

One-Pot Multicomponent Synthesis of Diversely Substituted 2-Aminopyrroles. A Short General Synthesis of Rigidins A, B, C, and D[†]

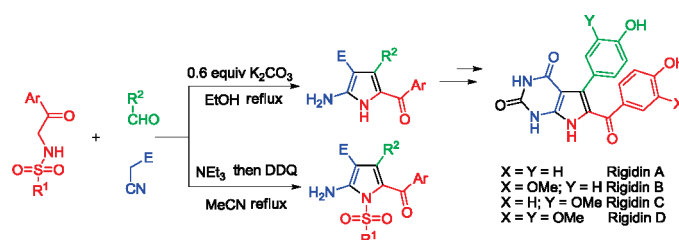
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Received December 27, 2010

ABSTRACT



Privileged medicinal scaffolds based on the structures of tetra- and pentasubstituted 2-aminopyrroles were prepared via one-pot multicomponent reactions of structurally diverse aldehydes and *N*-(aryl-, hetaryl-, alkylsulfonamido)acetophenones with activated methylene compounds. This methodology was used in a four-step synthesis of alkaloids rigidins A, B, C, and D in overall yields of 61%, 58%, 60%, and 53%, respectively. Of these, rigidins B, C, and D were synthesized for the first time.

Polysubstituted pyrroles are an important class of heterocycles that display diverse pharmacological activities.¹ Furthermore, they are useful building blocks in the synthesis of natural products and heterocyclic chemistry. Although a large number of new pyrrole syntheses,² including multicomponent reactions (MCRs),³ have been reported in recent years, relatively few examples are known for the preparation of polysubstituted 2-aminopyrroles.⁴ Aminopyrroles are not readily available through general

pyrrole ring-formation methods. At the same time the 2-aminopyrrole fragment is part of many different bioactive compounds and it is recognized as a privileged medicinal structure. Known bioactivities for this class of compounds include anti-inflammatory,⁵ anticancer,⁶ antiviral,⁷ antifungal,⁸ pesticidal,⁹ radioprotective,¹⁰ MEK inhibitory,¹¹ MK2 inhibitory,¹² FAK, KDR and Tie2 inhibitory,¹³ PDE inhibitory,¹⁴ anti-interleukin-6,¹⁵ TNF- α production inhibitory,¹⁶ and afferent pelvic nerve activity

[†] This paper is dedicated to Prof. Yuri I. Smushkevich on the occasion of his 75th birthday.

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(1) For recent reviews, see: (a) Furstner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3582–3603. (b) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J.-F. *Chem. Rev.* **2008**, *108*, 264–287. (c) Nakao, Y.; Fusetani, N. *J. Nat. Prod.* **2007**, *70*, 689–710. (d) Urban, S.; Hickford, S. J. H.; Blunt, J. W.; Munro, M. H. G. *Curr. Org. Chem.* **2000**, *4*, 765–807.

(2) For selected examples, see: (a) Lu, Y.; Arndtsen, B. *Org. Lett.* **2009**, *11*, 1369–1372. (b) Blangetti, M.; Deagostino, A.; Prandi, C.; Tabasso, S.; Venturello, P. *Org. Lett.* **2009**, *11*, 3914–3917. (c) Aponick, A.; Li, C.-Y.; Malinge, J.; Marques, E. F. *Org. Lett.* **2009**, *11*, 4624–4627. (d) Egi, M.; Azechi, K.; Akai, S. *Org. Lett.* **2009**, *11*, 5002–5005. (e) Satito, A.; Konishi, T.; Hanzawa, Y. *Org. Lett.* **2010**, *12*, 372–374. (f) Wang, H.-Y.; Mueller, D. S.; Sachwani, R. M.; Londino, H. N.; Anderson, L. L. *Org. Lett.* **2010**, *12*, 2290–2293 and references cited therein.

inhibitory.¹⁷ Moreover, 2-aminopyrroles are precursors for the synthesis of purine analogues — pyrrolopyrimidines, pyrrolotriazines, and pyrrolopyridines.^{18–24} These

pyrrole-containing heterocycles are widely investigated for their multiple bioactivities, which, among many others, are known to include anti-inflammatory,¹⁸ anticancer,¹⁹ antiviral,²⁰ antifungal,²¹ adenosine A₁ receptor inhibitory,²² adenosine kinase,²³ and dihydrofolate reductase²⁴ inhibitory. The pyrrolo[2,3-*d*]pyrimidine ring system is also a common motif in several natural products, such as nucleoside antibiotics tubercidin, toyocamycin, sangivamycin,²⁵ and marine alkaloids rigidins A, B, C, D, and E.²⁶

