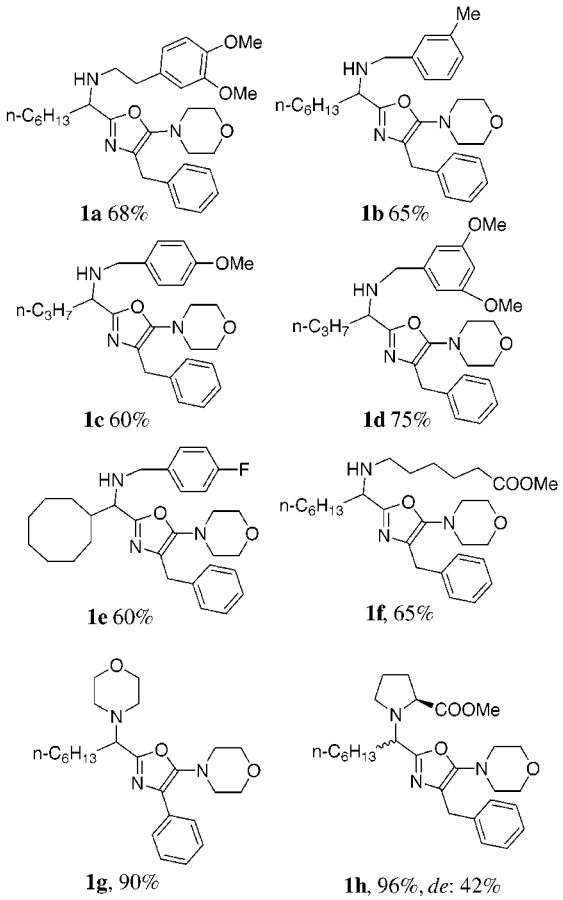

Figure 3.

oxazoles were obtained when enantiomerically pure isonitriles **5** (R = Bn, phenyl) were used as inputs. On the other hand, using proline methyl ester as amine input, a moderate asymmetric induction was observed leading to two separable diastereomers in a ratio of 2.5/1 (**1h**). To the best of our knowledge, this procedure consists of the first multicomponent synthesis of 2,4,5-trisubstituted oxazole.[34]

From 5-Aminooxazole to Pyrrolo[3,4-*b*]pyridin-5-one by a Triple Domino Process. The 6,7-dihydro-5*H*-pyrrolo[3,4-*b*]-pyridin-5-one (**2**), a cyclic analogue of nicotinamide and an aza nalogue of isoindolinones, has been used as pharmacophore by many research laboratories,[35] which has led to the development of number of new synthetic routes.[36−38] Except for Bhandari and Gallop's elegant multistep solid-phase synthesis,[38] most of the syntheses started from the azaphthalimide and hence are limited in scope as they were not amenable for diversity incorporation on the heterocyclic ring.

It has been known for half a century thanks to the seminal contribution of Kondrat'eva[39] that the aza−diene system of 5-alkoxyoxazole reacts readily with the activated dienophile to give a [2 + 4] cycloadduct. Based on this reaction, a landmark synthesis of vitamine B_6 (pyridoxine) was developed by Merck chemists in the 1960s.[40] By analogy, we thought to exploit similar chemistry to develop a one-pot domino process to access the pyrrolopyridine **2**. Interestingly enough, studies on the cycloaddition of the 5-amino derivative were relatively rare in contrast to its 5-alkoxy counterpart. Kondrat'eva et al. showed that the intermolecular reaction of 5-aminooxazole with dienophile was quite sensitive to the reaction conditions and various pathways involving [2 + 4], [2 + 3], and even [2 + 2] cycloaddition could occur.[41,42] To channel these different reactivities into a productive process, we set out to examine the previously unexplored intramolecular cycloaddition of 5-aminooxazole.[43] The presence of the secondary amine in compounds **1** provided an ideal handle for realization of this endeavor. Eventually, stirring a solution of oxazole **1a** and acid chloride **13a** (R_5 = COOEt) in toluene at 0 °C for 30 min followed by heating to reflux provided the pyrrolopyridine **2a** in 65% yield (Scheme 3). Toluene was the solvent of choice as the same reaction performed in other solvents such as THF, MeCN, and benzene produced only a low yield of the desired pyrrolopyridine. Other acyl chlorides, such as *p*-nitrocinnamic acid chloride (**13b**; R_5 = 4-NO_2−C_6H_5) and *p*-methoxycinnamic acid chloride (**13c**; R_5 = 4-MeO−C_6H_5) can also be used as dienophile leading to pyrrolopyridines with a biaryl unit (Figure 4). The presence of an ester and a nitro function is particularly interesting since it provided an extra diversity point. One of such an example is shown in Scheme 3. Thus, stirring a solution of pyrrolopyridine **2a** and 2-(3′,4′-dimethoxy)phenethylamine (**4a**) in dichloromethane in the presence of 2-hydroxypyridine (**14**) provided the amide **15** in over 95% yield.[44] In the absence

