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Novel intramolecular aza-Diels–Alder reaction: a facile synthesis of *trans*-fused 5*H*-chromeno[2,3-*c*]acridine derivatives

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ABSTRACT

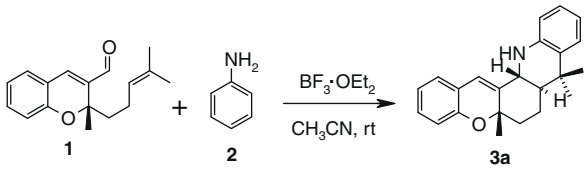
A novel series of 5*H*-chromeno[2,3-*c*]acridine derivatives has been prepared through the intramolecular aza-Diels–Alder reaction of alkene-tethered chromene-3-carboxaldehyde with various aromatic amines. This is the first example of the preparation of pentacyclic poly aromatic compounds in a single-step operation at ambient temperature.

Many naturally occurring biologically active oxygenated heterocycles contain the 2*H*-chromene nucleus as their key structural component. 2,2-Dimethylchromene derivatives isolated from *propolis*, a resinous product known for over 2000 years for its healing properties, is one of the best known examples.[1] Calonolide F, isolated from *Calophyllum tesymannii*, also contains the 2,2-dimethylchromene moiety and exhibits anti-HIV activity,[2] while synthetic analogues have been shown to possess anti-hypertensive[3] and anti-ischaemic activities.[4] Due to fascinating structural features and their biological activity, the syntheses of these molecules have attracted great attention. Consequently, several approaches have been developed for the synthesis of 2*H*-chromene derivatives.[5] However, there have been no reports on the synthesis of angularly *trans*-fused chromenoacridines from alkene-tethered chromene-3-carboxaldehyde and aromatic amines.

In this Letter, we report a novel and efficient approach for the synthesis of angularly fused chromenoacridines by means of intramolecular [4+2] cycloaddition. We initially attempted the coupling of alkene-tethered chromene-3-carboxaldehyde[6] (**1**) with aniline (**2**) using $BF_3{\cdot}OEt_2$. The reaction proceeded smoothly in acetonitrile at room temperature affording the corresponding chromenoacridine **3a** in 88% yield (Scheme 1). The product was obtained as a mixture of *cis*- and *trans* favoring *trans*-isomer. The ratio of cis/trans was determined by NMR spectra of a crude product.

The *trans* stereochemistry of **3a** was confirmed on the basis of coupling constants of ^{1}H NMR spectra and also by direct comparison with the reported data in the literature.[7] The signal of the allylic proton in **3a** appears as a doublet (J = 11.33 Hz) at δ = 3.81. In *trans*-fused cyclo-adducts of other known compounds, the coupling constant for the proton at the ring junction is in the range of J = 9–12 Hz whereas in the *cis*-fused analogues the coupling constant is found to be J = 4–6 Hz.

Encouraged by the results obtained with aniline, we turned our attention to various aryl amines and substituted chromene-3-carboxaldehydes. Interestingly, aryl amines such as *p*-bromo-, *p*-fluoro, *p*-chloro-, *p*-nitro-, *p*-methoxy-, *p*-methyl-, *p*-hydroxy- and *p*-phenyl-anilines participated well in this reaction (Table 1, entries a–i). Ortho-substituted aryl amines such as *o*-bromo-, *o*-chloro-, *o*-methyl, *o*-methoxy- and *o*-hydroxy-anilines were also equally effective (Table 1, entries j–n). The reaction was also quite successful with bromo-substituted chromene-3-carboxaldehyde (Table 1, entries o–r). The electronic effects of the substituents on anilines are studied well. It is observed that strong electron-withdrawing groups at *para*-position decrease the yields compared to the electron-donating ones (Table 1, entries c–e). In the case of *ortho*-substituted anilines, no such effect is observed. Irrespective of the electronic or steric effects, the reaction underwent smoothly



Scheme 1. Reaction of alkene-tethered chromene-3-carboxaldehyde and aniline.

