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# Thermally induced [3 + 2] cyclization of aniline-tethered alkylidenecyclopropanes: a facile synthetic protocol of pyrrolo[1,2-*a*]indoles†

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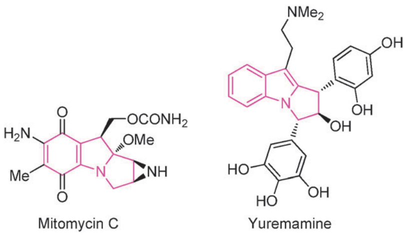
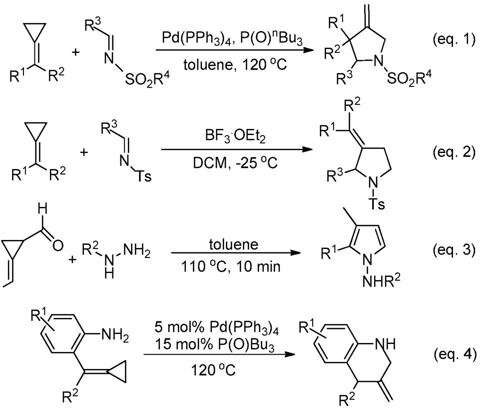
**A facile synthetic method of functionalized pyrrolo[1,2-*a*]indoles has been developed *via* a thermally-induced ring-opening and cyclization reaction from aniline-tethered alkylidenecyclopropanes with aldehydes.**

The indole ring system is probably the most ubiquitous heterocycle in nature.[1] Their importance in medicinal chemistry has encouraged the development of new synthetic strategies to prepare these compounds.[2] The pyrrolo[1,2-*a*]indoles, tricyclic indole derivatives, are common cores found in a number of natural products.[3] For example, the alkaloid Mitomycin C has attracted considerable attention due to its potent antitumoral and antibacterial activity (Scheme 1).[4] Moreover, another member of the alkaloids, Yuremamine, is a new phytoindole isolated from the stem bark of Mimosa hostilis (Scheme 1).[5] These previous findings have stimulated our interest to develop facile synthetic approaches to access the pyrrolo[1,2-*a*]indole structure motif owing to its biological profile and fascinating molecular architecture.

Methylenecyclopropanes (MCPs), as highly strained but readily accessible molecules, can undergo a variety of ring-opening reactions in the presence of transition metals or Lewis acids because the relief of ring strain can provide a potent thermodynamic driving force.[6,7] These ring-opening processes can trigger various reactions of MCPs with other substrates, giving efficient access to enhanced molecular complexity in organic syntheses.[8] For example, in 2003, Yamamoto and co-workers have disclosed palladium-catalyzed intermolecular [3 + 2] cycloaddition of alkylidenecyclopropanes with imines to give 3-methylenepyrrolidines in good yields (Scheme 2, eq. 1).[9] In 2004, we reported that MCPs could undergo [3 + 2] cycloaddition with aldimines to give the corresponding pyrrolidine skeletons in the presence of $BF_3.OEt_2$ under mild reaction conditions (Scheme 2, eq. 2).[10] More recently, we have also found an efficient route to 2-substituted *N*-(1-amino-3-methylpyrrol)amides by ring-opening cyclization of benzylidene- and alkylidenecyclopropylcarbaldehydes with hydrazides (Scheme 2, eq. 3).[11] It should be noted that Yamamoto and co-workers have reported the only transformation using aniline-tethered alkylidenecyclopropanes to the six-membered exo-methylene nitrogen heterocyclic compounds in the presence of palladium catalysts (Scheme 2, eq. 4).[12] These interesting findings have encouraged us to continue to discover more useful transformations with these special MCPs tethered by an aniline moiety.



**Scheme 1** Mitomycin C and Yuremamine, highlighting the common pyrrolo[1,2-*a*]indole core.



**Scheme 2** Previous studies on the formation of heterocyclic compounds from MCPs.

These aniline-tethered alkylidenecyclopropanes were prepared according to the previous literature.[13] With these aniline-tethered alkylidenecyclopropanes in hand, we initially attempted to transform them to the corresponding imine derivatives. We found that the corresponding imine could be indeed obtained at room

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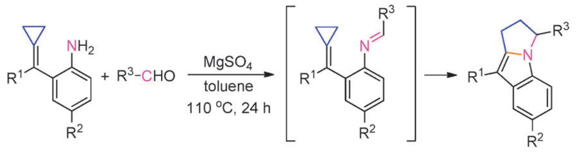
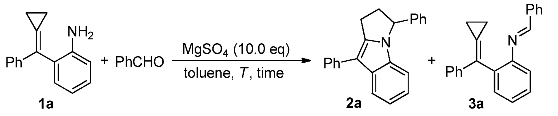


