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A novel and efficient synthesis of 3-carboxy-4-oxo-1,8-naphthyridines using magnesium chloride

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The authors would like to dedicate this manuscript to Professor Larry E. Overman on the occasion of his 65th birthday

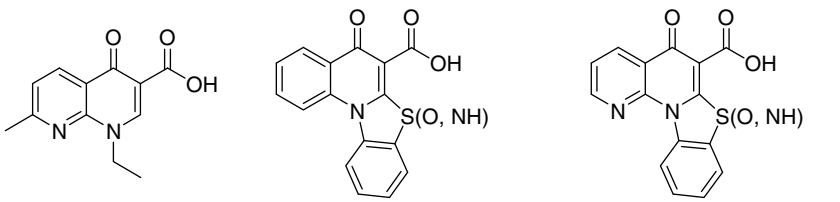
ABSTRACT

A novel and efficient synthesis of 5-oxo-6-carboxy-naphthyridines is reported in this Letter along with a discussion of scope and limitations. Activated 3-nicotinic acids readily acylate the magnesium anion of 2-(benzothiazol-2-yl) or 2-(benzimidazol-2-yl) acetates. The corresponding product can then undergo cyclization spontaneously or under very mild conditions to give the desired naphthyridine products. Only near stoichiometric ratios of reactants are required for this approach and the products are isolated in pure form after a trituration making this an efficient process.

The first commercial quinolone, Naxidixic acid **1**, represents a large and clinically successful class of man made antibacterial agents (Fig. 1).[1] The 5-oxo-4-carboxy quinoline scaffold **2** and the 5-oxo-6-carboxy naphthyridine scaffold **3** are a subclass of these molecules which display interesting biological properties.[2–4] Unfortunately, the existing methodology for accessing these compounds has limitations which prevented us from making certain molecules within this class of compounds. Herein, we report a novel and efficient method for rapidly constructing the 5-oxo-6-carboxy naphthyridine core starting with 2-halo - 3-carboxy pyridines and the anion of benzothiazolyl or benzimidazolyl acetate.

5-Oxo-6-carboxy-naphthyridines can be made via the condensation of an amino thiophenol or diaminobenzene with the corresponding bis(methylthio) acetal (Compound **5**, Scheme 1).[5] This approach can trace its origins back to the Grohe–Heitzer cycloacylation,[6] a versatile reaction which has been used to make commercial drugs such as ciprofloxacin, temafloxacin, and trovafloxacin. This process involves elevated temperatures and the generation of methane thiol, which is a toxic gas. Furthermore, the synthesis of the bis(methylthio) acetal involves the use of toxic reagents such as carbon disulfide and iodomethane, and generally the acetal requires purification prior to subsequent steps. Although this process is suitable for small scale, it is problematic for larger scale. Yields for the synthesis of compound **6** were about 4% over two steps. The application of Chu's method,[7] whereby the corresponding β-keto-ester was heated with 2-chlorobenzothiazole in the presence of base, did not produce any desired product in our hands.

As we looked for alternative approaches, we found that other methods for making this class of compounds were scarce. In developing our strategy, we felt that the disconnection which starts with 2-chloronicotinic acid and 2-benzothiazolyl acetate **8**[8,9] was a logical one as both are readily available from commercial sources. The initial bond formation between the acid carbon and



Nalidixic Acid **1** 5-oxo-6-carboxy quinoline **2** 5-oxo-6-carboxy naphthyridine **3**

Figure 1. Quinolones.

