

NHC-Catalyzed Spiro Bis-Indane Formation via Domino Stetter—Aldol—Michael and Stetter—Aldol—Aldol Reactions

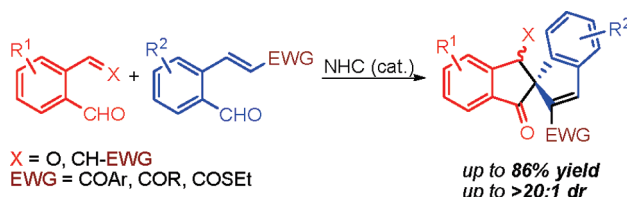
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Received November 10, 2010

ABSTRACT



Two novel domino NHC-catalyzed spirocyclizations are described herein, enabling the rapid construction of three new carbon–carbon bonds and a quaternary center with high diastereoselectivity. A variety of spiro bis-indane structures are assembled in a single step from simple o-phthalaldehyde derivatives.

Carbocyclic spiro motifs are found in a wide variety of natural products. Fredericamycin A (**1**)¹ and acutumine (**2**)² (Figure 1) are representatives of this large family of compounds which have attracted significant attention due to their biological properties and structural complexity. Non-natural carbocyclic spiro compounds have also been studied for their medicinal properties, as exemplified by the potent estrogen receptor ligand **3**.³ In this context, a number of synthetic methods have been devised for the synthesis of

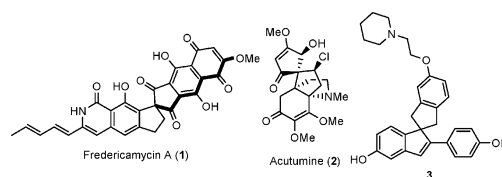


Figure 1. Examples of compounds containing a carbocyclic spiro motif.

this structural motif.⁴ The formation of carbocyclic spiro compounds typically relies on the sequential construction of each ring in a stepwise fashion, although a more efficient approach involves simultaneous formation of both rings in a single operation. In this paper, we report such an approach

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(2) (a) Goto, K.; Sudzuki, H. *Bull. Chem. Soc. Jpn.* **1929**, *4*, 220. (b) Tomita, M.; Okamoto, Y.; Kikuchi, T.; Osaki, K.; Nishikawa, M.; Kamiya, K.; Sasaki, Y.; Matoba, K.; Goto, K. *Tetrahedron Lett.* **1967**, *8*, 2421. (c) Tomita, M.; Okamoto, Y.; Kikuchi, T.; Osaki, K.; Nishikawa, M.; Kamiya, K.; Sasaki, Y.; Matoba, K.; Goto, K. *Tetrahedron Lett.* **1967**, *8*, 2425. (d) Tomita, M.; Okamoto, Y.; Kikuchi, T.; Osaki, K.; Nishikawa, M.; Kamiya, K.; Sasaki, Y.; Matoba, K.; Goto, K. *Chem. Pharm. Bull.* **1971**, *19*, 770.

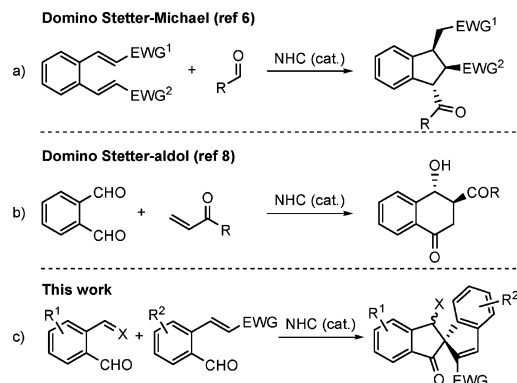
(3) Blizzard, T. A.; Morgan, J. D.; Mosley, R. T.; Birzin, E. T.; Frisch, K.; Rohrer, S. P.; Hammond, M. L. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 479.

(4) For reviews, see: (a) Krapcho, A. P. *Synthesis* **1974**, 383. (b) Krapcho, A. P. *Synthesis* **1976**, 425. (c) Krapcho, A. P. *Synthesis* **1978**, 77. (d) Sannigrahi, M. *Tetrahedron* **1999**, *55*, 9007. (e) Kotha, S.; Deb, A. C.; Lahiri, K.; Manivannan, E. *Synthesis* **2009**, 165.

in which both rings and three new carbon–carbon bonds are formed in one synthetic operation.

