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Microwave-assisted, one-pot reaction of 7-azaindoles and aldehydes: a facile route to novel di-7-azaindolylmethanes

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ABSTRACT

A novel and highly efficient synthetic method leveraging microwave-assisted organic synthesis (MAOS) to yield di-7-azaindolylmethanes (DAIMs) is reported. Under MAOS conditions, reaction of 7-azaindole with aldehydes resulted predominantly in DAIMs, as opposed to the expected 7-azaindole addition products that form at ambient temperature. Based upon studies of different indoles and azaindoles with various aromatic and aliphatic aldehydes, we herein propose a mechanism where rapid and efficient microwave heating promotes nucleophilicity of 7-azaindoles toward the corresponding alkylidene–azaindolene intermediate to form the DAIM. This sequence provides a versatile approach to efficiently synthesize novel DAIMs that may be useful pharmaceuticals.

Bisindolylmethanes, or diindolylmethanes (DIMs), are a unique class of compounds with select members exhibiting biological activity in diseased states, including chemopreventive and therapeutic properties.[1] In nature, DIMs are found in vegetables of the cruciferae family, particularly those of the brassica genus, such as broccoli, brussels sprouts, cabbage, and cauliflower, and are reportedly associated with reduced risk of breast, prostate, and colorectal cancer.[2] In cancer cells, DIMs promote apoptosis and confer protection against DNA-damage.[3] For example, DIMs have been shown to inhibit estrogen-induced growth of breast cancer cell lines and human breast-tumors,[4] with responses associated with G1 cell-cycle arrest.[5] In leukemia cells, DIMs have been shown to inhibit extracellular signal-regulated kinase activation, which leads to apoptosis.[6] Similarly, antitumor properties have recently been reported in pancreatic cancer using DIM-C-pPhOH (**1a**) (Fig. 1).[7] In addition to use in oncology, DIMs have also conferred neuroprotective properties in preclinical models of Parkinson's disease.[8] While the importance of DIMs is relatively well established in medicinal chemistry, a daughter class of this molecular scaffold is the di-7-azaindolylmethanes (DAIMs), which may possess unique biological properties (**1b**) (Fig. 1).[9b] These studies highlight the attractiveness of these chemical classes and demonstrate the importance of developing robust, yet practical, synthetic methods. Herein, we report the development of a novel synthetic method that can be used to rapidly synthesize candidate DAIMs and DIMs using microwave irradiation.

Prior syntheses of DIMs have featured a wide variety of reagents and reaction conditions, including acid-catalyzed condensation of indoles with aldehydes under ultrasound irradiation,[10] condensation of benzyl alcohols and indoles under visible light irradiation,[11a] and metal-catalyzed reactions of indole with select aldehydes[11b] and aldimines.[11c] Interestingly, there are only

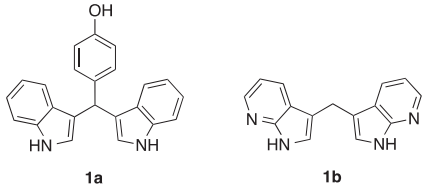

Figure 1. Representative DIM, (**1a**) DIM-C-pPhOH, and DAIM, di-7-azaindolylmethane (**1b**).

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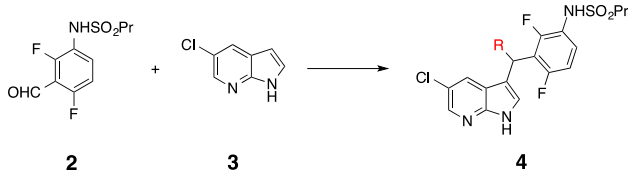
Table 1
Evaluation of additives and reaction conditions[a]



2 **3** **4**

Entry	Additive	Solvent	Conditions	Results[b]
1	KOH	DMSO	MW[c]	NR[e]
2	K_2CO_3	MeOH H_2O (1:1)	MW[c]	**4a**: R = 3-(5-Cl-7-azaindole (72%)
3	KOH	MeOH	Rt[d]	**4b**: R = OH (54%)
4	KOH	DME	MW[c]	NR[e]
5	K_2CO_3	MeOH H_2O (1:1)	Rt[d]	**4b**: R = OH (88%)
6[f]	I_2	MeCN	Rt[d]	NR[e]
7[f]	I_2	MeCN	MW[c]	NR[e]
8	None	MeOH H_2O (1:1)	MW[c]	NR[e]

[a] Reaction conditions: Aldehyde (0.19 mmol), azaindole/indole (0.38 mmol), base (1.27 mmol), solvent (2.5 mL).
[b] Isolated yield after chromatography.
[c] MW heating at 130 °C, 30 min.
[d] Room temperature, 48 h.
[e] NR = no reaction.
[f] Iodine (0.04 mmol).