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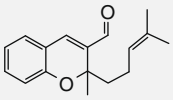
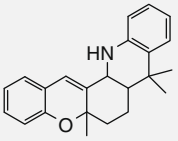
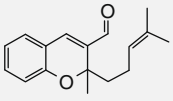
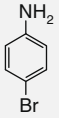
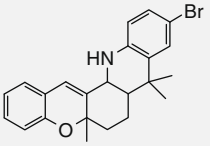
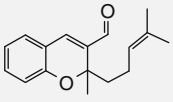
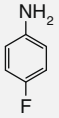
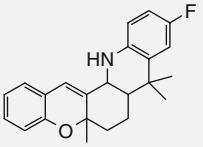
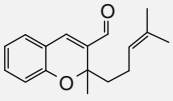
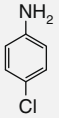
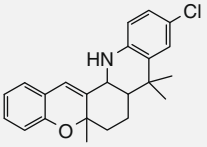
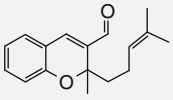
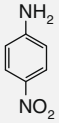
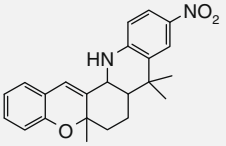
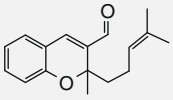
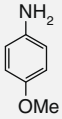
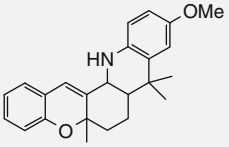
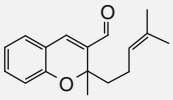
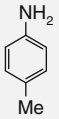
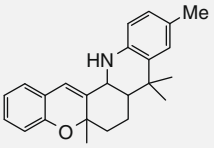
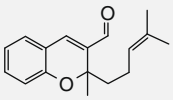
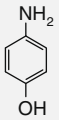
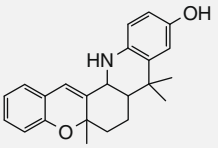
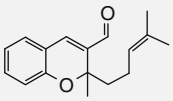
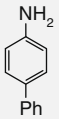
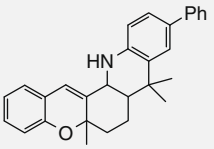
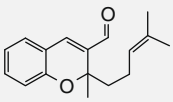
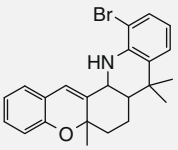
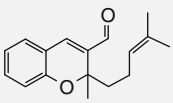
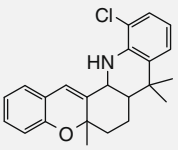
Table 1
Synthesis of chromeno[2,3-*c*]acridines via aza-Diels–Alder reaction

Entry	Enal	Aryl amine	Product[a]	Time (min)	Yield[b] (%)	Cis/trans[c]
a				30	88	05:95
b				30	79	06:94
c				30	66	05:95
d				30	70	05:95
e				30	68	10:90
f				30	85	08:92
g				30	85	05:95
h				30	85	05:95
i				30	80	10:90
j				30	88	05:95
k				30	79	06:94

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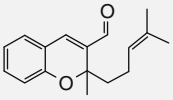
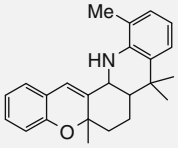
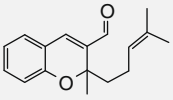
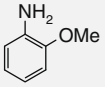
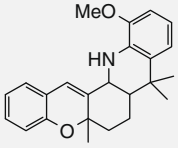
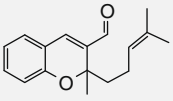
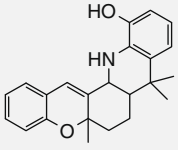
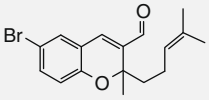
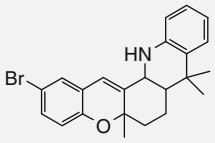
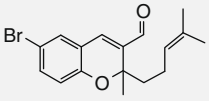
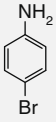
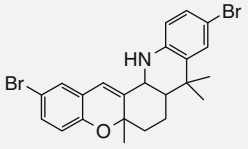
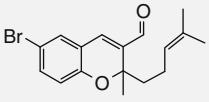
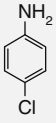
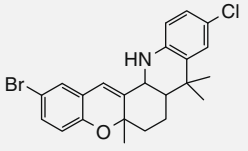
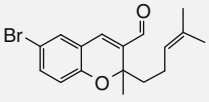
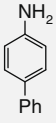
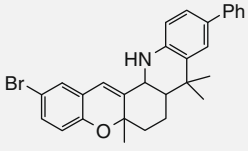
l				30	66	05:95
m				30	70	05:95
n				30	68	10:90
o				30	85	08:92
p				30	85	05:95
q				30	85	05:95
r				30	80	10:90

[a] All products were characterized by NMR, IR and mass spectrometry.
[b] Yield refers to pure products after chromatography.
[c] Ratio was determined by ^{1}H NMR spectra of a crude product.