We have recently reported the first example of a domino reaction⁵ making use of the enolate intermediate formed in a Stetter reaction (Scheme 1a).^{6,7} In that case, the initial

Scheme 1. Domino Stetter Reactions

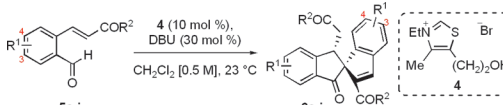


Stetter reaction was followed by an intramolecular conjugate addition step leading to indane frameworks. Subsequently, Ye and co-workers disclosed a cascade Stetter–aldol reaction providing access to 4-hydroxytetralones from vinyl ketones and phthalaldehyde (Scheme 1b).^{8,9} We now document remarkable domino Stetter–aldol–Michael (SAM) and Stetter–aldol–aldol (SAA) reactions giving access to spiro bis-indanes from readily available *o*-formyl chalcone derivatives (Scheme 1c). The usefulness of this methodology is demonstrated by the preparation of analogs of the spiro bis-indane dione core of fredericamycin A.

At the outset of our studies, we investigated the domino SAM process employing **5a** as a model substrate and catalytic amounts of various *N*-heterocyclic carbene (NHC) catalysts.¹⁰ Following a brief optimization of the reaction

conditions (see Supporting Information), the desired spiro bis-indane **6a** was obtained in good yield and excellent diastereoselectivity (Table 1, entry 1). Prolonged exposure

Table 1. Domino Stetter–Aldol–Michael (SAM) Reaction



| entry | R ¹ | R ² | <i>t</i> (min) | product ^a | yield (%) ^b | dr ^c |
|----------------|----------------|---------------------------------------|-------------------|----------------------|---------------------------|-----------------|
| 1 | H | Ph | 15 | 6a | 79 | 17:1 |
| 2 | H | 4-Cl(C ₆ H ₅) | 5 | 6b | 86 | 12:1 |
| 3 | H | 4-MeO(C ₆ H ₅) | 45 | 6c | 68 | >20:1 |
| 4 | 4-F | Ph | 5 | 6d | 64 | 11:1 |
| 5 ^d | 4-F | 4-Cl(C ₆ H ₅) | 15 | 6e | 80 | 16:1 |
| 6 | 3-MeO | Ph | 9 | 6f | 85 | >20:1 |
| 7 | 3-MeO | 4-Cl(C ₆ H ₅) | 5 | 6g | 81 | 10:1 |
| 8 | H | Me | 195 | 6h | 75 | 7:1 |
| 9 | H | SEt | 120 | 6i | 31 ^e | 13:1 |

^a The relative configuration was determined by X-ray crystallography (see Supporting Information). ^b Combined yield of pure isolated product diastereomers. ^c Determined from ¹H NMR analysis of the crude reaction mixture. ^d Concentration of the reaction = 0.1 M. ^e The corresponding alcohol intermediate (see **7**, Scheme 3) was also isolated in 14% yield.

to the reaction conditions or use of larger amounts of base led to reduced diastereomeric ratios (not shown). The presence of electron-withdrawing or -donating groups on the ketone portion of the *o*-formyl chalcone derivatives **5b** and **5c** allowed the fine-tuning of their reactivity. Thus, the 4-chlorophenyl substituent in **5b** resulted in an increase in the rate of the reaction at the expense of the diastereoselectivity (entry 2), whereas the reactivity of 4-methoxyphenyl-substituted **5c** was reduced while higher diastereocontrol was achieved (entry 3).

Consistent with earlier observations that electron-poor aldehydes provide faster rates in the Stetter reaction,⁶ *p*-fluoro or *m*-methoxy groups relative to the aldehyde resulted in enhanced reactivity (entries 4–7). Interestingly, the presence of the methoxy group in substrates **5f** and **5g** did not prevent the Stetter or the Michael addition steps (Scheme 3). Methyl ketone **5h** showed a slower reaction rate compared to aromatic ketones (entry 8). The reduced diastereomeric ratio in this case likely reflects the thermodynamic equilibrium (*vide infra*). Although unsaturated esters did not provide the SAM product, thioesters could be employed to generate the desired product **6i** in moderate yield and high diastereoselectivity (entry 9).

The modulating effect of the various substituents on the aromatic ring also allows the selective formation of cross-SAM products in moderate yield (i.e., a nonstatistical distribution of products). Indeed, spiro bis-indane **6j** was obtained as the major spiro bis-indane product (out of a possible four) in the SAM reaction of **5f** and **5j** (Scheme 2). The methoxy group at C3 of **5f** increases the electrophilicity of the formyl group making it more prone to react with the catalyst, while it lowers the reactivity of the Stetter acceptor moiety. On the other hand, the methoxy group at C4 of **5j**