(33) Ring-chain tautomization of α-isocyanoacetate to oxazole is well known; see: (a) Chupp, J. P.; Leschinsky, K. L. *J. Heterocycl. Chem*. **1980**, 705−709. (b) Maeda, I.; Togo, K.; Yoshida, R. *Bull. Chem. Soc. Jpn*. **1971**, *44*, 1407−1410.

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(38) Bhandari, A.; Li, B.; Gallop, M. A. *Synthesis* **1999**, 1951−1960.

(39) For a review, see: (a) Karpeiskii, M. Ya, Florent'ev, V. L. *Russ. Chem. Rev*. **1969**, *38*, 540−546. For general reviews on oxazole chemistry, see: (b) Hassner, A.; Fischer, B. *Heterocycles* **1993**, *35*, 1441−1465. (c) Turchi, I. J.; Dewar, M. J. S. *Chem. Rev*. **1975**, *75*, 389−437. (d) Lakhan, R.; Ternai, B. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York, 1974; Vol. *17*, 99−211. (e) Boger, D. L. *Chem. Rev*. **1986**, *86*, 781−793. (f) Lipshutz, B. H. *Chem. Rev*. **1986**, *86*, 795−819.

(40) (a) Harris, E. E.; Firestone, R. A.; Pfister, K., III; Boettcher, R. R.; Cross, F. J.; Currie, R. B.; Monaco, M.; Peterson, E. R.; Reuter, W. *J. Org. Chem*. **1962**, *27*, 2705−2706. (b) Firestone, R. A.; Harris, E. E.; Reuter, W. *Tetrahedron* **1967**, *23*, 943−955.

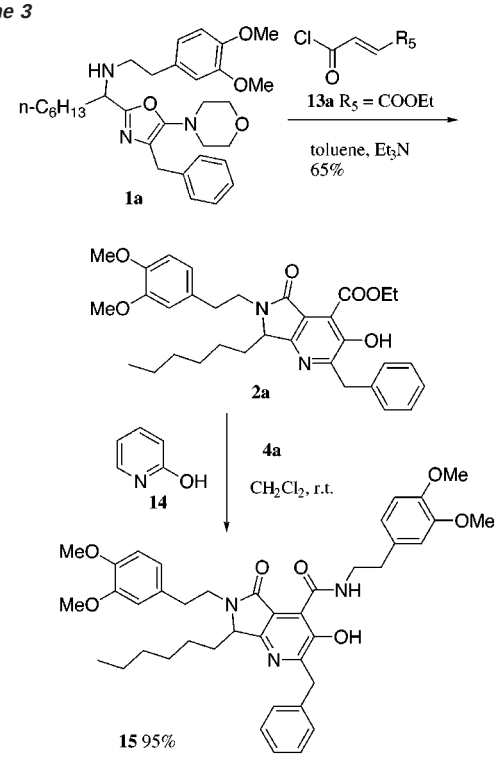
(41) (a) Kondrat'eva, G. Y.; Aitzhanova, M. A.; Bogdanov, V. S. *Izv. Akad. Nauk. SSSR. Ser. Khim*. **1976**, 2146−2147; *Chem. Abstr*. **1977**, *86*, 121223j. (b) Kondrat'eva, G. Y.; Aitzhanova, M. A.; Bogdanov, V. S.; Chizhov, O. S. *Izv. Akad. Nauk. SSSR. Ser. Khim*. **1979**, 1313−1322; *Chem. Abstr*. **1979**, *91*, 140753b. (c) Bogdanov, V. S.; Kondrat'eva, G. Y.; Aitzhanova, M. A. *Izv. Akad. Nauk. SSSR. Ser. Khim*. **1980**, 1017−1029; *Chem. Abstr*. **1980,** *93*, 185242s.