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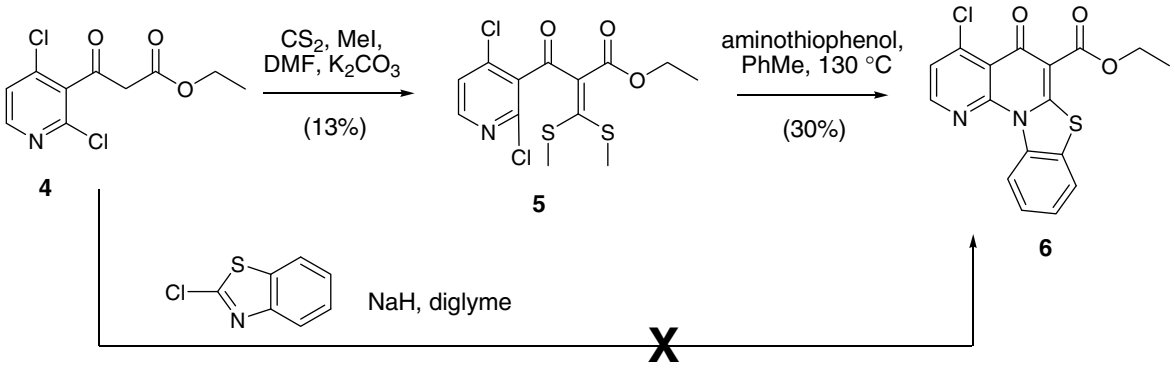
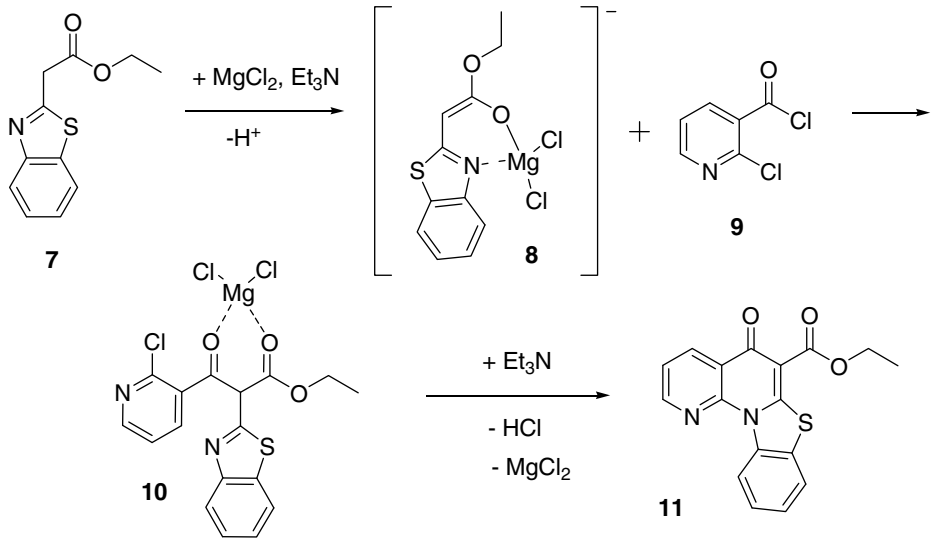


Scheme 1. Previously disclosed methods.



Scheme 2. Proposed mechanism.

the alpha-carbon of malonate system is well precedented and should give compound **10** which would be analogous to the intermediate produced in the condensation reaction of the bis(methylthio) acetal. Subsequent cyclization would then give rise to the desired 5-oxo-6-carboxy naphthyridine **11**. To our delight, this process worked well (Scheme 2).

In some cases, spontaneous cyclization was appreciable and the reaction could be left to stir at room temperature until completion. Alternatively, additional base such as potassium carbonate or Hunig's base and a polar aprotic solvent could be added concomitant with stirring and elevated temperatures to complete the cyclization. In the cases where cyclization is not spontaneous, the acyclic intermediate can be isolated and characterized. Subsequent treatment with base and heat furnishes the final product. Purification of the acyclic intermediate can help remove trace impurities.

Our initial test substrate, 2-chloronicotinic acid chloride, formed the desired product in 77% yield after a simple trituration (Table 1, entry 1). 2,6-Dichloronicotinic acid chloride contains an additional electrophilic chlorine atom which presents a regiochemical issue, but as expected, the intramolecular cyclization is much faster than any potential intermolecular bond formations resulting in the formation of the product in 75% yield (entry 2).