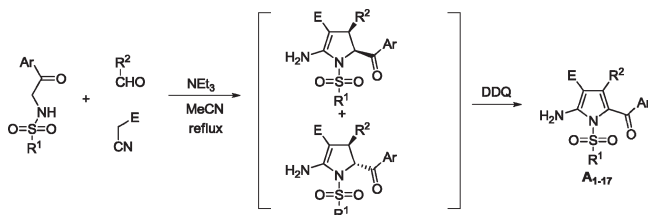
Previously, we described a novel method for the synthesis of multisubstituted pyrrolines using a multicomponent reaction of various *N*-(aryl- and alkylsulfonamido)acetophenones with aldehydes and malononitrile (see Table 1 graphic).²⁷ While the reaction is regioselective, it is not stereoselective and gives mixtures of *cis*- and *trans*-2-pyrrolines, which are not easily separable. Utilizing this methodology as a starting point, we developed a new multicomponent one-pot method for the synthesis of diversely tetra- and pentasubstituted 2-aminopyrroles. In addition, we utilized the new method for a short total synthesis of alkaloids rigidins A, B, C, and D.

Pentasubstituted 2-aminopyrroles **A**_{1–17} were prepared by a multicomponent reaction of *N*-(aryl-, hetaryl-, and alkylsulfonamido)acetophenones, aldehydes, and cyanoacetic acid derivatives in acetonitrile, followed by oxidation with DDQ in one pot (Table 1). This three-component process works well for any tested combination of aliphatic, aromatic (including sterically hindered or heteroaromatic) aldehydes and malononitrile, cyanoacetamide, or ethyl cyanoacetate. Because of the lower reactivity of the intermediate Knoevenagel products of cyanoacetamide or ethyl cyanoacetate, the reactions were sluggish in acetonitrile (**A**₁₆ and **A**₁₇). In these cases the pyrrolines were obtained in ethanol, the solvent was then evaporated, and the crude material was redissolved in acetonitrile for the subsequent oxidation with DDQ. When phenylsulfonyl- or 4-methoxybenzoylacetoneitriles were used in this reaction, a mixture of pyrrolines was obtained, which did not undergo oxidation to the corresponding pyrroles.

This methodology was also used for the synthesis of tetrasubstituted NH-pyrroles by base-promoted dehydro-sulfinylation of the 2-pyrroline mixtures. It was previously reported that DBU was able to promote the elimination of toluenesulfinic acid from *N*-tosyl-3-pyrrolines to give pyrroles.²⁸ In our case, the treatment of mixtures of 2-pyrrolines with DBU in DMF leads to the formation of tetrasubstituted

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Table 1. Synthesis of Pentasubstituted Pyrroles **A**

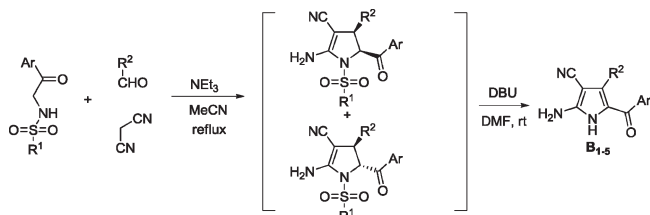
Pyrrole	Ar	R ¹	R ²	E	yield %
A ₁	Ph	4-O ₂ N-Ph	4-Cl-Ph	CN	81
A ₂	Ph	2,4,6- <i>i</i> -Pr-Ph	3,4,5-MeO-Ph	CN	91
A ₃	Ph	4-MeO-Ph	3,4,5-MeO-Ph	CN	89
A ₄	4-MeO-Ph	4-MeO-Ph	3-Br-4,5-MeO-Ph	CN	78
A ₅	Ph	Me	3-Br-4-MeO-Ph	CN	37
A ₆	Ph	4-MeO-Ph	3,5-Br-Ph	CN	56
A ₇	Ph	4-MeO-Ph		CN	41
A ₈	Ph	4-MeO-Ph	2,6-Cl-Ph	CN	78
A ₉	Ph	4-F-Ph	2,6-Cl-Ph	CN	55
A ₁₀	Ph	Bu	4-O ₂ N-Ph	CN	71
A ₁₁	Ph	4-Me-Ph	Pr	CN	55
A ₁₂	Ph	Me		CN	50
A ₁₃	Ph		4-MeOOC-Ph	CN	96
A ₁₄	Ph	Me	2-Cl-6-F-Ph	CN	88
A ₁₅	Ph	Me	2,6-Cl-Ph	CN	65
A ₁₆ ^a	Ph	4-MeO-Ph	4-Br-Ph	CONH ₂	38
A ₁₇ ^a	Ph	4-MeO-Ph	3,4,5-MeO-Ph	COOEt	76

^a The intermediate pyrrolines were obtained in EtOH.