(42) (a) McEwen, W. E.; Grossi, A. V.; MacDonald, R. J.; Stamegna, A. P. *J. Org. Chem*. **1980**, *45*, 1301−1308. (b) Shimada, S. *J. Heterocycl. Chem*. **1987**, *24*, 1237−1241.

(43) For related examples, see: (a) Levin, J. L.; Weinreb, S. M. *J. Org. Chem*. **1984**, *49*, 4325−4332. (b) Jung, M. E.; Street, L. J. *J. Am. Chem. Soc*. **1984**, *106*, 8327−8329. (c) Subramanyam, C.; Noguchi, M.; Weinreb, S. M. *J. Org. Chem*. **1989**, *54*, 5580−5585. (d) Levin, J. I. *Tetrahedron Lett*. **1989**, *30*, 2355−2358. (e) Jung, M. E.; Dansereau, S. M. K. *Heterocycles* **1994**, *39*, 767−778. (f) Vedejs, E.; Piotrowski, D. W.; Tuci, F. C. *J. Org. Chem*. **2000**, *65*, 5498−5505. (g) Padaw, A.; Dimitroff, M.; Liu, B. *Org. Lett*. **2000**, *2*, 3233−3235. (h) Paquette, L. A.; Efrenov, I. *J. Am. Chem. Soc*. **2001**, *123*, 4492−4501.

(44) Rony, P. R. *J. Am. Chem. Soc*. **1969**, *91*, 6090−6096.

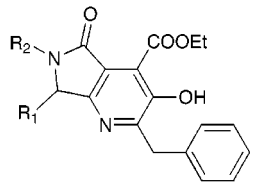
Scheme 3



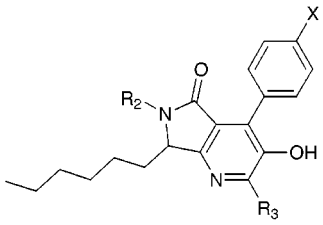
of bifunctional catalyst **14**, no transamidation occurred under such mild conditions.

Ammonium Chloride-Promoted Three-Component Reaction in Toluene and a Four-Component Synthesis of Pyrrolopyridine. Having developed a two-step synthesis of pyrrolopyridine using 5-aminooxazole as the chemical platform, a one-pot four-component reaction to the same pyrrolopyridine was next sought. To be able to combine two steps in a single operation, an appropriate choice of solvent is crucial. Since N-acylation was involved in the conversion of aminooxazole **1** to pyrrolopyridine **2**, the protic solvent that was the solvent of choice for the three-component synthesis of oxazole is better avoided. On the other hand, toluene has been found to be a good solvent for the triple domino process. We therefore thought to examine conditions that could allow us to perform the three-component synthesis of oxazole in the same solvent. Experimentally, it was observed that three-component reaction of heptaldehyde (**3a**), *n*-butylamine (**4g**), and isocyanoacetamide (**5a**) proceeded very slowly in toluene and long reaction time was required to obtain a reasonable conversion (Table 1, entries 1−3). To accelerate the oxazole formation, we surmised that either a Brönstedt acid or a Lewis acid would be required. Toward this end, a number of reaction conditions varying additives were examined and the results are summarized in Table 1.

