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Synthetic Methods

Synthesis of Triarylpyridines in Thiopeptide Antibiotics by Using a C–H Arylation/Ring-Transformation Strategy

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Abstract: We have described a C–H arylation/ring-transformation strategy for the synthesis of triarylpyridines, which form the core structure of thiopeptide antibiotics. This synthetic method readily gave 2,3,6-triarylpyridines in a regioselective manner by a two-phase approach: C–H arylation (a nickel-catalyzed decarbonylative Suzuki–Miyaura cross-coupling and decarbonylative C–H coupling for the synthesis of 2,4-diaryloxazoles) and ring transformation ([4+2] cycloaddition of 2,4-diaryloxazoles with (hetero)arylacrylic acids). To showcase these methods, we have accomplished the formal synthesis of thiopeptide antibiotics GE2270 s and amythiamicins.

Many recently emerging thiopeptide antibiotics, such as GE2270s and amythiamicins, are composed of a 2,3,6-triarylpyridine moiety and a macrocyclic oligopeptide (Figure 1 A).[1] Biological assays of these compounds have shown that they are protein-synthesis-inhibitor candidates against Gram-positive bacteria, and one of these derivatives LFF571, developed by Novartis, is now undergoing phase II clinical trials.[2] Owing to their interesting structures and remarkable biological activities, these compounds have attracted considerable attention as synthetic targets.[1c,3–5] To date, a number of strategies toward these molecules, particularly the synthesis of their core 2,3,6-triarylpyridine structure, have been devised, which includes a hetero-Diels–Alder/dimerization process, a Bohlmann–Rahtz or Hantzsch pyridine synthesis and a cross-coupling reaction of organometallic compounds with aryl halides. Although excellent strategies and syntheses have been reported, the development of a diverse method to form and derivatize the core structure of these heterocyclic oligopeptides is in high demand.

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Herein, we describe a new method for the synthesis of 2,3,6-triarylpyridines by using a C–H arylation/ring transformation strategy (Figure 1 B):[6] this consists of a sequence of C–H arylation and [4+2] cycloaddition (Kondrat'eva reaction)[7] with suitable alkenes. Such a sequence would begin with 4-aryloxazoles as starting material, which in turn would be prepared by decarbonylative coupling of a phenyl ester with arylboronic acid derivatives (Figure 1 B).[8] Recently, transition-metal-catalyzed direct C–H arylation has attracted much attention as a next-generation coupling method for the construction of (hetero)-biaryl frameworks.[9,10] But although the C–H arylation of five-membered heteroarenes is well established with controlled regioselectivity, the C–H arylation of six-membered (hetero)aromatics, such as pyridine, has considerable room for further investigation in terms of overcoming challenges in reactivity and regioselectivity.[11] One way to access diverse multi-arylated pyridines would be to diarylate five-membered heteroaromatics by decarbonylative arylation and C–H arylation, followed by a ring transformation from a five-membered ring to a six-membered ring.

To realize this plan, we first synthesized a variety of 2,4-diaryloxazoles that can undergo [4+2] cycloaddition. Although 4-aryloxazoles can be prepared by using a known method, the yields were moderate to low.[12] Therefore, we prepared them by developing a coupling method (Scheme 1).[8] To this end, phenyl oxazole-4-carboxylate was coupled with arylboroxines in the presence of $Ni(OAc)_2/P(nBu)_3$ catalyst and Na_2CO_3 in toluene at 150 °C to give 4-aryloxazoles **1a**–**d** in 45–57% yield. Next, **1a**–**d** were coupled with phenyl esters **2a** and **b** using our C–H coupling method under the following conditions: $[Ni(cod)_2]$/dcype (cod = 1,5-cyclooctadiene; dcype = 1,2-bis(dicyclohexylphosphino)ethane; 1:2 molar ratio; 10 mol% Ni), K_3PO_4 (2.0 equiv), 1,4-dioxane, 150 °C, 24 h.[13] Phenyl 2-phenylthiazole-4-carboxylate (**2a**) and phenyl thiophene-2-carboxylate (**2b**) were coupled with 4-phenyloxazole (**1a**) to give 2,4-diaryloxazoles **3a** and **b**, respectively, in excellent yield. The coupling of 4-(4-methoxyphenyl)oxazole (**1b**) and **2a** gave the product **3c** in moderate yield. Compounds 4-(*p*-tolyl)oxazole (**1c**) and 4-(2-naphthyl)oxazole (**1d**) were reacted with **2a** under the same conditions to produce the corresponding coupling products **3d** and **e** in good to excellent yields.