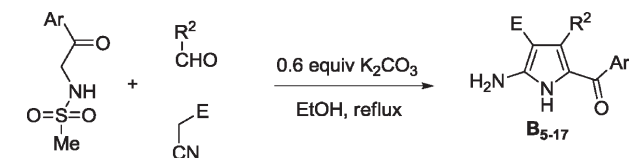
NH-pyrroles **B**_{1–5} (Table 2). We found that 4-MeO-PhSO₂– and MeSO₂– leaving groups are the best for this reaction, but it is necessary to change the solvent from acetonitrile to DMF. Furthermore, after the experimentation with different solvents, bases, and reaction temperatures we found that simply refluxing a solution of the three reactants containing 0.6 equiv of K₂CO₃ in ethanol results in pyrroles **B**_{5–17} (Table 3).²⁹

The reaction scope encompasses the use of aliphatic, aromatic, and heterocyclic aldehydes as well as diverse activated methylene compounds including cyano, acyl, sulfono, alkoxycarbonyl, and carbamido acetonitriles.

Tetrasubstituted 2-aminopyrroles, containing a 3-carbamido-group, are a structural unit of marine alkaloids

Table 2. Synthesis of Tetrasubstituted Pyrroles **B**

Pyrrole	Ar	R ¹	R ²	yield %
B ₁	Ph	Me	Pr	43
B ₂	Ph	4-MeO-Ph		80
B ₃	Ph	4-MeO-Ph	2,6-Cl-Ph	70
B ₄	Ph	4-MeO-Ph	3,5-Br-Ph	70
B ₅	Ph	4-O ₂ N-Ph	3,4,5-MeO-Ph	19
B ₅	Ph	2,4,6- <i>i</i> -Pr-Ph	3,4,5-MeO-Ph	24
B ₅	Ph	4-Me-Ph	3,4,5-MeO-Ph	45
B ₅	Ph	4-MeO-Ph	3,4,5-MeO-Ph	59
B ₅	Ph	Me	3,4,5-MeO-Ph	78

Table 3. Synthesis of Tetrasubstituted Pyrroles **B**

pyrrole	Ar	R ²	E	yield, %
B ₅	Ph	3,4,5-MeO-Ph	CN	80
B ₆	Ph	2-Cl-6-F-Ph	CN	76
B ₇	Ph	4-MeO-Ph	CN	55
B ₈	4-MeO-Ph	3,4,5-MeO-Ph	CN	85
B ₉	Ph	4-Br-Ph	CN	73
B ₁₀	4-MeO-Ph	4-MeO-Ph	4-MeO-Bz	48
B ₁₁	Ph	4-O ₂ N-Ph	SO ₂ Ph	28
B ₁₂	Ph	4-Br-Ph	SO ₂ Ph	40
B ₁₃	Ph	3,4,5-MeO-Ph	SO ₂ Ph	52
B ₁₄	Ph	3,4,5-MeO-Ph	COOEt	57
B ₁₅	Ph	2,6-Cl-Ph	CONH ₂	48
B ₁₆	Ph	4-MeO-Ph	CONH ₂	93
B ₁₇	4-MeO-Ph	4-MeO-Ph	CONH ₂	89

rigidins (Figure 1). These alkaloids have been isolated from tunicates obtained near Okinawa and New Guinea and have been shown to possess calmodulin antagonistic and cytotoxic activities.²⁶ Several syntheses of rigidins **A** and **E** have been reported.³⁰ Using our methodology for the synthesis of tetrasubstituted pyrroles, we developed the

(29) As our work was in progress (Frolova, L. V.; Magedov, I. V.; Kornienko, A. *Abstracts of Papers*, 239th National Meeting of the American Chemical Society, San Francisco, CA; American Chemical Society: Washington, DC, 2010; ORGN-1069) a report of a similar synthesis of tetrasubstituted pyrroles appeared, see: Wang, K.; Domling, A. *Chem. Biol. Drug Des.* **2010**, *75*, 277–283.