While a strong Lewis acid led to the formation of intractable tars due most probably to the instability of the 5-aminooxazole,[45] a weak Lewis acid such as LiBr was found to be able to promote the 3CR, leading to oxazole in 49% yield (entry 5).[46] On the other hand, the weak Brönstedt acids proved to be far better



2b $R_1 = nC_6H_{13}$, R_2 = 2-(3',4'-dimethoxy)phenethyl, 58%
2c $R_1 = nC_3H_7$, R_2 = 4-methoxybenzyl, 57%
2d $R_1 = nC_3H_7$, R_2 = 3,5-dimethoxybenzyl, 68%
2e R_1 = Cyclooctyl, R_2 = 4-fluorobenzyl, 66%
2f $R_1 = nC_3H_7$, R_2 = 3,4-dioxolanylphenyl, 58%



2g R_2 = 2-(3,4-dimethoxy)phenethyl, R_3 = Bn, X = NO_2, 63%
2h R_2 = 2-(3,4-dimethoxy)phenethyl, R_3 = Bn, X = OMe, 55%
2i $R_2 = nC_4H_9$, R_3 = iPr, X = NO_2, 59%

Figure 4.

Table 1. Three-Component Synthesis of Oxazole in Toluene, a Salt Effect

entry	additive[b]	temp (°C)/time (h)	yield (%)[a]
1	none	rt/4	24
2	none	rt/96	68
3	none	60/4	32
4	$BF_3{\cdot}Et_2O$	60/4	nd[c]
5	LiBr	60/4	49
6	$Et_3N{\cdot}HCl$	60/4	71
7	pyridine·HCl	60/4	69
8	2,6-lutidine.HCl	60/4	69
9	NH_4Cl	60/4	73
10	$BuMe_3NCl$	60/4	34
11	Bu_4NI	60/4	36
12	CSA[d]	60/4	67
10	Bu_4NI/CSA[e]	60/4	69

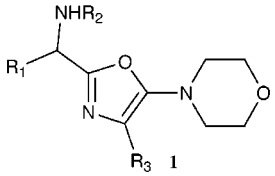
[a] Unless specified, 1.5 equiv of additive was used. [b] Isolated yield of pure 5-aminooxazole. [c] Intractable tars. [d] Additive, 0.1 equiv. [e] A total of 1.5 equiv of Bu_4NI together with 0.1 equiv of CSA.

promoters, the best being ammonium chloride (entry 9). Thus, simply heating the amine **4g**, the aldehyde **3a**, and the isonitrile **5a** in toluene in the presence of 1.5 equiv of ammonium chloride, the desired oxazole **1m** was isolated in 73% yield. Several points deserve further comments. First, the hydrochloride salts of tertiary amines (triethylamine, entry 6), as well as those of pyridine and 2,6-lutidine, are capable of accelerating the reaction (entries 7 and 8), and so did a catalytic amount of camphorsulfonic acid (CSA, 0.1 equiv). However, addition of an excess of protic acid is detrimental due to the decomposition of 5-aminooxazole. Second, increasing the ionic strength of the reaction medium seems not to be responsible for the rate-accelerating effect of ammonium salt since only a negligible effect was observed when trimethylbenzylammonium chloride or tetrabutylammonium iodide (Bu_4NI) was used as the promotor (entries 10 and 11).[47] On the other hand, a combined use of Bu_4NI (1.5 equiv) and CSA (0.1 equiv) restored the efficiency

(45) For Lewis acid-catalyzed reaction of isocyanide, see: (a) Müller Von, E. Zeeh, B. *Liebigs Ann.* **1966**, *696*, 72−80. (b) Ito, Y.; Kato, H.; Saegusa, T. *J. Org. Chem*. **1982**, *47*, 741−743. (c) Kobayashi, K.; Irisawa, S.; Matoba, T.; Matsumoto, T.; Yoneda, K.; Morikawa, O.; Konishi, H. *Bull. Chem. Soc. Jpn*. **2001**, *74*, 1109−1114.

(46) For a LiBr-promoted three-component synthesis of tetracyclic tetrahydroisoqunoline, see: Gonzalez-Zamora, E.; Fayol, A.; Bois-Choussy, M.; Chiaroni, A.; Zhu, J. *J. Chem. Soc., Chem. Commun*. **2001**, 1684−1685.

(47) McFarland, J. M. *J. Org. Chem.* **1963**, *28*, 2179−2181.