Next, we examined the [4+2] cycloaddition of 2,4-diaryloxazoles **3** with (hetero)arylalkenes to generate triarylpyridines by ring transformation. When thiazolylacrylic acid **4a** was used as the dienophile, cycloaddition with **3a** proceeded in *o*-dichlorobenzene at 150 °C to give 2,3,6-triarylpyridine **5a** in 71% yield with virtually complete regioselectivity, structure of which was

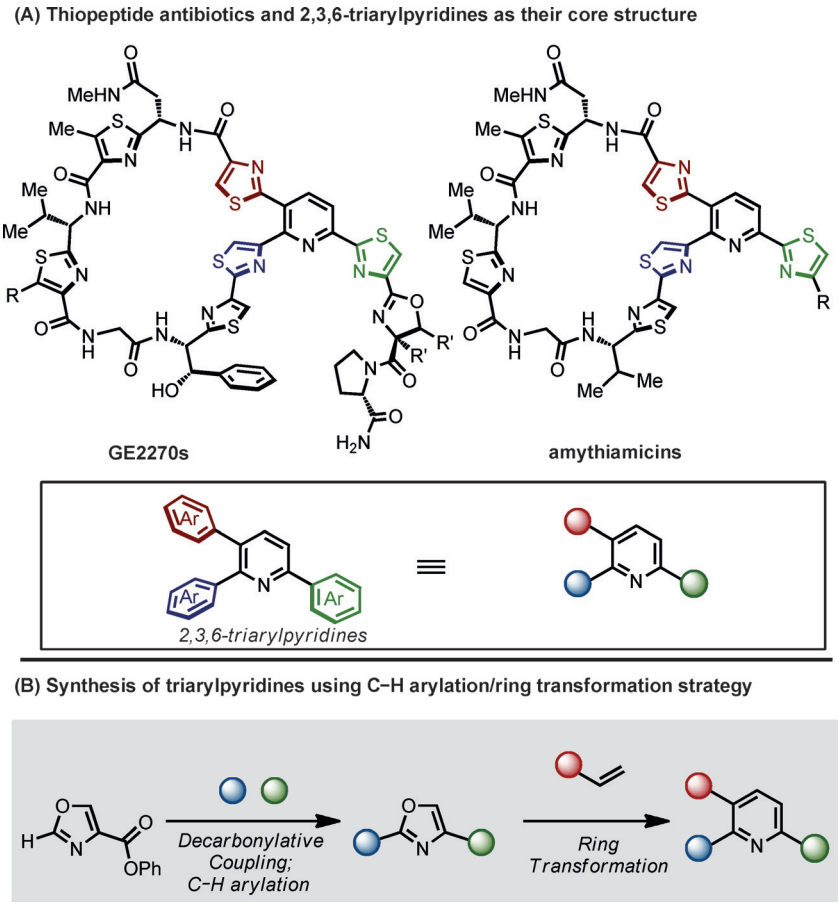


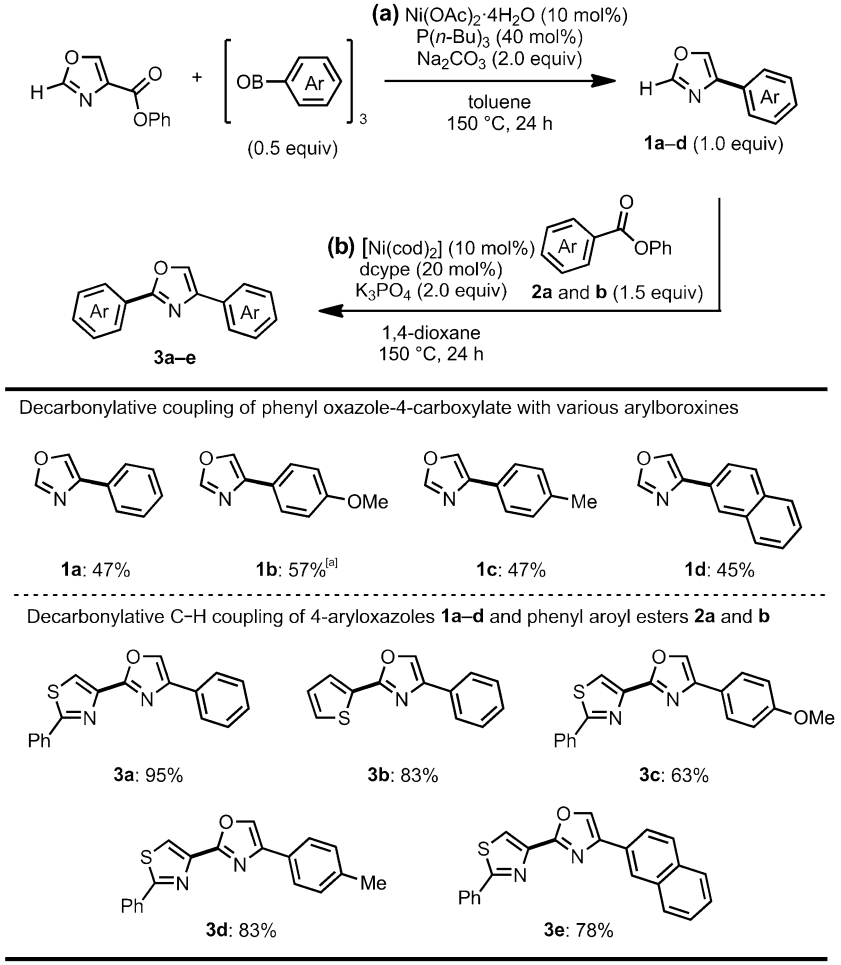
Figure 1. (A) Thiopeptide antibiotics and 2,3,6-triarylpyridines as their core structure. (B) C–H arylation/ring-transformation strategy for the synthesis of 2,3,6-triarylpyridines.