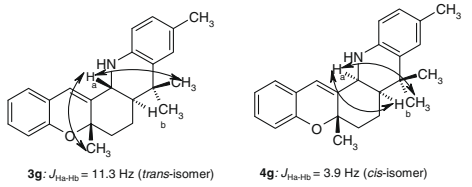
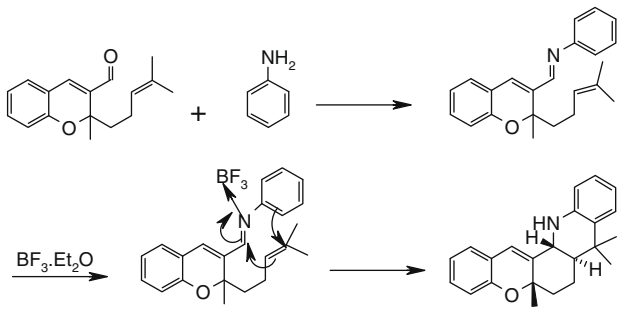


Figure 1. Characteristic NOEs and coupling constants of **3g** and **4g**.

without any significant differences. Therefore, these steric or electronic effects do not make any perceptible effects.

The relative stereochemistry of **3g** was established by NOE studies (Fig. 1). In major isomer, the coupling constant of proton Ha at δ 3.80 is J = 11.3 Hz, whereas in minor isomer for Ha at δ 4.30, the J_{Ha-Hb} = 3.9 Hz. The presence of a weak NOE between Ha and Hb in **3g** indicates that ring protons, Ha and Hb, are *trans* to each other. Further, the methyl group present at the ring junction in **3g** shows strong NOE with Ha and implies that Ha and Methyl groups are in relative *cis* configuration. This clearly provides the relative stereochemistry of all stereogenic centres. The presence of strong NOE between Ha and Hb in **4g** confirms the *cis* stereochemistry of the minor isomer (Fig. 1).



Scheme 2. A plausible reaction mechanism.

Mechanistically, the reaction proceeds via the formation of imine from aromatic amine and chromene-3-carboxaldehyde. Thus formed imine may undergo Lewis acid-induced intramolecular hetero-Diels–Alder reaction to furnish the desired product (Scheme 2).

The method gives good generality over a wide range of aromatic amines. This protocol works well for both electron-rich and electron-deficient aryl amines. In all cases, *trans*-isomer was found to be the major product. Attempts to extend this reaction to amines with fused aromatic system such as 2,5-diaminonaphthalene did not produce the desired product. Other Lewis acids such as $AlCl_3$, $FeCl_3$, $ZnCl_2$, $SnCl_4$, $Sc(OTf)_3$, $InCl_3$, $InBr_3$, $In(OTf)_3$, $Bi(OTf)_3$, TFA and $LiClO_4$ were found to be ineffective for this conversion in terms of both yield and selectivity. Acetonitrile is the best choice of the solvent as the reaction furnishes better results compared to the other solvents such as methanol, tetrahydrofuran, diethylether, dichloromethane and dichloroethane. The scope and limitations of the present protocol with respect to various aromatic amines are demonstrated in Table 1.[8]

In conclusion, we have demonstrated an efficient and versatile protocol for the preparation of chromenoacridines by means of [4+2] cycloaddition of chromene-3-carboxaldehyde with aryl amines. This method illustrates a highly selective synthesis of a novel class of *trans*-fused chromenoacridine derivatives in a one-pot operation. The use of commercially available boron trifluoride etherate makes this method quite simple, more convenient and practical.

