[4+3]-Annulation of 3-Cyano-4-aryl-2-iminochromenes with 1,2-Diaminobenzene: An Access to Novel Chromenobenzodiazepines

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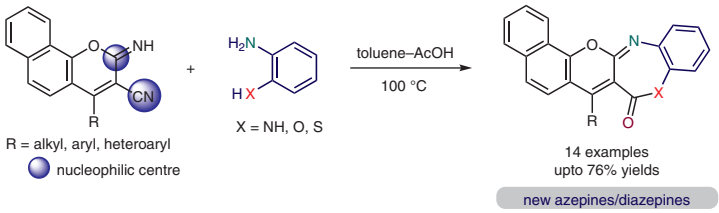

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Abstract 3-Cyano-4-aryl-2-iminochromenes undergo [4+3]-annulation with 1,2-diaminobenzene under mild acidic conditions to generate novel chromenobenzodiazepines in good yields. The annulation reaction was also successful with 2-aminophenol and 2-aminothiophenol. The chromenobenzodiazepines could be conveniently reduced to the corresponding 4*H*-chromenobenzodiazepines under mild acidic conditions.

Key words 3-cyano-4-aryl-2-iminochromene, 1,2-diaminobenzene, [4+3]-annulation, chromenobenzodiazepine, chromenobenzoazepine

Benzodiazepines have emerged as a 'privileged heterocyclic scaffold' in medicinal chemistry.[1] More than 40 benzodiazepines have been commercialized as drugs and pharmaceuticals. A few biologically and medicinally important fused benzodiazepines are depicted in Figure 1. Benzodiazepines are known to possess anticancer, antioxidant, and antibacterial activities.[2–5] Several benzodiazepine drugs greatly affect the central nervous system, especially in the brain and are used as antianxiety drugs.[6] Benzodiazepines are believed to form a supramolecular complex with $GABA_A$ chloride ion channel, which modulates the action of gamma-aminobutyric acid on chloride ion flux.

2-Amino-3-cyano-4-aryl 4*H*-chromenes exhibit widespread biological profiles including anticancer, anti-HIV and antibacterial activities.[7] Several 4*H*-chromene-derived heterocycles have also been found to possess important biological activities. For example, Kamal et al. generated chromenopyrimidine derivatives and showed that the compounds exhibit antitumor activities.[8] Similarly, Proencą et al. reported the synthesis of fused chromenopyridines having antifungal activities.[9] It has been observed that benzodiazepines when fused with heterocyclic compounds exhibit superior activities.[10] Recently, we reported the selective dehydrogenation of 2-amino-3-cyano-4-aryl 4*H*-chromenes using diisopropyl azodicarboxylate in a polar aprotic solvent under neutral reaction conditions.[11] The method provided easy access to 2-iminochromenes and thereby allowed us test their reactivity. Herein, we report an annulation reaction of 2-iminochromenes with 1,2-diaminobenzene to generate novel chromenobenzodiazepines in good yields (Scheme 1).

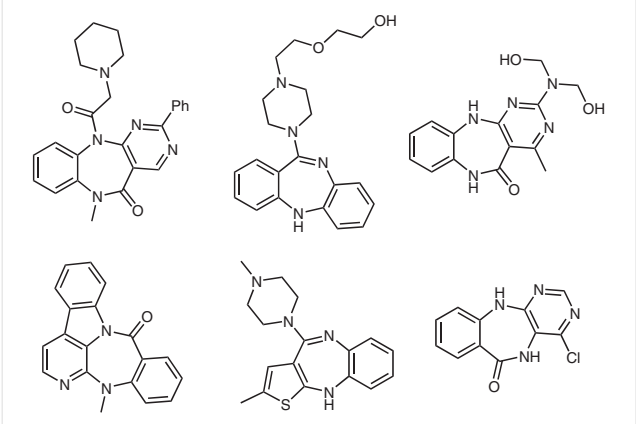
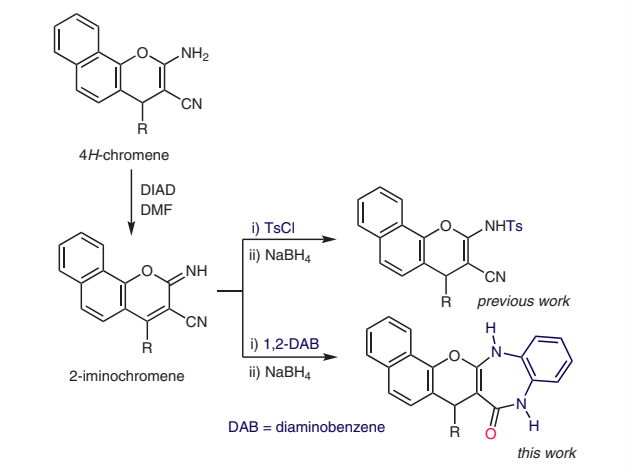