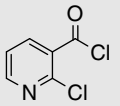
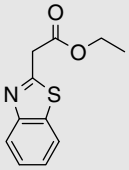
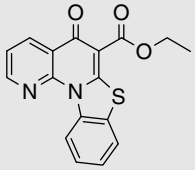
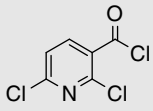
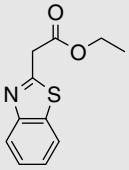
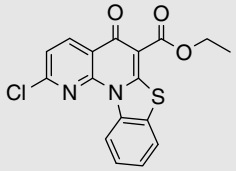
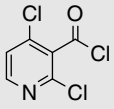
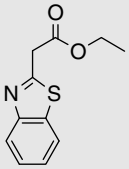
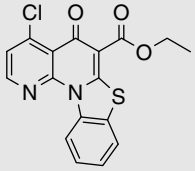
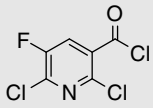
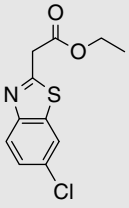
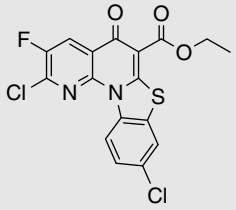
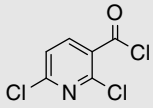
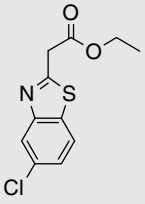
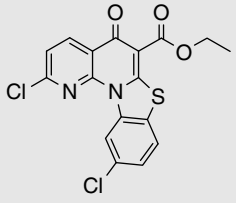
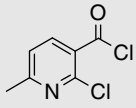
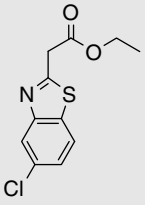
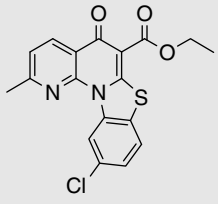
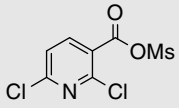
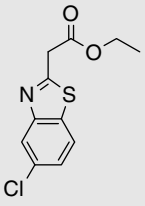
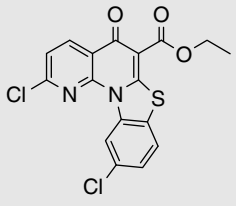
In our problematic example, which gave only trace amounts of desired product under the previously disclosed method via the bis(methylthio) acetal, 2,4-dichloronicotinic acid chloride reacted efficiently with the corresponding thiazole to give a 2:1 mixture of regioisomeric products in 90% yield (entry 3). The highly substituted 2,6-dichloro-5-fluoronicotinic acid chloride was also problematic to cyclize using the bis(thiomethyl) acetal approach as nucleophilic attack by aminobenzenethiol occurred predominantly at the 6-position. Gratifyingly, the reaction of 2,6-dichloro-5-fluoronicotinic acid chloride gave 76% of the desired product under the typical reaction conditions (entry 4).

Often quinolones are very sparingly soluble in water and solvents such as tetrahydrofuran or acetonitrile which makes them highly suitable for purification via a simple trituration protocol. Our best example to date is the reaction between 2,6-dichloronicotinic acid chloride and ethyl 2-(5-chlorobenzothiazol-2-yl) acetate which gives the desired naphthyridine in 98% yield (entry 5).

The solubility of the uncyclized intermediate could also have an influence on the rate of cyclization step. As previously mentioned, the uncyclized intermediates could often be isolated as a solid. In these cases, the ring forming cyclization requires more forcing conditions. In the case of the reaction of 6-methyl nicotinic acid chloride (entry 6), the reaction was homogenous after the initial acyl bond formation step. Cyclization occurs rapidly at room temperature with this substrate. In contrast, the cyclization for a very similar substrate (entry 1) was slower as the acyclic intermediate was not soluble in the reaction media resulting in a heterogeneous solution.

