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# Synthesis of a tetracyclic lactam system of Nuevamine by four-component reaction and free radical cyclization

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ABSTRACT

A series of aza-analogs of nuevamine were prepared from readily available aldehyde, amine, and isonitrile compounds and maleic anhydride by combining a novel four-component reaction and free radical cyclization. The operational simplicity of this novel heterocycle synthesis process will be valuable for the synthesis of fused ring systems.



Tetracyclic lactam alkaloids are of interest in drug research due to their biological activities. One of the most important tetracyclic systems that incorporates an isoindolo[2,1-a]isoquinoline skeleton is nuevamine, **1**, Figure 1. This alkaloid was the first reported isoindoloquinoline natural product.[1] The structure of **1** is interesting from a pharmacological perspective due to the potential biological activity of many of its derivatives: anti-inflammatory, anti-microbial, anti-leukemic, and anti-tumoral properties. Many synthetic approaches have been developed in an effort to obtain nuevamine and its analogs.[2–4]

Microwave radiation is widely used as an easily-controlled heat source for a number of applications, particularly the acceleration of organic reactions.[5] Microwave treatment shortens the reaction times and gives high yields. Multicomponent reactions are very important in synthetic organic chemistry.[6] The Passerini three-component reaction (P-3CR) and the Ugi three- and four-component reactions (U-3R, and U-4CR) are of particular importance. An isocyanide derivative is a common component in all three of these coupling processes. Thus, these reactions have become known as isocyanide-based multicomponent reactions (IMCR).[6]

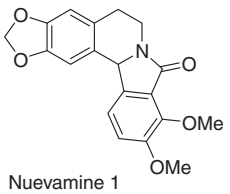
IMCRs, which lead to an interesting heterocyclic scaffold, are particularly useful for the construction of diverse chemical libraries of drug-like compounds,[6c] however the combination of this methodology with the appropriate postfunctionalization is an extremely powerful synthetic tool for the preparation of structurally diverse complex molecules.[7]

In connection with our ongoing project using IMCR and with the goal of developing a new synthetic methodology for gaining rapid access to new compound libraries, we describe the synthesis of new molecules containing the aza-tetracyclic skeleton of nuevamine by means of a novel four-component reaction and the intramolecular free radical cyclization as a postfunctionalization in a one-pot process.

Three-component condensation of 2-bromo benzaldehyde **2a**, allylamine **3**, and the isonitrile **4** in methanol yielded, after 48 h at room temperature, low yields of 5-amino-oxazole **5a**, 27%. After a brief systematic variation of the reaction parameters, it was found that using microwaves as a heat source, $Sc(OTf)_3$ as a catalyst,[8] and benzene as a solvent, promoted this transformation. Stirring a solution containing aldehyde **2a**, allylamine **3**, and the isonitrile **4** for 15 min in a sealed tube in a microwave reactor provided the 5-amino-oxazol **5a** intermediate in an excess of 82% yield, Scheme 1.

The Diels–Alder cycloaddition between the oxazol **5a**, as an aza-diene, and maleic anhydride **6**, as a dienophile, in benzene at 60 °C for 15 min using microwave radiation provided the pyrrolopyridinone **8a** via the oxa-bridged intermediate **7a**.[9] This intermediate spontaneously gave the compound **8a** by a triple domino sequence: lactamization, dehydration, and decarboxylation, and could not be isolated. The pyrrolopyridinone **8a** was produced in 73% overall yield, Scheme 1.

This novel reaction was studied using the amine **3**, isonitrile **4**, maleic anhydride **6**, in benzene, and four aldehydes **2a**, **2b**,[10] **2c**,[11] and **2d**,[12,13] as starting materials. In all cases, the reaction was performed with a catalytic quantity of $Sc(OTf)_3$ and was completed