1i $R_1 = nC_6H_{13}$, $R_2 = nC_4H_9$, R_3 = Ph, 53%
1j R_1 = 4-MeO-C_6H_4, $R_2 = nC_4H_9$, R_3 = Bn, 60%
1k $R_1 = C_6H_5$, R_2 = 4-Br-C_6H_4, R_3 = Bn, 67%
1l $R_1 = nC_6H_{13}$, $R_2 = nC_4H_9$, R_3 = iPr, 52%
1m $R_1 = nC_6H_{13}$, $R_2 = nC_4H_9$, R_3 = Bn, 73%

Figure 5.

observed with protic additives. Therefore, we assume that the role of ammonium chloride was to provide a proton source that is able to form an hydrogen bond with the imine intermediate, favoring subsequently the nucleophilic attack of isonitrile. It is worthy noting that ammonium chloride, a potential donor of NH_3, did not participate in this reaction under these mild conditions.[48] Some representative oxazoles synthesized using ammonium chloride as promoter in toluene are listed in Figure 5. Interestingly, the present conditions allowed us to use aromatic aldehydes as input to give compounds **1j** and **1k** in good yield.

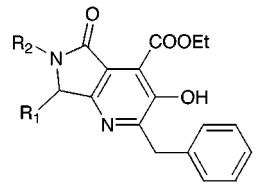
If a hydrochloride salt of amine was used as input, neutralization in situ with triethylamine in toluene followed by addition of aldehyde and isonitrile led to the corresponding 5-aminooxazole **1f** in 75% yield. Apparently, the stoichiometric amount of $Et_3N{\cdot}HCl$ generated in situ is enough to promote this multicomponent reaction.

With these conditions in hand, the development of a one-pot four-component synthesis of pyrrolopyridine was straightforward. Thus, a solution of an aldehyde, an amine, and an isonitrile (60 °C) in the presence of 1.5 equiv of ammonium chloride was stirred at room temperature. Once oxazole formation was deemed complete by TLC analysis, an appropriate $\alpha,\beta-$unsaturated acyl chloride and triethylamine was added at 0 °C. Heating to reflux produced pyrrolopyridine in good yield. Some representative structures synthesized by this novel procedure were listed in Figure 6. Both aromatic and aliphatic aldehydes participate well in this reaction. Amino ester took part in this reaction, effectively leading to the functionalized pyrrolopyridine as a separable mixture of two diastereomers. The conditions are sufficiently mild so that no epimerization was observed. It is nevertheless appropriate to point out that 4-nitrobenzaldehyde did not participate in the reaction sequence, nor did the methyl valinate. The former may be the result of electronic effect while the latter may be due to the severe steric congestion around the nitrogen atom. The yield is generally higher than the two-step procedure, which signifies that oxazole formation is in fact a much cleaner reaction than the isolated yield may indicate. Partial degradation of the oxazole during the column chromatography purification (SiO_2) may account for the phenomenon.

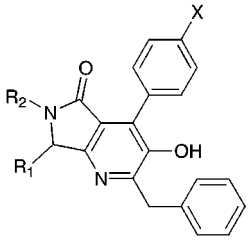
Discussion

For the conversion of 5-aminooxazole to pyrrolopyridine, a possible reaction scenario involving a triple domino process is

(48) For NH_4Cl as a doner of NH_3, see: (a) Matier, W. L.; Owens, D. A.; Comer, W. T.; Deitchman, D.; Ferguson, H. C.; Seidehamel, R. J.; Young, J. R. *J. Med. Chem.* **1973**, *16*, 901−908. (b) Larsen, S. D.; Grieco, P. A. *J. Am. Chem. Soc*. **1985**, *107*, 1768−1769.