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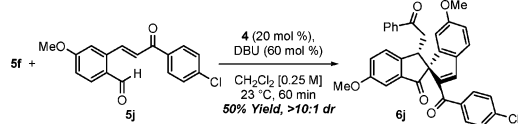
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Scheme 2. NHC-Catalyzed Cross-SAM



increases the electrophilicity of the Stetter acceptor moiety, while decreasing the reactivity of the aldehyde. Thus, spiro bis-indane **6j** was selectively obtained by tuning the electronic properties on the donor (**5f**) and acceptor (**5j**) substrates.¹¹

On the basis of previous domino NHC-catalyzed reactions,^{6,8} we postulate that the Breslow intermediate **I**¹² participates in a Stetter reaction to form enolate intermediate **II**. This enolate undergoes an aldol reaction prior to the release of the NHC as proposed by Ye et al.⁸ Subsequently, β -hydroxy ketone **IV** is deprotonated to form enolate intermediate **V** which cyclizes to spiro bis-indane **7**. Formation of intermediates **III** and **7** probably occurs through highly diastereoselective aldol and Michael reactions since a single diastereomer of intermediate **7a** ($R = \text{Ph}$) was isolated in 40% yield (Scheme 3a, structure determined by X-ray analysis; see Supporting Information). During the Michael addition step, the acceptor approaches the less hindered *Re* face of the favored *Z*-enolate. The observed selectivity could be explained by a hydrogen bond between the carbonyl and the initially formed alcohol, exposing the *Si* face of the enone and activating it toward enolate attack (Scheme 3b). Dehydration of this intermediate affords the final spiro bis-indane product **VI**. It was also found that when product **6a** was subjected to prolonged basic conditions (DBU), a thermodynamic ratio of 7:1 was obtained. This equilibrium ratio, which is presumably reached through a retro-Michael–Michael isomerization, supports the notion that the diastereomer ratios obtained in Table 1 are the result of kinetic control.

We reasoned that the SAM methodology could be further exploited in an analogous Stetter–aldol–aldol (SAA) process. Specifically, a 1,2-dialdehyde substrate would have one formyl group involved in the initial Stetter reaction, and the other one would serve as the electrophile in the second ring closure. We decided to test this proposed domino SAA reaction starting with phthalaldialdehyde **8a**. Gratifyingly, when **8a** and the acceptor **5a** were reacted employing thiazolium **4** as a precatalyst, the desired spiro bis-indane **9a** was obtained in excellent yield as a ca. 1:1 mixture of diastereomers (Table 2, entry 1).^{13,14} Nevertheless, this lack of diastereocontrol was inconsequential for the purpose of

Scheme 3. Proposed Mechanistic Pathway for the NHC-Catalyzed Stetter–Aldol–Michael Reaction

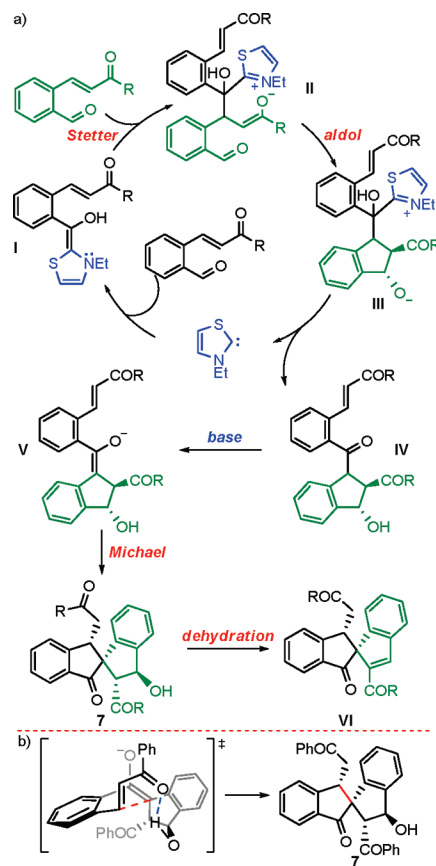
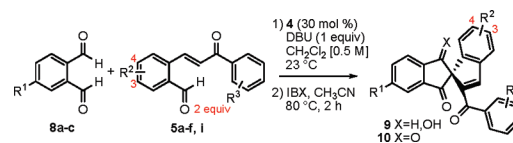


Table 2. Domino Stetter–Aldol–Aldol (SAA) Reaction



| entry | R ¹ | R ² | R ³ | <i>t</i> (min) ^a | product | yield(%) ^b |
|----------------|----------------|----------------|----------------|-----------------------------|-----------------------|-----------------------|
| 1 ^c | H | H | H | 20 | 9a^d | 71 |
| 2 | H | H | 4-Cl | 30 | 10b | 58 |
| 3 | H | H | 4-MeO | 60 | 10c | 25 |
| 4 | MeO | H | H | 35 | 10d | 42 |
| 5 | H | 4-F | H | 5 | 9e^d | 72 |
| 6 | F | 4-F | 4-Cl | 60 | 10f | 50 |
| 7 | H | 3-MeO | H | 100 | 10g | 36 |
| 8 | H | 4-MeO | 4-Cl | 15 | 10h | 75 |

^a Reaction time for the Stetter–aldol–aldol (SAA) step. ^b Yield of pure isolated product. ^c Reaction performed on a gram scale. ^d Each diastereomer of products **9a** and **9e** was isolated prior to the oxidation step.