confirmed by X-ray crystal-structure analysis (Scheme 2). This reaction likely occurs by [4+2] cycloaddition of **3a** and **4a** to produce a cycloadduct as an intermediate, followed by dehydration and decarboxylation. Building on this result, we tested several 2,4-diaryloxazoles and (hetero)arylacrylic acids. 2,4-Diaryloxazoles **3b**, **c**, **d**, and **e** were reacted with **4a** to give the corresponding multisubstituted pyridine derivatives **5b**, **c**, **d**, and **e** in moderate to good yield and regioselectivity. Furthermore, the [4+2] cycloaddition could be applied to **3a** with cinnamic acid (**4b**) and its derivatives **4c**, **d**, and **e** under solvent-free conditions at 180 °C to generate the corresponding products **5f**, **g**, **h**, and **i** in moderate yields.

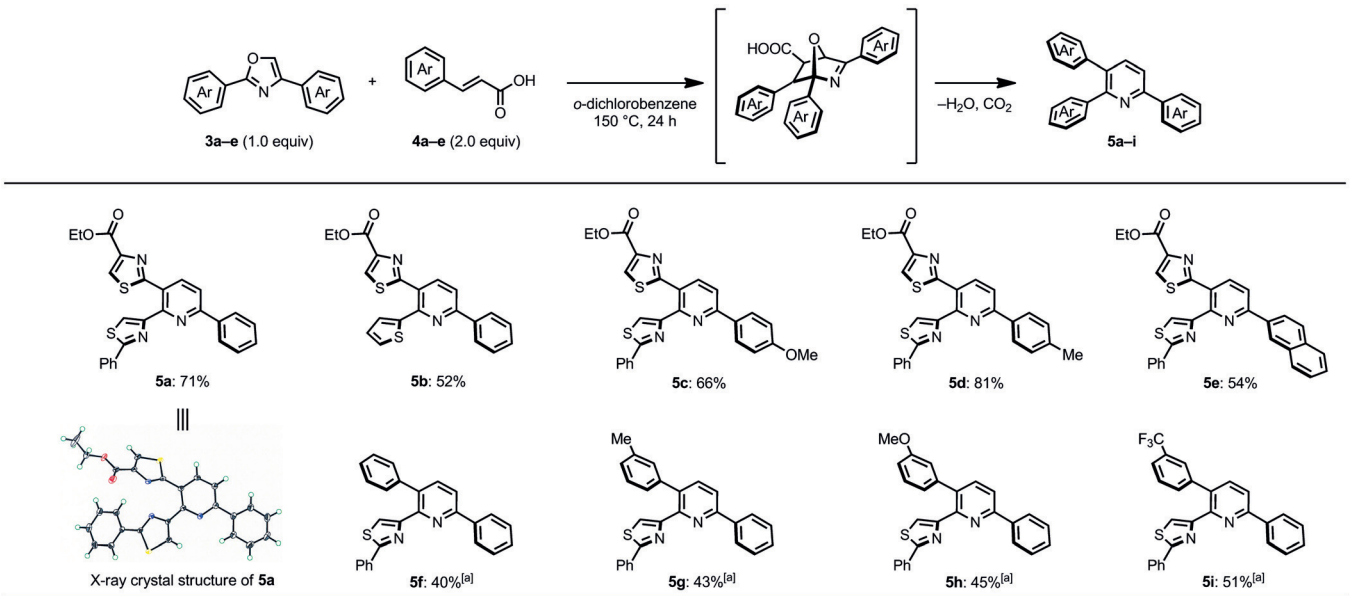
With these results in hand, we then envisaged that this C–H arylation/ring-transformation strategy could allow a convergent synthesis of thiopeptide antibiotics, amythiamicins and GE2270s (Schemes 3 and 4). To achieve this goal, two azole esters **6** and **7**, which were prepared in five steps and three steps respectively from commercially available compounds, were coupled under optimized conditions to afford the corresponding coupling product **8** in 49% yield.[14] The coupling product was reacted with thiazolyl acrylic acid **4a** in *o*-dichlorobenzene at 150 °C to give the corresponding trithiazolylpyridine **9**. Finally, removal of the acetal group by trifluoroacetic acid (TFA) proceeded to afford the pyridine product **10** in 38% yield over two steps (Scheme 3).