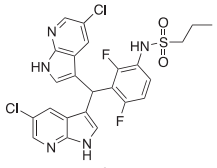
a limited number of reported syntheses of DAIMs, these include CH_3-activation[12] and condensation of azaindole with $RMgBr$[9a] or CH_2Br_2.[9b] Unfortunately, these methods are limited by variable yields and exotic reagents. Thus, methods for rapid and efficient synthesis of DAIMs remain a synthetic challenge.

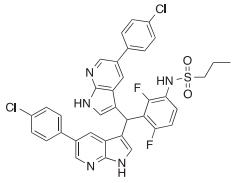
Our interest in the synthesis of azaindole stems from our previous studies of inhibiting mutant *BRAF* in oncology. We recently reported an MAOS of Vemurafenib (PLX-4032) and PLX-4720, wherein we achieved the synthesis of these V600E-*BRAF* targeted anticancer molecules in reduced total reaction time.[13] As part of an ongoing program to develop technology-assisted synthesis methods for novel azaindoles, we discovered DAIMs as an unexpected byproduct under MAOS conditions when azaindole was in excess (2X) to aldehyde.

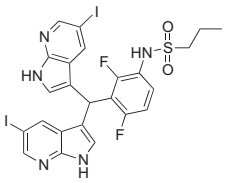
To explore this phenomenon more closely and potentially elucidate a mechanism, we examined the effects of base, solvent, and heating upon condensation of our model aldehyde and azaindole, *N*-(3-5-difluoro-4-formylphenyl)propane-1-sulfonamide (**2**) and 5-chloro-7-azaindole (**3**) (Table 1). This initial series of experiments revealed that an aqueous solvent and inorganic base were necessary for condensation (Table 1: 5 vs 1, 4, 8) and that microwave heating facilitated DAIM (**4a**) formation over the alcohol (**4b**) (Table 1: 2 vs 5).[13,14] In the absence of microwave and water, the reaction gave the expected addition product (**4b**) (Table 1, entry 3). Conversely, conventional heating provided only trace amounts of **4a** as a mixture with **4b**, even after prolonged heating. Using iodine as a Lewis acid did not promote DAIM formation regardless of microwave irradiation (Table 1: 6, 7).[15,16] In our prior work with Vemurafenib and PLX-4720, DAIM (**4a**) formation was not significant using equivalent amounts of **2** and **3** under MAOS.[13]

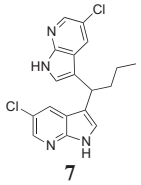
Prompted by these results, we examined the scope of this MAOS reaction, coupling 5-substituted-7-azaindoles with different aromatic and aliphatic aldehydes under MAOS, with K_2CO_3 as the base and MeOH/H_2O (1:1) as the solvent system (Table 2). Reaction of various 5-substituted-7-azaindoles with the sulfonamide-functionalized aldehyde **2** yielded the corresponding DAIM in good yields (Table 2: **4a**, **5**, **6**). In addition to the sulfonamide, other aliphatic and aromatic aldehydes reacted with **3** under identical reaction conditions to give the desired DAIM product in good to excellent yields (Table 2: **5**–**24**). However, some reaction bias was observed regarding the functional group tolerance within the aldehyde. While amido-functionalized substrates such as

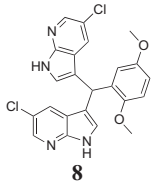
Table 2
DAIMs synthesized using MAOS[a,b]

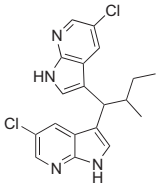

4a
(72%)

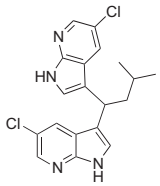

5
(64%)


6
(53%)


7
(82%)


8
(76%)