Nuevamine 1

**Figure 1.**

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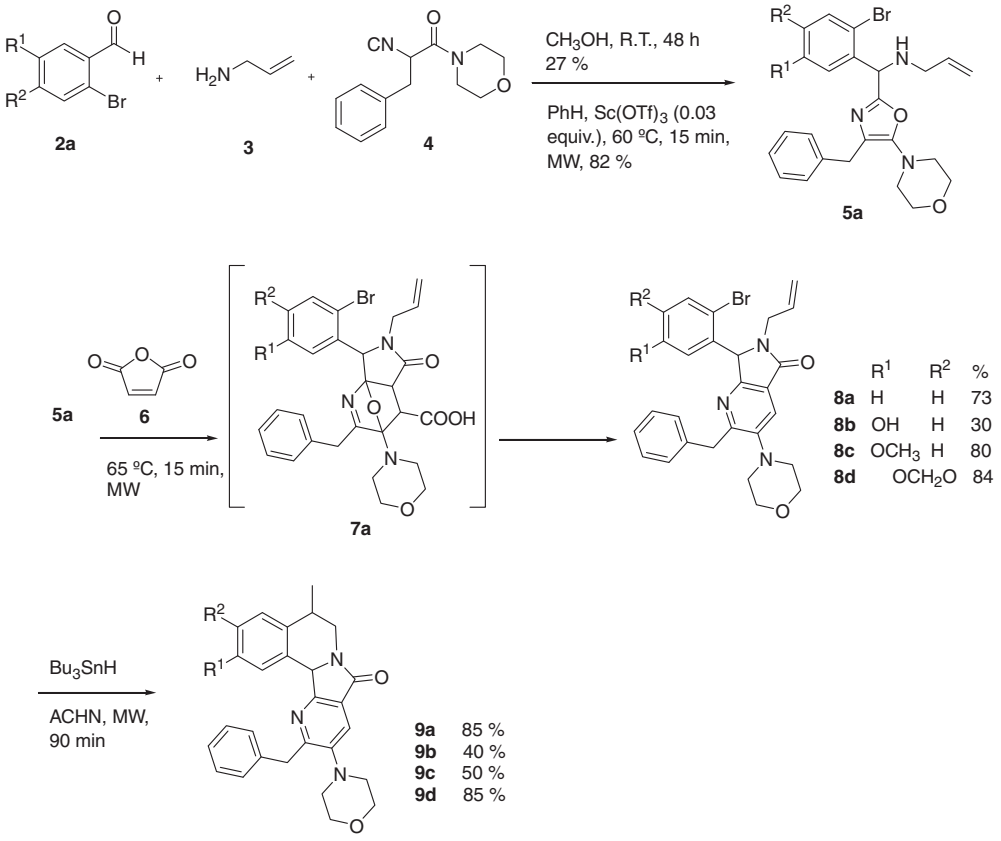


**Scheme 1.**

within 40 min in only one step. The pyrrolopyridinones **8a–d** were produced in good yields, except for **8b**, which was produced in 30% yield (the reaction was not optimized). The low yield for **8b** may have been due to an interaction between $Sc(OTf)_3$ and the hydroxy group of the starting compound, **2b**, Scheme 1.

Closure of the pyridine **8a**, under the classical conditions of the Heck reaction, did not give the expected compound **9a**. However, the use of a free radical reaction employing 1,1′-azobis(cyclohexanecarbonitrile) (ACHN) as the initiator along with $Bu_3SnH$ yielded the expected compound **9a** in low yields.[14] After optimizing conditions using a microwave reactor, the yields for this transformation were improved. The optimal conditions included $Bu_3SnH$, ACHN, and benzene as the solvent, with three sequential additions, followed by irradiation at 138 °C, to yield four diastereomers of the tetracycle **9a** in 85% yield, Scheme 1.

Under these conditions, the desired aza-analogs of nuevamine **1** were prepared from moderate to good yields using the pyrrolopyridinones **8b–d** as starting materials. In all cases, the expected compounds **9b–d** were obtained in a mixture with a difficult separation of the four diastereomers by silica gel column chromatography. Only one diastereoisomer of the compounds **9a** and **9d** was isolated by the use of preparative plates.

The scope of this novel multicomponent domino reaction was evaluated by the inclusion of a free radical cyclization into the full process. Thus, under the conditions established previously in the multistep synthesis, the allylamine **3** and 2-bromo benzaldehyde **2a** were sealed in a reaction tube and irradiated for 5 min at 50 °C. Subsequently, $Sc(OTf)_3$ was introduced and the irradiation was continued for an additional 5 min at the same temperature, after which the isonitrile **4** was added and the mixture was irradiated for 15 min at 80 °C. Next, the maleic anhydride **6** was introduced and the irradiation was continued at 60 °C for an additional 15 min. Finally, three portions of $Bu_3SnH$ and ACHN in benzene were added sequentially and the irradiation was continued at 138 °C for 30 min (each of them) in a single one-pot process, and the isolated four diastereomers of **9a** were obtained in over 72% yield. The major diastereoisomer was isolated using preparative plates.