(11) Various other spiro bis-indanes were formed in minor amounts, with the most important one present in a ca. 1:6 ratio relative to **6j**. The yield for **6j** is 40% of pure, isolated product and 10% present in impure fractions following column chromatography.

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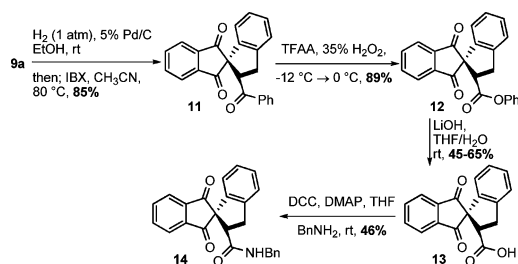
(13) The product probably undergoes a facile retro-aldol reaction under these conditions, leading to a thermodynamic equilibrium.

(14) The use of a lower catalyst loading did not provide a satisfactory yield of **9a**.

making spiro bis-indane diketones related to fredericamycin A. Indeed, IBX oxidation of the crude reaction mixture provided a single triketone (**10a**) whose purification by silica gel chromatography was further facilitated. Whereas the use of electron-withdrawing aromatic groups on the ketone

portion of the acceptor was tolerated, employing electron-donating groups resulted in markedly decreased yields (entries 2 and 3). Interestingly, the use of methoxy-substituted phthalaldialdehyde derivative **8b** provided the SAA product as a single regioisomer prior to its oxidation to the triketone (entry 4). When a fluoro substituent was introduced on the acceptor (**5d**), the reaction proceeded smoothly and in high yield (entry 5). Surprisingly, the presence of an electron-withdrawing group on the phthalaldialdehyde **8c** considerably reduced the rate while still affording the product in good yield (entry 6). As expected, the presence of an electron-donating group at C3 of the Stetter acceptor resulted in a sluggish reaction and a low yield (entry 7). Conversely, when the methoxy substituent was installed on C4 of the Stetter acceptor **5j**, its inductive effect increased the rate of the reaction (entry 8). Finally, it should be noted that the domino SAA reaction can be performed on a gram scale without a detrimental effect on the yield (entry 1).

Scheme 4. Derivatization of **9a**



We then applied the SAA methodology to the synthesis of analogs of fredericamycin A, as shown in Scheme 4. Through a reduction–oxidation sequence, **9a** was cleanly

transformed into the triketone **11** in high yield. To our delight, **11** underwent a completely site-selective and regioselective Baeyer–Villiger oxidation using Emmons’ protocol.¹⁵ Hydrolysis of the resulting ester **12** gave the corresponding carboxylic acid **13** which was converted into *N*-benzylamide **14** via standard amidation conditions.

In conclusion, we described new NHC-catalyzed domino Stetter–aldol–Michael (SAM) and Stetter–aldol–aldol (SAA) reactions featuring the formation of two rings, three new carbon–carbon bonds, and a quaternary center. This new methodology was applied to the synthesis of simplified fredericamycin A analogs.

Acknowledgment. This work is dedicated to the memory of Michael M. Pollard. We thank the Natural Sciences and Engineering Research Council (NSERC) of Canada (Discovery Grant to M.G. and Postgraduate Scholarship to J.M.H.), the Canada Foundation for Innovation, and the University of Saskatchewan for financial support and Dr. Gabriel Schatte (University of Saskatchewan) for X-ray crystallographic analysis.

Supporting Information Available: Detailed experimental procedures, ¹H and ¹³C NMR spectra for all new compounds, ORTEP representations and CIF files for **6d**, **7**, and **9a**.¹⁶ This material is free of charge via the Internet at <http://pubs.acs.org>.

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(16) Crystallographic data for compounds **6d**, **7**, and **9a** have been deposited with the Cambridge Crystallographic Data Centre (deposition numbers CCDC 800683, 800684, 800685). Copies of the data can be obtained, free of charge, on application to the director, CCDC 12 Union Road, Cambridge CB2 1EZ, U.K. (fax: +44 1223 336033 or email: deposit@ccdc.cam.ac.uk).