The key trithiazolylpyridine **10** was then converted to thiopeptide antibiotic precursors. Compounds **10** and **10′** (prepared through ester exchange under acidic conditions) were treated with TBSOTf and NEt_3 followed by bromination with *N*-bromosuccinimide (NBS) to afford brominated products. These products were treated with thioamide **11** or **12** followed by trifluoroacetic anhydride (TFAA) to afford **13** and **14** in 44% yield (three steps) and 36% yield (four steps), respectively. Since the conversions of **13** to amythiamicins and **14** to GE2270 s were described previously by Nicolaou and co-workers,[3,4] we have accomplished the formal syntheses of amythiamicins and GE2270s through common intermediate **10** (Scheme 4).

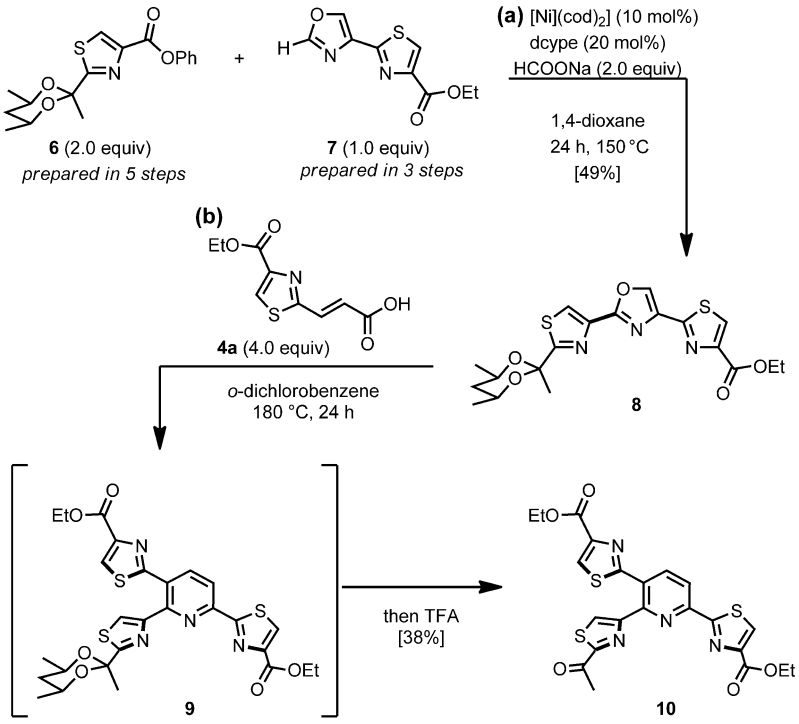
In summary, we have established a new method for the synthesis of triarylpyridines by using a C–H arylation/ring-transformation approach. Key steps include a nickel-catalyzed C–H coupling reaction for the synthesis of 2,4-diaryloxazoles and a [4+2] addition of the resulting diaryloxazoles with (hetero)arylacrylic acids to give triarylpyridines. By using this strategy, we have synthesized six heterocyclic core structures, which constitute formal syntheses of thiopeptide antibiotics. The synthesis of unexplored thiopeptide antibiotics and their derivatives, as well as biological-activity testing, are ongoing in our laboratory.