9
(66%)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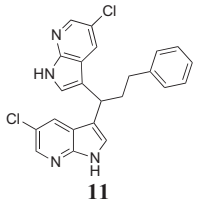
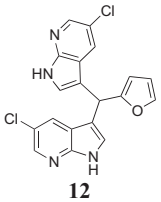
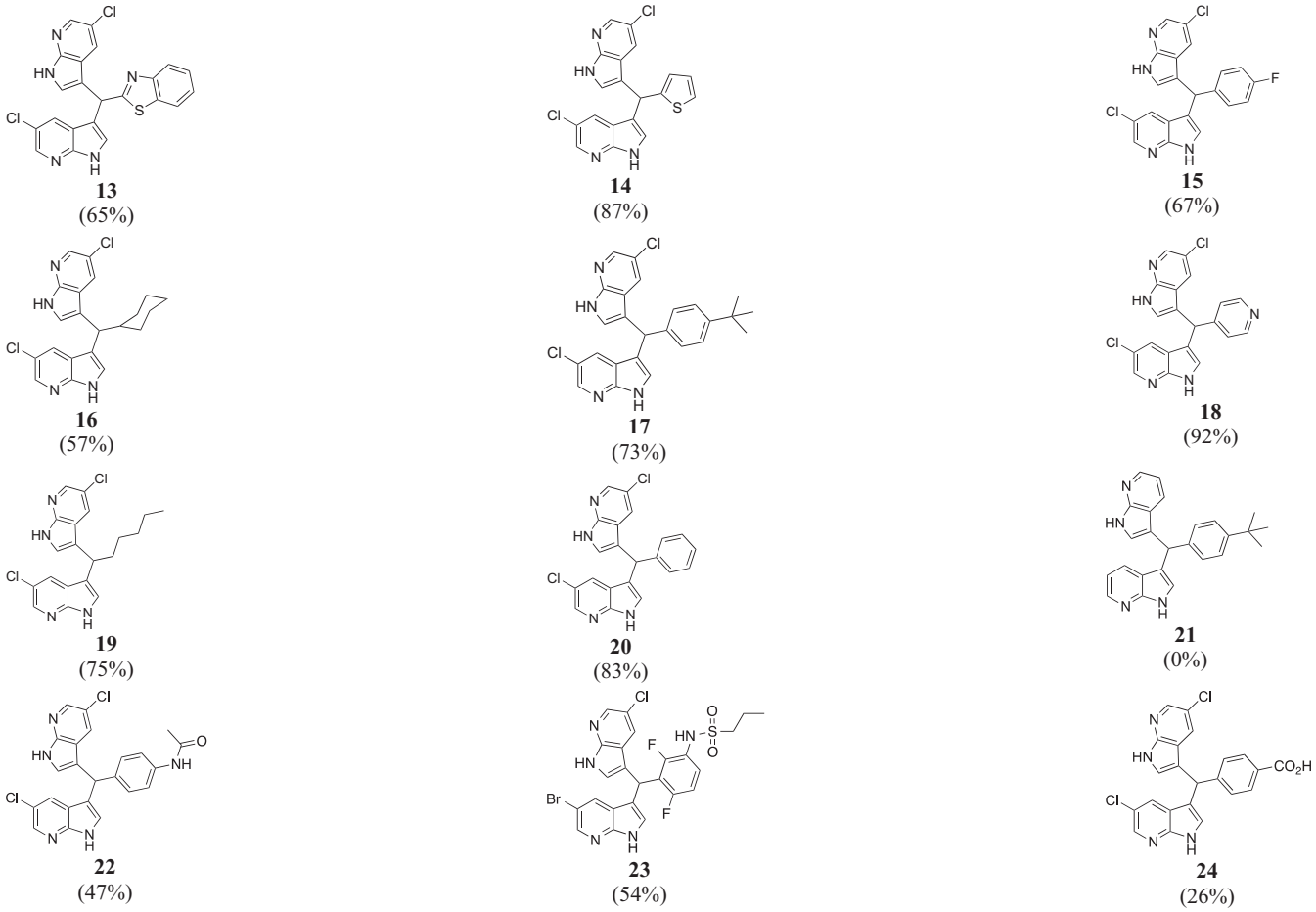
(66%)


11
(76%)


12
(71%)



[a] Reaction conditions: Aldehyde (0.19 mmol), azaindole (0.38 mmol), K_2CO_3 (1.27 mmol), MeOH/H_2O (1:1), MW heating at 130 °C, 30 min.
[b] Isolated yield after chromatography.