$R^1$ = Ph, Me; $R^2$ = H, Cl; $R^3$ = aromatic group, alkenyl group, H

**Scheme 3** Unexpected formation of pyrrolo[1,2-*a*]indoles upon heating of aniline-tethered MCPs and aldehydes.

**Table 1** Optimization of the reaction conditions of **1a** with benzaldehyde



| Entry | Amount of PhCHO | $T$/°C | Time/h | Yield[a] (%) 2a | Yield[a] (%) 3a |
|---|---|---|---|---|---|
| 1 | 1.2 equiv. | 20 | 24 | 0 | 88 |
| 2 | 1.2 equiv. | 80 | 24 | 42 | 54 |
| 3 | 1.2 equiv. | 100 | 72 | 89 | 0 |
| 4 | 1.2 equiv. | 110 | 48 | 91 | 0 |
| 5 | 2.0 equiv. | 110 | 24 | 93 | 0 |

[a] Isolated yield.

temperature in toluene in the presence of $MgSO_4$. To our delight, when the reaction was carried out at 110 °C, tricyclic indole derivatives could be formed in good yields rather than the imine derivatives, affording a novel synthetic approach to the useful pyrrolo[1,2-*a*]indole derivatives (Scheme 3). In this paper, we wish to report the details of this interesting transformation.

We initially investigated the [3 + 2] cyclization reaction of aniline-tethered alkylidenecyclopropane **1a** with benzaldehyde in toluene at different temperature and the results are summarized in Table 1. The reaction of **1a** with 1.2 equiv. benzaldehyde in the presence of 10.0 equiv. anhydrous magnesium sulfate afforded imine **3a** in 88% yield at room temperature after 24 h (Table 1, entry 1). Raising the reaction temperature to 80 °C produced the [3 + 2] cyclization product **2a** in 42% yield along with the formation of imine **3a** in 54% yield (Table 1, entry 2). Upon heating the reaction mixture at 100 °C for 72 h, **2a** was obtained in 89% yield as a sole product (Table 1, entry 3). Its structure has been unambiguously determined by X-ray diffraction. Its ORTEP drawing is indicated in Fig. 1 and the corresponding CIF data have been presented in the ESI.†[14] Carrying out the reaction at 110 °C (under reflux) led to the formation of **2a** in 91% yield (Table 1, entry 4). Increasing the employed amounts of benzaldehyde to 2.0 equiv. delivered **2a** in 93% yield within 24 h (Table 1, entry 5).

Under the optimized conditions (2.0 equiv. of aldehyde and 10.0 equiv. anhydrous magnesium sulfate in toluene at 110 °C for 24 h), we next examined the substrate scope of this reaction and the results are shown in Table 2. As for various aryl aldehydes ($R^3$ = Ar), the reactions with substrate **1a** proceeded smoothly to furnish the desired products **2b–2f** in 86–93% yields, regardless of whether they have electron-rich or electron-poor aromatic rings (Table 2, entries 1–5). Heteroaromatic aldehydes and naphthyl aldehyde were also tolerable, giving the desired products **2g–2i** in 81–91% yields (Table 2, entries 6–8). When $R^3$ is a hydrogen atom or an alkenyl group, the reactions still proceeded efficiently to afford the desired products **2j–2k** in 88–92% yields (Table 2, entries 9–10). Changing the $R^2$ substituent to chlorine, the reactions proceeded smoothly, furnishing the desired products **2l** and **2m** in 85–86% yields (Table 2, entries 11–12). When $R^1$ is a methyl group, the reaction still proceeded very well to afford the desired product **2n** in 70% yield at 140 °C in *ortho*-xylene (Table 2, entry 13).

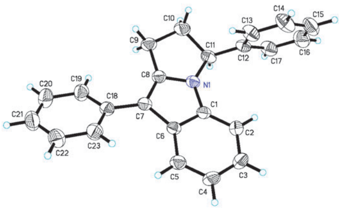
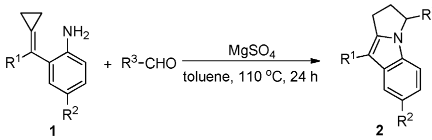


**Fig. 1** ORTEP drawing of **2a**.

**Table 2** Substrate scope of the [3 + 2] cyclization reaction of aniline-tethered alkylidenecyclopropanes **1** to pyrrolo[1,2-*a*]indoles **2**[a]