As one would expect, the methanesulfonic anhydride, works equally well in this reaction. In entry 7, the methanesulfonic acid

Table 1
Acylation–cyclizations with benzothiazole acetate[10]

Entry	Activated acid	Azole-acetate	Product	Isolated yield (%)
1				77
2				75
3				90[a]
4				76
5				98
6				95
7				75

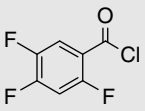
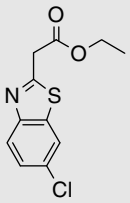
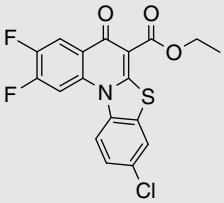
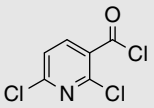
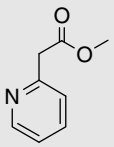
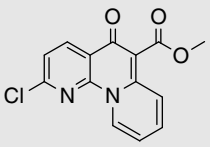
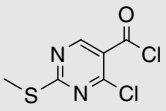
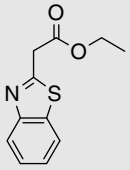
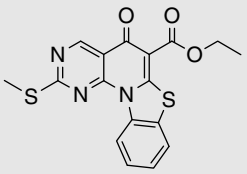
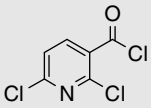
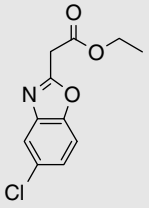
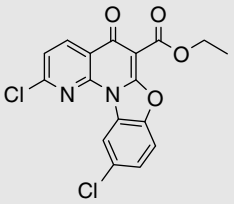
[a] 2:1 mix, major regioisomer shown.

anhydride of 2,6-dichloronicotinic acid reacts efficiently to produce the desired naphthyridine in 75% yield.

The cyclization is facile when the nucleophilic attack occurs on a 2-halo pyridine moiety. This process also works for activated benzene rings that can undergo nucleophilic aromatic substitution (Table 2, entry 1). 2,4,5-Trifluorobenzoic acid chloride reacts with ethyl 2-(5-chlorobenzothiazol-2-yl) acetate to produce the desired quinolone in 60% yield.

The cyclization can occur with weaker nucleophiles. 2-Pyridine acetic acid methyl ester efficiently formed the initial bond with 2,6-dichloronicotinic acid and to our surprise, the cyclization also occurs even at 0 °C. Warming to room temperature for a few hours

Table 2[a]

Entry	Activated acid	Azole-acetate	Product	Isolated yield (%)
1				60
2				84
3				77
4				68

[a] Representative experimental procedure: Hunig's base (2.0 equiv) was added to a mixture of the acid chloride (1.15 equiv) and azole-acetate (8.5 mmol) in acetonitrile (20 mL) at such a rate that the internal temperature was <5 °C. The solution was then stirred at ambient temperature for 2 h. For entries 1 and 4, the reaction was not complete until DMF (10 mL) and potassium carbonate were added and the mixture was stirred at reflux overnight (12–18 h).

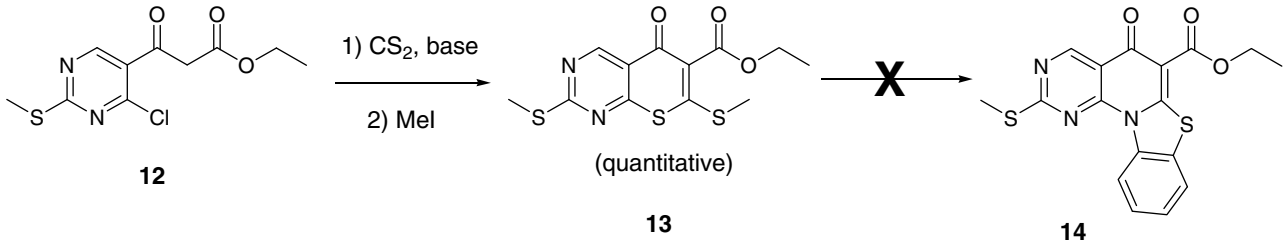
allowed the reaction to go to completion and furnish the desired product in 84% yield (entry 2).