4-acetamidobenzaldehyde successfully gave the corresponding DAIM (**22**), maintaining the amide functionality, the ester-functionalized aldehyde methyl 4-formylbenzoate gave compound **24** in modest yield, and only with hydrolysis of the ester functionality to the carboxylic acid (Table 2). This could suggest a possible one-pot DAIM synthesis/ester deprotection approach. Functional group tolerance for the azaindole proved intriguing as well, with the unsubstituted 7-azaindole proving recalcitrant to DAIM formation (Table 2: **21**), but rather undergoing decomposition (by TLC). This could suggest potential electronic tolerances for substituents at the 7-position of the ring, wherein electron-withdrawing groups appear preferred. Structural assignment of the new DAIMs was carried out with high-field NMR analysis, which confirmed a plane of symmetry along the central methyl carbon. These results were further supported by X-ray crystallographic analysis of compound **18** (Fig. 2).

We next tested our reaction conditions toward synthesis of DIMs with select indoles and aldehydes. Substituted indoles reacted in a manner similar to their 7-azaindole counterparts, including

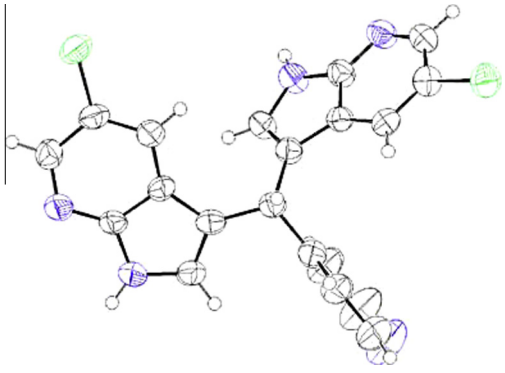
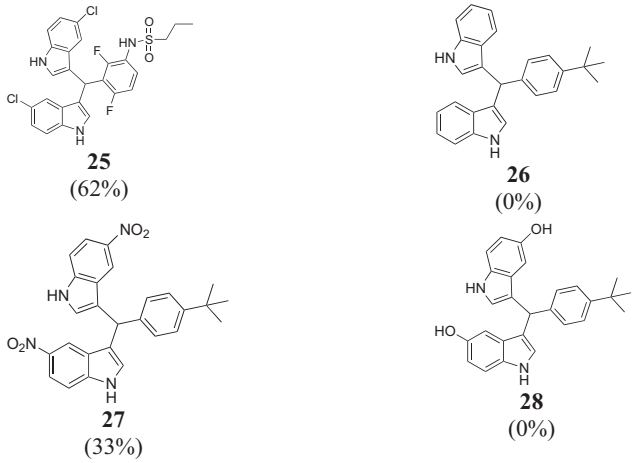
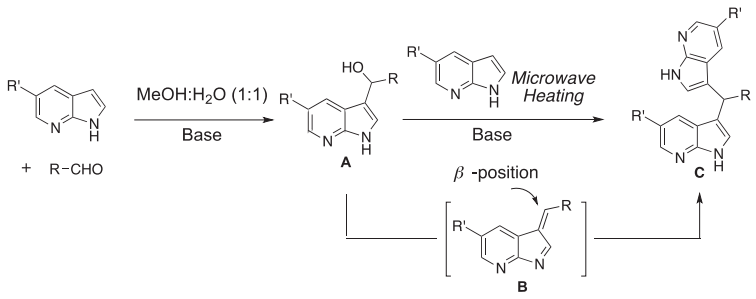


Figure 2. X-ray crystal structure (ORTEP drawing) of compound **18**.

Table 3
DIMs synthesized using MAOS[a,b]



[a] Reaction conditions: Aldehyde (0.19 mmol), indole (0.38 mmol), K_2CO_3 (1.27 mmol), MeOH/H_2O (1:1), MW heating at 130 °C, 30 min.
[b] Isolated yield after chromatography.