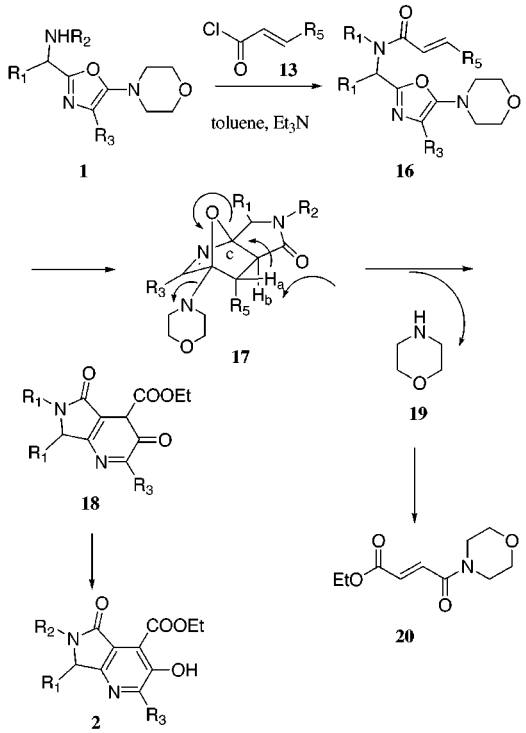
2j $R_1 = C_6H_{13}$, R_2 = MeOOC$(CH_2)_5$, 50%
2k R_1 = 4-MeO-C_6H_4, $R_2 = nC_4H_9$, 55%
2l $R_1 = nC_6H_{13}$, R_2 = (*R*)-CH(PhCH_2)COOMe, 54%
2m $R_1 = nC_6H_{13}$, R_2 = (*S*)-CH(PhCH_2)COOMe, 48%
2n $R_1 = nC_6H_{13}$, R_2 = (*S*)-CH(CH_2COOMe)COOMe, 40%



2o R_1 = 4-Cl-C_6H_4, $R_2 = nC_4H_9$, X = NO_2, 32%
2p $R_1 = nC_6H_{13}$, R_2 = MeOOC$(CH_2)_5$, X = NO_2, 75%
2q $R_1 = nC_6H_{13}$, $R_2 = nC_4H_9$, X = NO_2, 71%
2r $R_1 = nC_6H_{13}$, R_2 = 2-(3',4'-dimethoxy)phenethyl, X = NO_2, 70%
2s $R_1 = C_6H_5$, $R_2 = nC_4H_9$, X = NO_2, 70%
2t $R_1 = C_6H_5$, R_2 = MeOOC$(CH_2)_5$, X = NO_2, 35%
2u $R_1 = nC_6H_{13}$, R_2 = MeOOC$(CH_2)_5$, X = MeO, 65%

Figure 6.

Scheme 4



shown in Scheme 4. Thus, acylation of the secondary amine of oxazole **1** gave the amide **16**, which underwent intramolecular Diels−Alder reaction affording the bridged tricycle intermediate **17**. Base-catalyzed retro-Michael cycloreversion then furnished the pyrrolopyridine. The following facts are in accord with this reaction sequence: (1) in sharp contrast to Kondrat'eva's reports, reaction between oxazole **1a** and *N*-phenylmaleimide did not

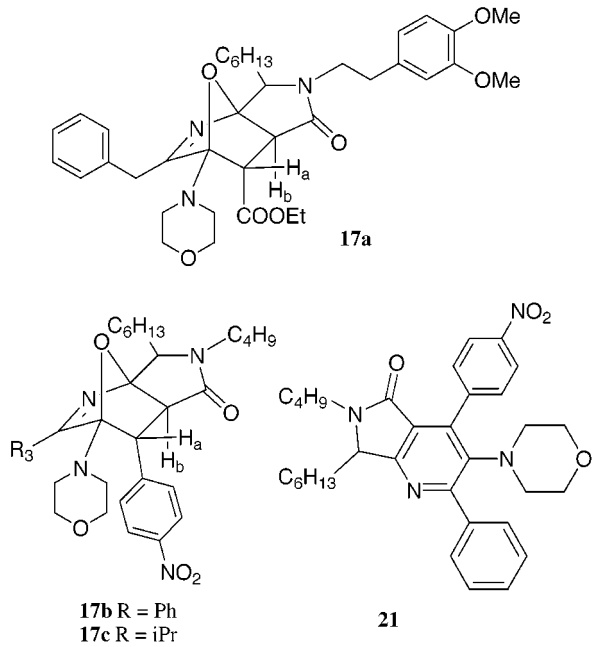


Figure 7.