Pyrimidine analogs are also readily made using this methodology, but in our hands, these were not accessible using the Grohe–Heitzer cyclo-acylation (Table 2, entry 3). Under previously disclosed conditions, treatment of the malamute **12** with carbon disulfide in the presence of base resulted in the quantitative formation of an intermediate which when treated with methyl iodide produced **13** (Scheme 3). Unfortunately, **13** was not reactive with 2-aminobenzenethiol. Alternatively, 4-chloro-2-(methylthio)pyrimidine-5-carbonyl chloride reacted smoothly with ethyl 2-(benzothiazol-2-yl)acetate to give the desired product in 77% yield (Table 2, entry 3).

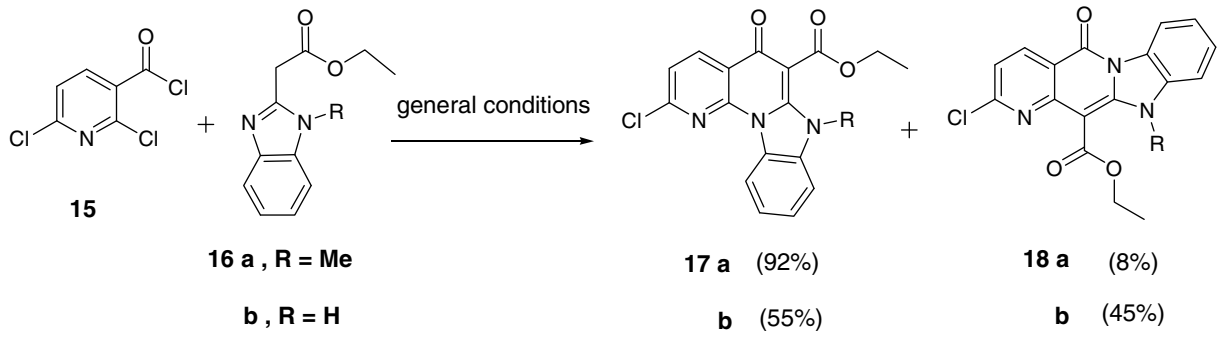
Benzoxazoles also react with 2,6-dichloronicotinic acid chloride efficiently. Although the product was somewhat labile with hydrolysis of the oxazole being problematic, the corresponding product could be isolated in 68% yield (Table 2, entry 4).

The reaction also proceeds well when the reacting partner was changed to the corresponding benzimidazole. In the case of imidazole **16a**, a minor product **18a** can be produced in 5–15% yield. Compound **18a** arises due to loss of chemoselectivity presumably because the endocyclic nitrogen is slightly more reactive in the benzimidazole than in the benzothiazole. Hence, the initial bond formation can occur between the acid chloride and the nitrogen of the benzimidazole. Fortunately, the minor side product is much more soluble than **17a** in tetrahydrofuran and is readily removed by trituration (Scheme 4).

In the case of **16b**, where the imidazole nitrogen is not substituted and even more nucleophilic, formation of the minor regioisomer **18b** becomes even more significant.

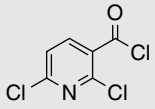
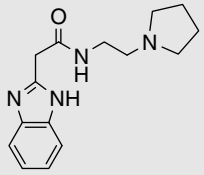
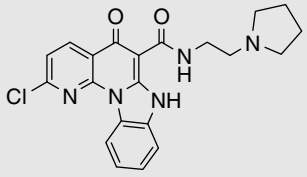
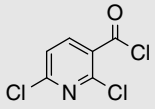
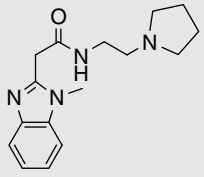
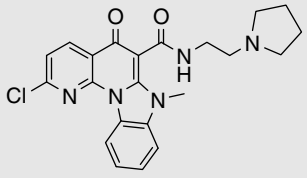
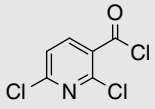
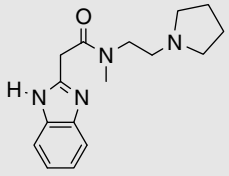
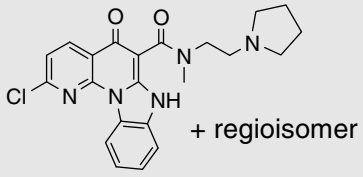


Scheme 3. Attempted synthesis of pyrimidine analogs.