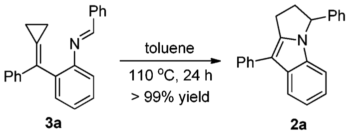


| Entry | Substrate ($R^1$/$R^2$) | $R^3$ | Product 2 | Yield[b] (%) |
|---|---|---|---|---|
| 1 | **1a** (Ph/H) | 4-$MeC_6H_4$ | **2b** | 93 |
| 2 | **1a** (Ph/H) | 4-$BrC_6H_4$ | **2c** | 86 |
| 3 | **1a** (Ph/H) | 4-$NO_2C_6H_4$ | **2d** | 91 |
| 4 | **1a** (Ph/H) | 3-$NO_2C_6H_4$ | **2e** | 89 |
| 5 | **1a** (Ph/H) | 2-$NO_2C_6H_4$ | **2f** | 92 |
| 6 | **1a** (Ph/H) | 3-thienyl | **2g** | 88 |
| 7 | **1a** (Ph/H) | 2-furyl | **2h** | 91 |
| 8 | **1a** (Ph/H) | 1-naphthyl | **2i** | 81 |
| 9 | **1a** (Ph/H) | H | **2j** | 92[c] |
| 10 | **1a** (Ph/H) | $CH_3CH{=}CH$ | **2k** | 88[d] |
| 11 | **1b** (Ph/Cl) | $C_6H_5$ | **2l** | 86 |
| 12 | **1b** (Ph/Cl) | H | **2m** | 85[c] |
| 13 | **1c** (Me/H) | $C_6H_5$ | **2n** | 70[e] |

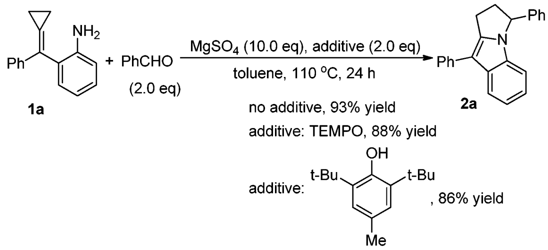
[a] *Reaction conditions*: aldehyde (2.0 equiv.), anhydrous magnesium sulfate (10.0 equiv.), toluene (2.0 mL), 110 °C, 24 h. [b] Isolated yield. [c] Paraformaldehyde (10.0 equiv.). [d] Product mixtures were obtained as *trans*-and *cis*-isomeric mixtures, major : minor = 3 : 1. [e] *ortho*-Xylene (1.0 mL), 140 °C.

To gain more insight into this cascade cyclization reaction mechanism, a control experiment was performed as shown in Scheme 4. We first investigated the thermal induced reaction of imine **3a** and found that upon heating at 110 °C for 24 h, **3a** could be easily transformed to **2a** in > 99% yield on the basis of $^1H$ NMR analysis, suggesting that imine **3a** is the real intermediate of this [3 + 2] intramolecular cyclization reaction.

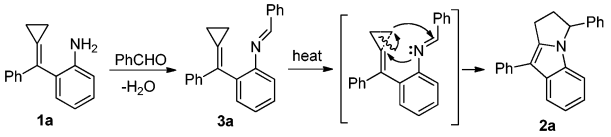
Moreover, the control experiment has confirmed that this cyclization reaction under the optimized conditions was unaffected by the addition of the radical inhibitors such as TEMPO (2.0 equiv.) and 2,6-di-*tert*-butyl-4-methylphenol (BHT) (2.0 equiv.), rendering unlikely the intervention of a radical pathway (Scheme 5).



**Scheme 4** Control experiment for the formation of **2a** from **3a**.



**Scheme 5** The control experiments of **1a** and benzaldehyde in the presence of TEMPO or 2,6-di-*tert*-butyl-4-methylphenol.



**Scheme 6** A plausible reaction mechanism.

Based on above control experiments and the reported literature,[15] a plausible mechanism for this reaction is outlined in Scheme 6. The aniline-tethered alkylidenecyclopropane **1a** reacts with benzaldehyde to give imine **3a**. Then, the thermal induced [3 + 2] cyclization takes place leading to the formation of **2a** through a three-membered ring opening pathway.

In summary, a facile synthetic method for the synthesis of functionalized pyrrolo[1,2-*a*]indoles has been developed from the thermal-induced [3 + 2] cyclization of easily available aniline-tethered alkylidenecyclopropanes with aldehydes *via* a cyclopropane ring-opening process. The product **2** has an important structural motif in organic and medicinal chemistry. The potential utilization and extension of the scope of this synthetic methodology are currently under investigation.

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