give the corresponding cycloadduct. This result supported the idea that acylation preceded cycloaddition.[49] (2) When the reaction was carried out in CH_2Cl_2 at room temperature, we were able to isolate the intermediate **17a** (R_1 = *n*-C_6H_{13}, R_2 = 2-(3′,4′-dimethoxy)phenethyl, R_3 = Bn, R_5 = COOEt; Figure 7) The coupling constant between H_a and H_b (J_{Ha-Hb} = 4.1 Hz) indicated a gauche relationship (dihedral angle of 40°c or so) between these two protons. For the inherent ring strain imposed by the connecting bridge, only the lactam exo−ester endo mode of cycloaddition was possible leading to observed compound **17**. In this intermediate, the proton H_b is properly aligned with the C_c−O bond, facilitating the difficult 5-endo-trig reversal. The morpholine **19** generated was in situ acylated leading to amide **20**.[50] Thus, for conformational reasons, this retro-Michael cycloreversion dominated over the alternative fragmentation assisted by the lone pair electrons on the morpholine nitrogen, an otherwise "normal process". It is worth noting that alternative reaction pathways of 5-aminooxazoles such as [2 + 3] cycloaddition were not observed under these reaction conditions.

The residue R_3 exerted influence on both the stability of oxa-bridged tricyclic compound **17** and the fragmentation pathway. Thus, compound **17b** bearing a phenyl substituent is stable and did not fragment to the pyrrolopyridine under standard reaction conditions (toluene, Et_3N, 110 °C). Under acidic conditions, **17b** was either recovered from the reaction mixture (AcOH, room temperature to 80 °C) or completely decomposed to an intractable mixture (AcOH, refluxing in toluene and TFA, CH_2Cl_2, room temperature). Only by refluxing a toluene solution of **17b** in the presence of DBU did the fragmentation occur to provide pyrrolopyridine **21** in 65% yield. It is interesting to note that, in this case, the fragmentation was assisted by the lone pair of nitrogen leading to **21** with a morpholinyl substituent. While no clear-cut explanation can be offered at the present time, we assume that steric effect is not responsible for such an "anomaly" since **17c** readily fragmented by a retro-Michael process to give the pyrrolopyridine **2i**.

Conclusion

In summary, we reported a novel multicomponent reaction leading to polysubstituted 5-aminooxazole starting from simple and readily available inputs. Its subsequent new scaffold-generating reaction involving a triple domino sequence, acylation/IMDA/retro-Michael cycloreversion, led to polyfunctionalized pyrrolopyridine in a single operation. Key to the sequence design is the use of α-isocyanoacetamide instead of the α-isocyanoacetate that completely suppressed the alternative reaction pathway initiated by the α-methylene carbon nucleophilicity. The observation that ammonium chloride can accelerate the oxazole formation in toluene permitted us to develop subsequently a one-pot four-component synthesis of pyrrolopyridine. The observed beneficial effect of ammonium chloride may be a general phenomenon and should find application in designing novel multicomponent reactions based on the isonitrile chemistry.[51] The reaction sequence developed herein is especially suitable for combinatorial synthesis since the skeleton of both 5-aminooxazole and pyrrolopyridine can be decorated by different substituents. Further work based on the pairwise use of MCR/Domino process is in progress and will be reported in due course.[52]

Experimental Section

Three-Component Synthesis of 5-Aminooxazole (1) (Procedure A, in Methanol). A solution of amine (0.20 mmol, 1.3 equiv) and aldehyde (0.18 mmol, 1.2 equiv) in dry methanol (1 mL) was stirred at room temperature for 30 min. Isocyanide (0.15 mmol) was then added. The reaction mixture was stirred at 60 °C, and the reaction course was followed by TLC. After the disappearance of isonitrile (typically 4 h), the reaction mixture was cooled to room temperature and the solvent was evaporated. The crude reaction mixture was purified by flash chromatography (silica gel, eluent: AcOEt/Hept or CH_2Cl_2/MeOH) to give the corresponding oxazole.