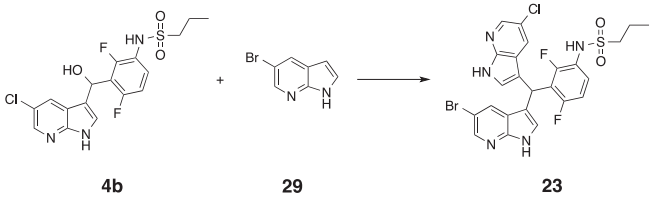


Scheme 1. Proposed mechanism yielding DAIMs via nucleophilic addition of **A** to alkylidene–azaindolene **B** under microwave irradiation.

5-chloroindole and **2** to give the desired DIM in 62% yield (Table 3: **25**), compared to **4a** in Table 2. However, as with the 7-azaindole substrates, there seemed to be similar electronic constraints for substitutions at the 7-position of the indole ring, as highlighted by unsubstituted indole and the electron-donating hydroxyl group of the 5-hydroxyindole, both of which yielded no DIM product (Table 3: **26**, **28**), but rather decomposition (by TLC). Moreover, as with the azaindoles, electron-withdrawing groups seemed to have a net positive effect overall (Table 3: **25**), though not without an apparent threshold, as with 5-nitroindole (Table 3: **27**), which gave a lower yield of 33%.

Toward a potential mechanism, we propose that the addition product (**A**) that initially forms undergoes dehydration in the presence of base and microwave irradiation to the corresponding alkylidene–azaindolene intermediate **B** (Scheme 1), an excellent Michael-acceptor for nucleophiles. Itoh and coworkers reported similar mechanistic observations for their synthesis of DIMs.[11] We envision the effects of microwave heating influencing the reaction by increasing nucleophilicity of the 7-azaindole toward **B** and promoting dehydration of **A** (Scheme 1).[17]

To test this postulated mechanism, we treated addition-product **4b** with 5-bromo-7-azaindole (**29**) and obtained the unsymmetrical DAIM-product **23** in 54% yield (Scheme 2). The formation of unsymmetrical compound **23** strongly supports the effect of microwave heating on increased nucleophilicity of 7-azaindoles since no DAIMs were observed at ambient temperature.



Scheme 2. Reaction of isolated addition-product intermediate **4b** with 5-bromo-7-azaindole (**29**) under microwave heating. Reaction conditions: **4b** (0.19 mmol), **29** (0.19 mmol), K_2CO_3 (1.27 mmol), MeOH/H_2O (1:1), MW heating at 130 °C for 30 min.

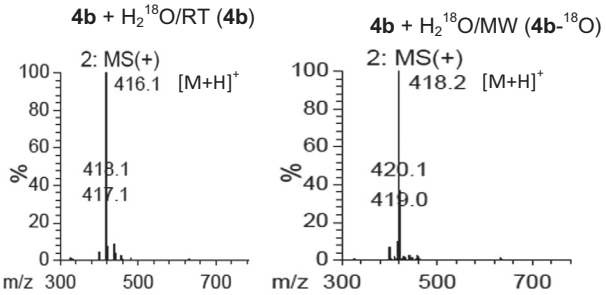


Figure 3. Mass spectrometry of **4b** at room temperature (left) and at microwave heating (right) at 130 °C, 30 min, using $H_2{}^{18}O$ in methanol (1:1) and K_2CO_3 (4 equiv).

To verify in part the effects of microwave heating on dehydration of **A** to form intermediate **B**, we performed an ^{18}O-labeling experiment, anticipating that rehydration in the presence of ^{18}O–water would label intermediate **B** with ^{18}O. Thus, treatment of alcohol **4b** in a mixture of methanol and $H_2{}^{18}O$ (1:1), in the presence of K_2CO_3, revealed that microwave heating appears to promote dehydration, followed by ^{18}O-incorporation (>90%), as there was no ^{18}O incorporation at room temperature (Fig. 3). Mass spectrometry analysis of the samples heated under microwave and at room temperature revealed ^{18}O-incorporation only in the microwave-heated reaction (Fig. 3).

In summary, we have developed an efficient method to provide functionalized di-7-azaindolylmethanes (DAIMs) and diindolylmethanes (DIMs) via a base-promoted reaction of 7-azaindoles and indoles, respectively, with various aldehydes using microwave heating. This stepwise reaction sequence, as shown in Scheme 2, lays the framework for developing larger libraries of asymmetrical heterodimeric azaindole and indole chemotypes. Biological application of these novel compounds is currently under investigation in our laboratory.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.10.143.

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