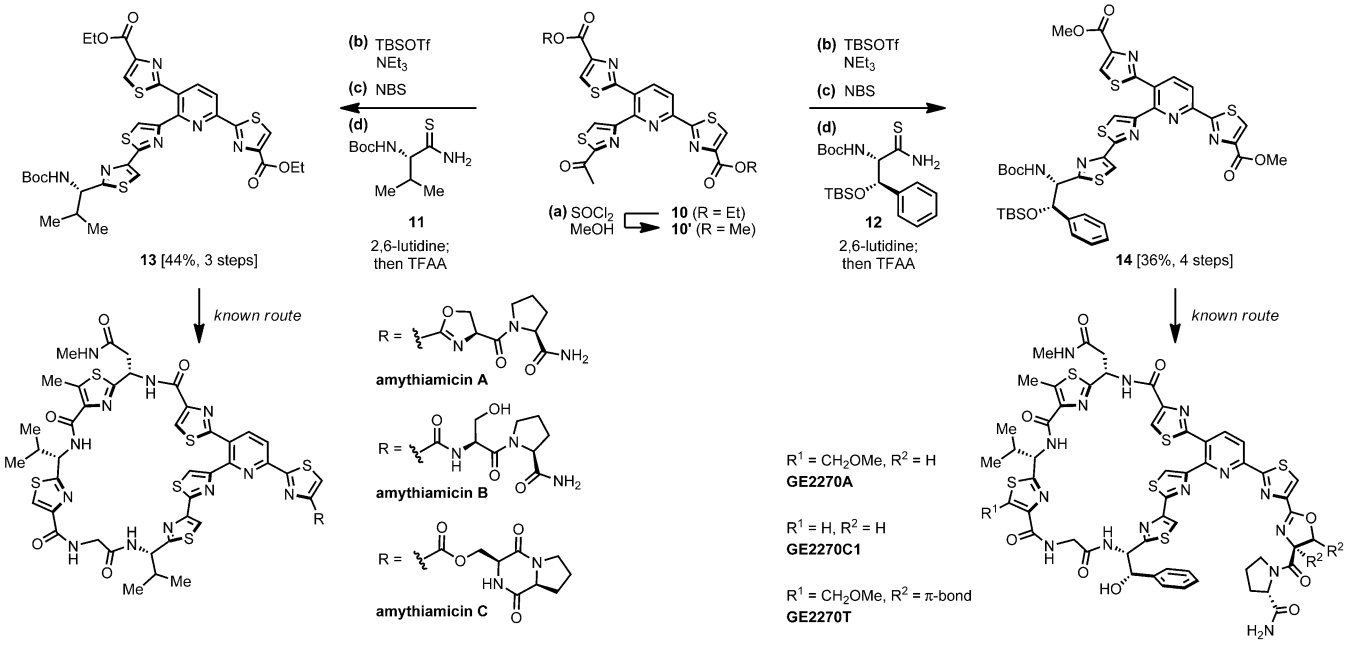
Scheme 1. Synthesis of 2,4-diaryloxazoles. Reaction conditions: (a) phenyl oxazole-4-carboxylate (1.0 equiv), arylboroxine (0.5 equiv), $Ni(OAc)_2{\cdot}4H_2O$ (10 mol%), $P(n\text{Bu})_3$ (40 mol%), Na_2CO_3 (2.0 equiv), toluene, 150 °C, 24 h; (b) **1a–d** (1.0 equiv), **2a** or **b** (1.5 equiv), $[Ni(cod)_2]$ (10 mol%), dcype (20 mol%), K_3PO_4 (2.0 equiv), 1,4-dioxane, 150 °C, 24 h. [a] $Ni(OAc)_2{\cdot}4H_2O$ (5 mol%) and $P(n\text{Bu})_3$ (20 mol%) were used.



Scheme 2. Synthesis of 2,3,6-triarylpyridines by ring transformation. Reaction conditions: **3** (1.0 equiv), **4a** (2.0 equiv), *o*-dichlorobenzene, 150 °C, 24 h. [a] **4b–e** (4.0 equiv), 180 °C, 24 h.



Scheme 3. Synthesis of trithiazolylpyridine **10**. Reaction conditions: (a) $[Ni(cod)_2]$ (10 mol%), dcype (20 mol%), HCOONa (2.0 equiv), 1,4-dioxane, 24 h, 150 °C, 49% yield; (b) **4a** (4.0 equiv), *o*-dichlorobenzene, 180 °C, 24 h; TFA (0.1 mL), 50 °C, 38% yield.



Scheme 4. Formal synthesis of GE2270s and amythiamicins. Reaction conditions: (a) $SOCl_2$ (3.3 equiv), MeOH, 70 °C, 7 h; (b) TBSOTf (2.2 equiv), NEt_3 (3.2 equiv), CH_2Cl_2, 0 °C; (c) NBS (1.0 equiv), THF, 0 °C; (d) **11** or **12** (1.5 equiv), 2,6-lutidine (3.0 equiv), CH_2Cl_2, 0 °C; then TFAA (1.2 equiv).

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