Ammonium Chloride-Promoted Three-Component Synthesis of 5-Aminooxazole (1) (Procedure B, in Toluene). A solution of amine (0.20 mmol, 1.3 equiv) and aldehyde (0.18 mmol, 1.2 equiv) in dry toluene (1 mL) was stirred at room temperature for 30 min. Isocyanide (0.15 mmol) and ammonium chloride (1.5 equiv.) were added, successively. The reaction mixture is stirred at 60 °C and followed by TLC (typically 4 h). After the disappearance of isonitrile, the reaction mixture was cooled to room temperature, diluted with aqueous sodium bicarbonate, and extracted with ethyl acetate. The combined organic phase was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The crude reaction mixture was purified by flash chromatography (silica gel, eluent: AcOEt/Hept or CH_2Cl_2/MeOH) to give the corresponding oxazole.

Three-Component Synthesis of 5-Aminooxazole (1) (Procedure C, in Toluene) Using the Hydrochloride Salt of the Amine as Input. A solution of the hydrochloride salt of amine (0.20 mmol, 1.3 equiv), Et_3N (0.23 mmol, 1.5 equiv), and aldehyde (0.18 mmol, 1.2 equiv) in dry toluene (1 mL) was stirred at room temperature for 30 min. Isocyanide (0.15 mmol) was then introduced, and stirring was continued at 60 °C After the disappearance of isonitrile, the reaction mixture was cooled to room temperature, diluted with aqueous sodium bicarbonate, and extracted with ethyl acetate. The combined organic extracts were

(49) Cyclic olefins are generally more reactive as dienophiles than their acyclic counterparts in a given Diels−Alder reaction; see: (a) Vaughan, W. R.; Anderson, K. S. *J. Org. Chem.* **1956**, *21*, 673−683. (b) Cookson, R. C.; Gilani, S. S. H.; Stevens, I. D. R. *Tetrahedron Lett.* **1962**, 615−618.

(50) Keay, B. A.; Rajapaksy, D.; Rodrigo, R. *Can. J. Chem.* **1984**, *62*, 1093−1098.

(51) Cristau, P.; Vors, J.-P.; Zhu, J. *Org. Lett.* **2001**, *3*, 4079−4082.

(52) See, for example: Zhao, G.; Sun, X.; Bienaymé, H. Zhu., J. *J. Am. Chem. Soc.* **2001**, *123*, 6700−6701.

washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The crude reaction mixture was purified by flash chromatography (silica gel, eluent: AcOEt/Hept or CH_2Cl_2/MeOH) to give the corresponding oxazole.

From 5-Aminooxazole (1) to Pyrrolo[3,4-*b*]pyridin-5-one (2). To a solution of oxazole (0.10 mmol) and Et_3N (0.50 mmol, 5 equiv) in dry toluene (2 mL) cooled at 0 °C, acid chloride (0.22 mmol, 2.2 equiv) was added in small portions. After being stirred at room temperature for 30 min, the reaction mixture was heated to reflux for 12 h. The reaction mixture, cooled to room temperature was diluted with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The crude reaction mixture was purified by flash chromatography (silica gel, eluent: AcOEt/Hept or CH_2Cl_2/MeOH) to give the corresponding pyrrolopyridine.

Four-Component Synthesis of Pyrrolo[3,4-*b*]pyridin-5-one (2). To a solution of amine (0.20 mmol, 1,3 equiv) in dry toluene (1 mL) was added aldehyde (0.18 mmol, 1.2 equiv). After being stirred at room temperature was for 30 min, isocyanide (0.15 mmol), and ammonium chloride (0,23 mmol, 1.5 equiv) were added, successively. The reaction mixture is stirred at 60 °C until the disappearance of isonitrile. The reaction mixture was cooled to 0 °C and diluted with toluene (1 mL). Et_3N (0.75 mmol, 5 equiv) was added followed by acid chloride (0.22 mmol, 2.2 equiv) in small portions. Stirring was continued at room temperature for 30 min and at 110° for 12 h. After cooling the mixture to room temperature, the reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The crude reaction mixture was purified by flash chromatography (silica gel, eluent: AcOEt/Hept or CH_2Cl_2/MeOH) to give the corresponding pyrrolopyridine.

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Supporting Information Available: Spectroscopic and analytical data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org. See any current masthead page for ordering information and Web access instructions.

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