Scheme 4. Asymmetric benzimidazoles.

Table 3
Acetamides

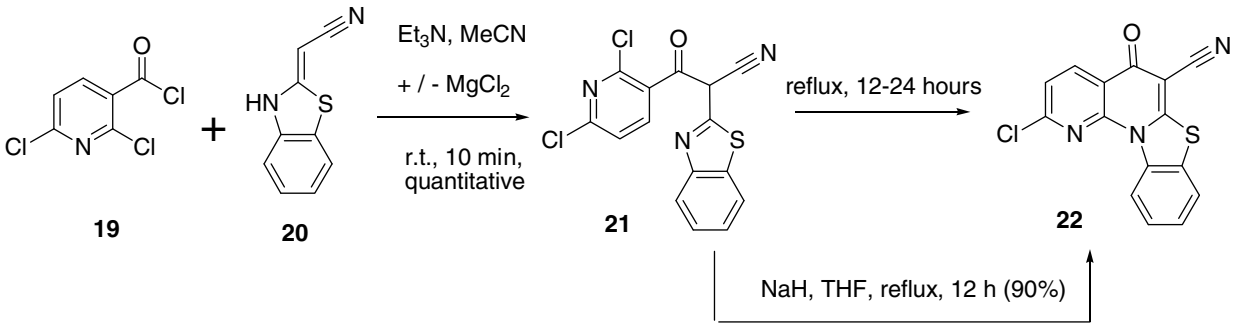
Entry	Activated acid (**a**)	Azole-acetate (**b**)	Product (**c**)	Isolated yield (%)
1				No product
2				No product
3			 + regioisomer	43

Benzimidazole acetamides with unsubstituted amide nitrogens did not react with 2,6-dichloronicotinic acid chloride (Table 3, entry 1). Presumably the unsubstituted nitrogens of the amide and imidazole decrease the Lewis acidity of the magnesium enough to nullify its effects and prevent the reaction from occurring. Alkylating one of the nitrogens in the imidazole ring (entry 2) was not fruitful. Methylation of the amide nitrogen was more successful. Product **3c** was formed in 43% yield (entry 3) concomitant with substantial amounts of the isomeric side product. Presumably reducing the enol character of the amide to make it more like the ester helps the reaction proceed more efficiently.