This reaction is atom economical, seven chemical bonds and three rings were created, and only water and $CO_2$ were lost in this multicomponent domino process via a combination of 4CR, Diels–Alder cycloaddition, and two intramolecular ring closures (lactamization, and 6-*exo*-trig free radical cyclization). Overall, the final compound **9a** was produced in good yield from the four readily available starting materials, Scheme 1.

In summary, the synthesis of four aza-analogs of nuevamine was achieved in a very short time via a multicomponent process that included intramolecular free radical cyclization and microwave assistance. The process involved reactions between aromatics aldehydes, allylamine, α-isocyanoacetamide, and maleic anhydride in the presence of catalytic quantities of $Sc(OTf)_3$. The operational simplicity involved in achieving these novel heterocycles is highly attractive for a range of diversity-oriented synthetic approaches. The development of this methodology as a one-pot synthesis using readily available reagents is currently underway.

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    *Typical procedure for obtaining the pyrrolopyridinone* **8**: allylamine (0.350 mmol) and the corresponding benzaldehyde (0.315 mmol) were placed in a 10 mL sealed CEM Discover™ microwave reaction tube to which 1 mL benzene was added. The sealed tube was placed in the microwave reactor and irradiated at 50 °C (power 4 W) for 5 min, then $Sc(OTf)_3$ was introduced (0.010 mmol) and the irradiation was continued at 50 °C (power 4 W) for 5 min. After this time, the isonitrile was added (0.420 mmol) and the solution was irradiated at 80 °C (power 180 W) for 15 min. Maleic anhydride was added (0.420 mmol) and irradiated at 60 °C (power 4 W) for 15 min. The crude product was purified by silica gel column chromatography (hexane/AcOEt 1:1).

    *6-Allyl-2-benzyl-7-(2-bromo-5-methoxyphenyl)-6,7-dihydro-3-morpholinopyrrolo [3,4-b]pyridin-5-one* **8c**. *Selected spectral data for* **8c**, yield 80%, yellow powder, mp: 95–97 °C; $^1$H NMR (500 MHz, $CDCl_3$, 298 K): $\delta$ 7.89 (s, 1H), 7.58 (d, $J$ = 8.8 Hz, 1H), 7.24–7.25 (m, 2H), 7.15–7.18 (m, 2H), 7.11–7.13 (m, 1H), 6.78 (dd, $J$ = 8.8, 3.0 Hz, 1H), 6.23 (d, $J$ = 3.0 Hz, 1H), 6.13 (s, 1H), 5.75–5.83 (m, 1H), 5.20 (dd, $J$ = 10.1, 1.0 Hz, 1H), 5.12 (dd, $J$ = 17.0, 1.0 Hz, 1H), 4.65 (dd, $J$ = 15.4, 5.0, 1H), 4.32 (d, $J$ = 13.6 Hz, 1H), 4.20 (d, $J$ = 13.6 Hz, 1H), 3.81–3.83 (m, 4H), 3.65 (s, 3H), 3.48 (dd, $J$ = 15.4, 7.2 Hz, 1H), 2.81–2.83 (m, 4H); $^{13}$C NMR (125 MHz, $CDCl_3$, 298 K): $\delta$ 167.1, 162.2, 160.2, 159.3, 147.8, 139.2, 136.0, 134.0, 132.1, 128.9, 128.1, 126.1, 123.8, 123.7, 118.5, 116.0, 115.8, 113.3, 67.1, 63.4, 55.4, 53.0, 43.0, 39.9; IR: 2842, 1694, 1441, 1112, 1015, 940, 701 cm$^{-1}$; HRMS: Calcd for $C_{28}H_{29}N_3O_3Br$ $[M+H]^+$: 534.1314. Found: 534.1395.

    *Typical procedure for the free radical cyclization*: The corresponding pyrrolopyridinone **8** (0.091 mmol) was placed in a 10 mL sealed CEM Discover™ microwave reaction tube, a solution containing $Bu_3SnH$ (0.364 mmol) and ACHN (0.046 mmol) in 1 mL benzene was added in a sequence of three portions, in 30 min intervals, and the irradiation was resumed at 138 °C (power 280 W). The solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/AcOEt 1:1). The major diastereoisomer was isolated using preparative plates.