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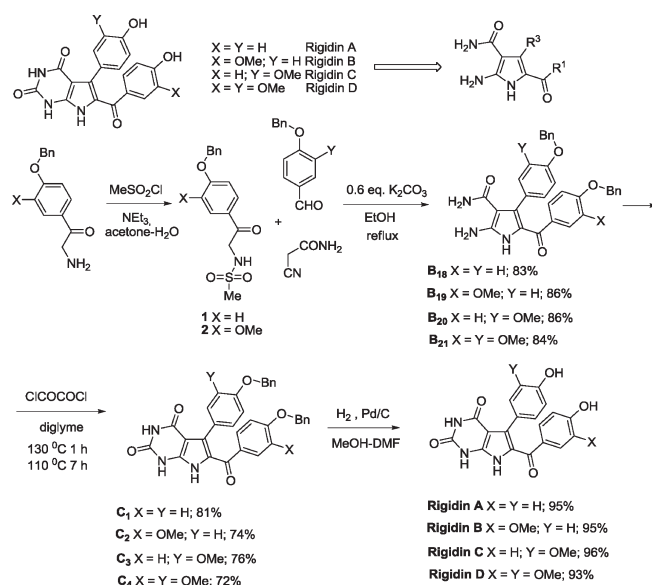


Figure 1. Total synthesis of rigidins A, B, C, and D.

shortest general approach to obtain these alkaloids. Moreover, rigidins B, C, and D were synthesized for the first time (Figure 1). Commercially available aminoacetophenones were converted to *N*-(methanesulfonamido)acetophenones **1** and **2** in almost quantitative yields and the latter were used in the three-component reaction to obtain 2-aminopyrroles **B₁₈–B₂₁**. Carbonylation was achieved with oxalyl chloride in diglyme to give pyrimidinediones **C₁–C₄**, which were subjected to hydrogenolysis to yield the desired rigidins with overall yields of 61% for **A**, 58% for **B**, 60% for **C**, and 53% for **D**. Our synthesis compares favorably with the published approaches for rigidin A (7–9 steps and 26–40% overall yields).³⁰ The spectral data are consistent with those published for the natural products.²⁶ At the present time, we are preparing a library of rigidin analogues for biological testing.

We performed a preliminary biological evaluation of the synthesized tetra- and pentasubstituted pyrroles for anticancer and antibacterial activities. The antiproliferative

Table 4. Biological Activities of Pyrroles **A** and **B**

	IC ₅₀ , μ M (HeLa)	MIC, μ M (<i>S. epi</i>)		IC ₅₀ , μ M (HeLa)	MIC, μ M (<i>S. epi</i>)
A₂	12.5	>200	B₂	37.5	>200
A₃	17	>200	B₃	>100	30
A₆	20	>200	B₄	3.1	>200
A₇	6.2	>200	B₅	75	>200
A₈	50	>200	B₆	>100	25
A₁₃	75	>200	B₈	37.5	>200
A₁₄	25	>200	B₁₀	20	50
A₁₅	>100	25			

activity was assessed by using the cancer cell line, HeLa, as a model for human cervical adenocarcinoma, through the measurements of mitochondrial dehydrogenase activities using the MTT method.³¹ In addition, pyrroles **A** and **B** were tested against *Staphylococcus epidermidis* (ATCC 75984), where Minimum Inhibitory Concentrations (MICs) were determined by the broth microdilution method.³² We found that selected synthesized pyrroles exhibit activities in these assays (Table 4), supporting the idea that diverse biological activities are likely to be found within the libraries of privileged medicinal structures such as 2-aminopyrroles. More detailed biological evaluation will be published elsewhere later.

In summary, a one-pot, multicomponent reaction of structurally diverse aldehydes, *N*-(aryl-, hetaryl-, and alkyl-sulfonamido)acetophenones, with activated methylene compounds results in the formation of tetra- and penta-substituted 2-aminopyrroles. This methodology was used for a four-step total synthesis of natural products rigidins A, B, C, and D. This synthesis is flexible and can be adapted to the preparation of a library of rigidin analogues.

Acknowledgment. This work is supported by the U.S. National Institutes of Health (grants RR-16480 and CA-135579) under the BRIN/INBRE and AREA programs. Collaboration with the Mass Spectroscopy Facility at the University of New Mexico is acknowledged.

Supporting Information Available. Experimental procedures and characterization of the compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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