Acknowledgement

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References and notes

1. Banskota, H.; Tezuka, Y.; Prasain, J. K.; Matsushige, K.; Saiki, I.; Kadota, S. *J. Nat. Prod.* **1998**, *61*, 896.
2. McKee, T. C.; Fuller, R. W.; Covington, C. D.; Cardellina, J. H.; Gulakowski, R. J.; Krepps, B. L.; McMahon, J. B.; Boyd, M. R. *J. Nat. Prod.* **1996**, *59*, 754.
3. (a) Ashwood, V. A.; Cassidy, F.; Coldwell, M. C.; Evans, J. M.; Hamilton, T. C.; Howlett, D. R.; Smith, D. M.; Stemp, G. *J. Med. Chem.* **1990**, *33*, 2667; (b) Cassidy, F.; Evans, J. M.; Hadley, M. S.; Haladij, A. H.; Leach, P. E.; Stemp, G. *J. Med. Chem.* **1992**, *35*, 1623.
4. (a) Atwal, K. S.; Grover, G. J.; Ferrara, F. N.; Ahmed, S. Z.; Sleph, P. G.; Dzwonczyk, S.; Normandin, D. E. *J. Med. Chem.* **1995**, *38*, 1966; (b) Atwal, K. S.; Grover, G. J.; Ahmed, S. Z.; Ferrara, F. N.; Harper, T. W.; Kim, K. S.; Sleph, P. G.; Dzwonczyk, S.; Russell, A. D.; Moreland, S.; McCullough, J. R.; Normandin, D. E. *J. Med. Chem.* **1993**, *36*, 3971.
5. Hepworth, J. D.. In *Comprehensive Heterocyclic Chemistry*; Boulton, A. J., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 3, p 741.
6. Manuel, C. B.; Volz, N.; Bräse, S. *Synlett* **2009**, 1383.
7. (a) Shanmugasundaram, M.; Manikandan, S.; Raghunathan, R. *Tetrahedron* **2002**, *58*, 997; (b) Tietze, L. F.; Geissler, H.; Fennen, J.; Brumby, T.; Brand, S.; Schulz, G. *J. Org. Chem.* **1994**, *59*, 182; (c) Lee, Y. R.; Hung, T. V. *Tetrahedron* **2008**, *64*, 7338.
8. *General experimental procedure*: A mixture of 2-methyl-2-(4-methylpent-3-enyl)-2*H*-chromene-3-carboxaldehyde (254 mg, 1 mmol), aniline (111 mg, 1.2 mmol) and $BF_3{\cdot}OEt_2$ (0.01 mL, 10 mol %) in acetonitrile (5 mL) was stirred at ambient temperature for the appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the reaction was quenched with ice cold water (20 mL) and the reaction mixture was extracted with dichloromethane (2×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate/hexane and 0.5:95) to afford pure product. The pure products thus obtained were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy. The spectral data of selected products: **3a**: *5a,8,8-trimethyl-6,7,7a,8,13,13a-hexahydro-5H-chromeno[2,3-c]acridine*: IR (neat): ν 3326, 2962, 1602, 1488, 1454, 1112, 1084, 747 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.16 (s, 3H), 1.37 (s, 3H), 1.48 (s, 3H), 1.64 (m, 2H), 1.99–2.06 (m, 1H), 2.08–2.14 (m, 2H), 3.81 (dd, 1H, J = 1.6 Hz, 11.3 Hz), 6.23 (s, 1H), 6.55–6.70 (m, 4H), 6.77 (t, 1H, J = 8.1 Hz), 6.90–9.98 (m, 1H), 7.00–7.12 (m, 1H), 7.18 (d, 1H, J = 6.4 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 24.5, 26.5, 26.9, 35.4, 40.0, 47.5, 51.0, 78.9, 114.0, 115.6, 117.9, 120.9, 126.1, 126.8, 128.7. LC–MS: m/z: 332 [M+H]; HRMS calculated for $C_{23}H_{25}NO$: 332.2014. Found: 332.2026. **3g**: *5a,8,8,10-tetramethyl-6,7,7a,8,13,13a-hexahydro-5H-chromeno[2,3-c]acridine*: IR (neat): ν 3331, 2972, 2930, 1665, 1460, 1242, 1031, 756 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.16 (s, 3H), 1.35 (s, 3H), 1.48 (s, 3H), 1.53–1.67 (m, 2H), 1.97–2.06 (m, 1H), 2.07–2.13 (m, 2H), 2.24 (s, 3H), 3.80 (dd, 1H, J = 2.2 Hz, 11.3 Hz), 6.23 (s, 1H), 6.49 (d, 1H, J = 7.5 Hz), 6.67 (d, 1H, J = 8.3 Hz), 6.74–6.80 (m, 2H), 6.90–7.06 (m, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 33.3, 38.4, 39.4, 40.7, 45.1, 48.0, 48.9, 50.6, 101.9, 137.1, 144.0, 146.2, 147.2, 149.8, 150.4, 150.8. LC–MS: m/z: 346 [M+H]; HRMS calculated for $C_{24}H_{27}NO$: 346.2171. Found: 346.2156. **3k**: *12-chloro-5a,8,8-trimethyl-6,7,7a,8,13,13a-hexahydro-5H-chromeno[2,3-c]acridine*: yellow solid, mp 105–106 °C. IR (KBr): ν 3423, 2967, 1600, 1492, 1245, 753 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.14 (s, 3H), 1.38 (s, 3H), 1.50 (s, 3H), 1.55–1.67 (m, 2H), 1.99–2.08 (m, 1H), 2.09–2.17 (m, 2H), 3.89 (d, 1H, J = 10.6 Hz), 6.28 (s, 1H), 6.53–6.60 (m, 1H), 6.68 (d, 1H, J = 8.3 Hz), 6.79 (t, 1H, J = 7.5 Hz), 6.96–7.04 (m, 2H), 7.05–7.12 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 21.7, 24.5, 35.8, 40.2, 47.0, 51.1, 78.8, 114.0, 115.6, 117.1, 120.9, 124.3, 126.3, 126.8, 128.8. LC–MS: m/z: 366 [M+H]; HRMS calculated for $C_{23}H_{24}NO$: 366.1624. Found: 366.1620.