    *10-Benzyl-5-methyl-9-morpholin-4-yl-5,11b-dihydro-6H-1,3-dio-xa-6a,11-diaza-indeno[5,6-c]fluoren-7-one* **9d**. *Selected spectral data for major diastereisomer* **9d**, yield 85%, yellow powder, mp: 63 °C; $^1$H NMR (500 MHz, $CDCl_3$, 298 K): $\delta$ 7.85 (s, 1H), 7.66 (s, 1H), 7.37–7.39 (m, 2H), 7.19–7.23 (m, 3H), 6.61 (s, 1H), 5.96 (d, $J$ = 1.41 Hz, 1H), 5.90 (d, $J$ = 1.41 Hz, 1H), 5.45 (s, 1H), 4.42 (d, $J$ = 14.25 Hz, 1H), 4.35 (d, $J$ = 14.25 Hz, 1H), 4.31 (dd, $J$ = 13.28, 2.27 Hz, 1H), 3.83–3.87 (m, 4H), 3.54 (dd, $J$ = 13.28, 4.31 Hz, 1H), 3.01–3.04 (m, 1H), 2.85–2.88 (m, 4H), 1.21 (d, $J$ = 7.05 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$, 298 K): $\delta$ 161.2, 158.6, 147.7, 147.1, 146.4, 139.3, 132.7, 129.2, 128.4, 128.3, 126.3, 124.6, 124.2, 123.7, 108.1, 106.7, 101.0, 67.1, 59.3, 53.0, 43.5, 39.9, 35.0, 22.7; IR: 2854, 1693, 1482, 1114, 1035, 932, 699 cm$^{-1}$; HRMS: Calcd for $C_{28}H_{28}N_3O_4$ $[M+H]^+$: 470.2001. Found: 470.2012.

    *Typical procedure for obtaining the tetracycle* **9** *in one-pot process*: allylamine (0.350 mmol) and the corresponding benzaldehyde (0.315 mmol) were placed in a 10 mL sealed CEM Discover™ microwave reaction tube to which 1 mL benzene was added. The sealed tube was placed in the microwave reactor and irradiated at 50 °C (power 4 W) for 5 min, then $Sc(OTf)_3$ was introduced (0.010 mmol) and irradiation was continued at 50 °C (power 4 W) for 5 min. After this time, the isonitrile was added (0.420 mmol) and the solution was irradiated at 80 °C (power 180 W) for 15 min. Maleic anhydride was added (0.420 mmol) and irradiated at 60 °C (power 4 W) for 15 min. A solution containing $Bu_3SnH$ (0.467 mmol) and ACHN (0.058 mmol) in 1 mL benzene was added in a sequence of three portions, in 30 min intervals, and the irradiation was resumed at 138 °C (power 280 W). The solvent was removed under reduced pressure. The crude product, purified by silica gel column chromatography (hexane/AcOEt 1:1) afforded four diastereomers of the tetracycle **9**. The major diastereoisomer was isolated by the use of preparative plates.

    *10-Benzyl-5-methyl-9-morpholin-4-yl-5,11b-dihydro-6H-6a,11-di-aza-benzo[c] fluoren-7-one* **9a**. *Selected spectral data for major diastereisomer* **9a**, yield 72 %, yellow powder, mp: 170–172 °C; $^1$H NMR (500 MHz, $CDCl_3$, 298 K): $\delta$ 8.11–8.13 (m, 1H), 7.85 (s, 1H), 7.35–7.38 (m, 2H), 7.27–7.31 (m, 2H), 7.20–7.24 (m, 3H), 7.16–7.17 (m, 1H), 5.57 (s, 1H), 4.46 (d, $J$ = 14.3 Hz, 1H), 4.36 (d, $J$ = 14.3 Hz, 1H), 4.35 (dd, $J$ = 13.0, 2.3 Hz, 1H), 3.82–3.85 (m, 4H), 3.58 (dd, $J$ = 13.0, 4.5 Hz, 1H), 3.11–3.17 (m, 1H), 2.83–2.86 (m, 4H), 1.25 (d, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$, 298 K): $\delta$ 166.8, 161.1, 158.5, 147.7, 139.4, 139.2, 131.7, 129.2, 128.5, 128.2, 127.5, 126.7, 126.4, 126.2, 124.4, 123.6, 67.1, 59.2, 52.9, 43.5, 39.9, 34.9, 22.6; IR: 1692, 1438, 1114, 1021, 952, 695 cm$^{-1}$; HRMS: Calcd for $C_{27}H_{28}N_3O_2$ $[M+H]^+$: 426.2176. Found: 426.2178.