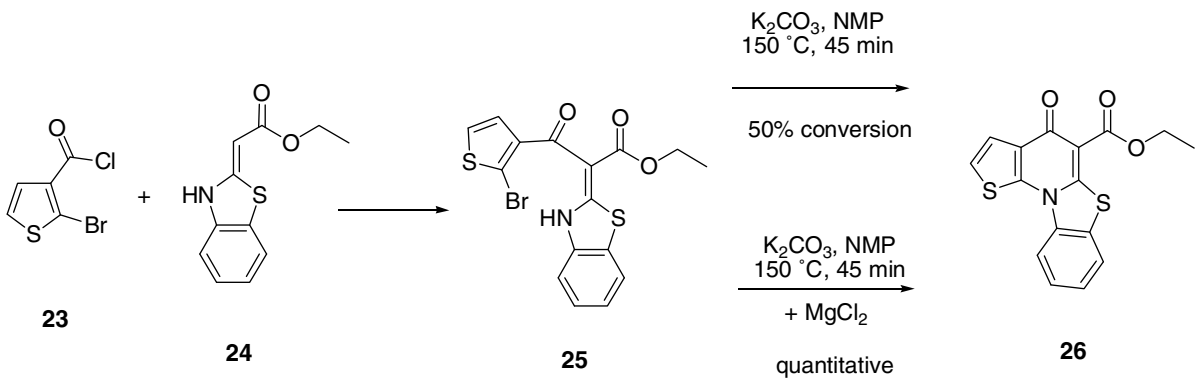
In the case of benzothiazole acetonitrile **20**, formation of the initial bond between the acyl and the methylene carbons occurs very rapidly, even in the absence of $MgCl_2$ (Scheme 5). In the subsequent ring closing cyclization, the reaction proceeds slowly and at the same rate with or without $MgCl_2$, whereas the analogous example bearing the ester moiety cyclizes spontaneously at room temperature (Table 1, entry 2). Furthermore, the acyclic intermediate **21** could also be isolated and treated with a stronger base to produce compound **22** in roughly the same time period. In other words, $MgCl_2$ is not required for the first bond formation and moreover, the absence or presence of $MgCl_2$ has no effect on the ring closure. A possible rational is that **21** does not form a bidentate chelate with magnesium which would accelerate the formation of **22**. Regardless, benzothiazole acetonitrile substrates do not benefit from the addition of $MgCl_2$ as much as the corresponding esters.

We also found certain thiophene analogs difficult to cyclize often requiring elevated temperatures for extended periods of time. Acyclic thiophene **25** was purified and isolated as it does not readily undergo cyclization. With the addition of 2 equiv of $MgCl_2$, the reaction to form **26** was complete in 45 min and was free of any impurities. In comparison, the reaction without $MgCl_2$ was less than 50% complete after 45 min and was contaminated with side products. Furthermore, this reaction without $MgCl_2$ would never go beyond 80% conversion even after prolonged heating (Scheme 6).

Herein, we report a novel methodology for the formation of various 5-oxo-6-carboxy-naphthyridines and quinolines. The method involves a mildly basic reaction media as well as mild temperatures in the case of most substrates. Less reactive substrates require elevated temperatures to cyclize. The method is efficient



Scheme 5. Benzothiazole acetonitrile.



Scheme 6. Thiophene analogs.

as it does not require a large excess of any reagents, and products are formed with very few side products. In the case of the examples shown within, pure products can be obtained after a simple trituration with organic solvents and/or water.

Acknowledgment

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References and notes

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10. Representative experimental procedure: (Table 1, entry 2) 2,6-dichloronicotinoyl chloride (2.31 g, 11.0 mmol) was slowly added to a solution containing ethyl 2-(benzothiazol-2-yl)acetate (2.21 g, 10.0 mmol), magnesium chloride (1.41 g, 15.0 mmol), and tetrahydrofuran (25 ml). The resulting suspension was cooled in an ice bath and triethylamine (2.02 g, 23.7 mmol) was added dropwise at such a rate that the internal temperature did not go over 10 °C as measured with an internal thermocouple probe. Once the addition was complete, the ice bath was removed and the mixture was allowed to stir while warming to room temperature over 2 h. The reaction was warmed to 80 °C for 1 h at which time LCMS indicated that the reaction was done. The reaction was diluted with water and filtered. The solid was dissolved in a mixture of dichloromethane and chloroform washed with water and the organic phase was dried over sodium sulfate. After concentration on a rotary evaporator, the product was purified by trituration with diethyl ether to give 2.71 g (75%) of the dichloro-ester as a beige solid. ^{1}H NMR (400 MHz, $CDCl_3$) 1.50 (t, 3H, J = 7.2 Hz), 4.52 (q, 2H, J = 7.2 Hz), 7.49 (t, 1H, J = 7.6 Hz), 7.58 (d, 1H, J = 8.4 Hz), 7.61 (t, 1H, J = 8.0 Hz), 7.77 (d, 1H, J = 8.0 Hz), 8.86 (d, 1H, J = 8.0 Hz), 9.55 (d, 1H, J = 8.8 Hz); MS (EI): 359.3 $(M+H)^+$.