Figure 1 A selection of biologically and medicinally important fused benzodiazepines

We hypothesized that the imino- and cyano groups of 2-iminochromene would be activated in the presence of an acid and behave as nucleophilic centers. This would create the opportunity for an annulation reaction with bidentate nucleophiles. With this aim, we screened several conditions for the annulation reaction of 2-iminochromene **1a** with 1,2-diaminobenzene (**2a**). As shown in Table 1, the annulation reaction occurs under weakly acidic conditions. Condensation in acetic acid provided chromenobenzodiazepine

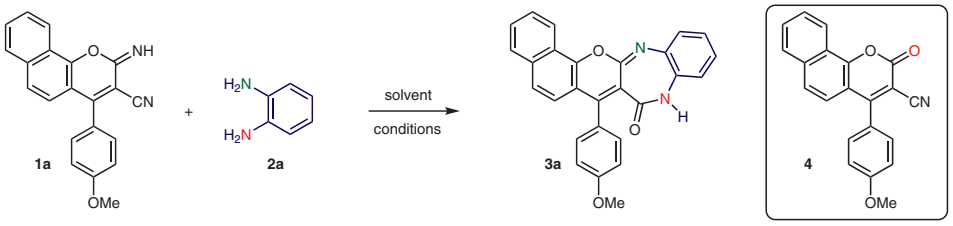


Scheme 1 Synthetic outline for chromenobenzodiazepine synthesis

3a in 55% yield (Table 1, entry 1). Reaction in pivalic acid and formic acid provided the benzodiazepine in low yields (46% and 42% yields, respectively). When TFA was used as a solvent, coumarin **4** was isolated as the predominant product. Condensations using mixed solvents were also tested and the results are presented in Table 1 (entries 5–9). In EtOH-AcOH (9:1), the reaction generated chromenobenzodiazepine **3a** in 40% yield. Reaction in DMF-AcOH (9:1) was rapid but generated unidentified polar compounds along with **3a** (52%). A low yield was observed when the condensation was carried out in dioxane-AcOH (9:1) mixture. However, an increase in isolated yield (64%) was observed when the reaction was carried out in toluene-AcOH (9:1) mixture, and the best result was obtained using toluene-AcOH (4:1) (entry 9). No condensation reaction was observed in the absence of AcOH (entry 11).

The best conditions were then employed for the annulation reaction of several iminochromenes generated from chromenes via diisopropyl azodicarboxylate-mediated dehydrogenation. As shown in Figure 2, the condensation reactions usually generate chromenobenzodiazepines in good yields in short reaction times. Chromenobenzodiazepine **3b**, with a phenyl group at the 4-position, was obtained in 72% yield. Iminochromene, with a 3,4-dimethoxyphenyl group at the 4-position, generated the corresponding chromenobenzodiazepine **3c** in 68% yields. When iminochromene having a *p*-nitrophenyl group at the 4-position was subjected to the annulation reaction, benzodiazepine **3d** was obtained in 72% yield. The iminochromene with a cyclohexyl group at the 4-position also underwent smooth condensation reaction with 1,2-diaminobenzene to generate chromenobenzodiazepine **3e** in 74% yield within three hours. The iminochromene containing a pyridyl group at the 4-position underwent effective condensation to furnish

Table 1 Optimization of Reaction Conditions for Annulation Reaction



Entry	Solvent	Conditions[a]	Yield (%)[d]
1	AcOH	100 °C, 4 h	55
2	Me_3CCO_2H	100 °C, 4 h	46
3	HCOOH	100 °C, 3 h	42
4	TFA	80 °C, 1 h	ND
5	EtOH-AcOH (9:1)	80 °C, 4 h	40
6	DMF-AcOH (9:1)	100 °C, 3 h	52
7	dioxane-AcOH (9:1)	100 °C, 3 h	42
8	toluene-AcOH (9:1)	100 °C, 3 h	64
9	toluene-AcOH (4:1)	100 °C, 2 h	70
10	toluene-$PhCO_2H$[b]	100 °C, 4 h	48
11	toluene[c]	100 °C, 1 h	NR

[a] All reactions were carried out using iminochromene **1a** (1.0 equiv), 1,2-diaminobenzene (1.0 equiv) in the appropriate solvent (0.25 M).
[b] $PhCO_2H$ (10 equiv) was used.
[c] Reaction was carried out in the absence of AcOH.
[d] ND = yield not determined; NR = no reaction.

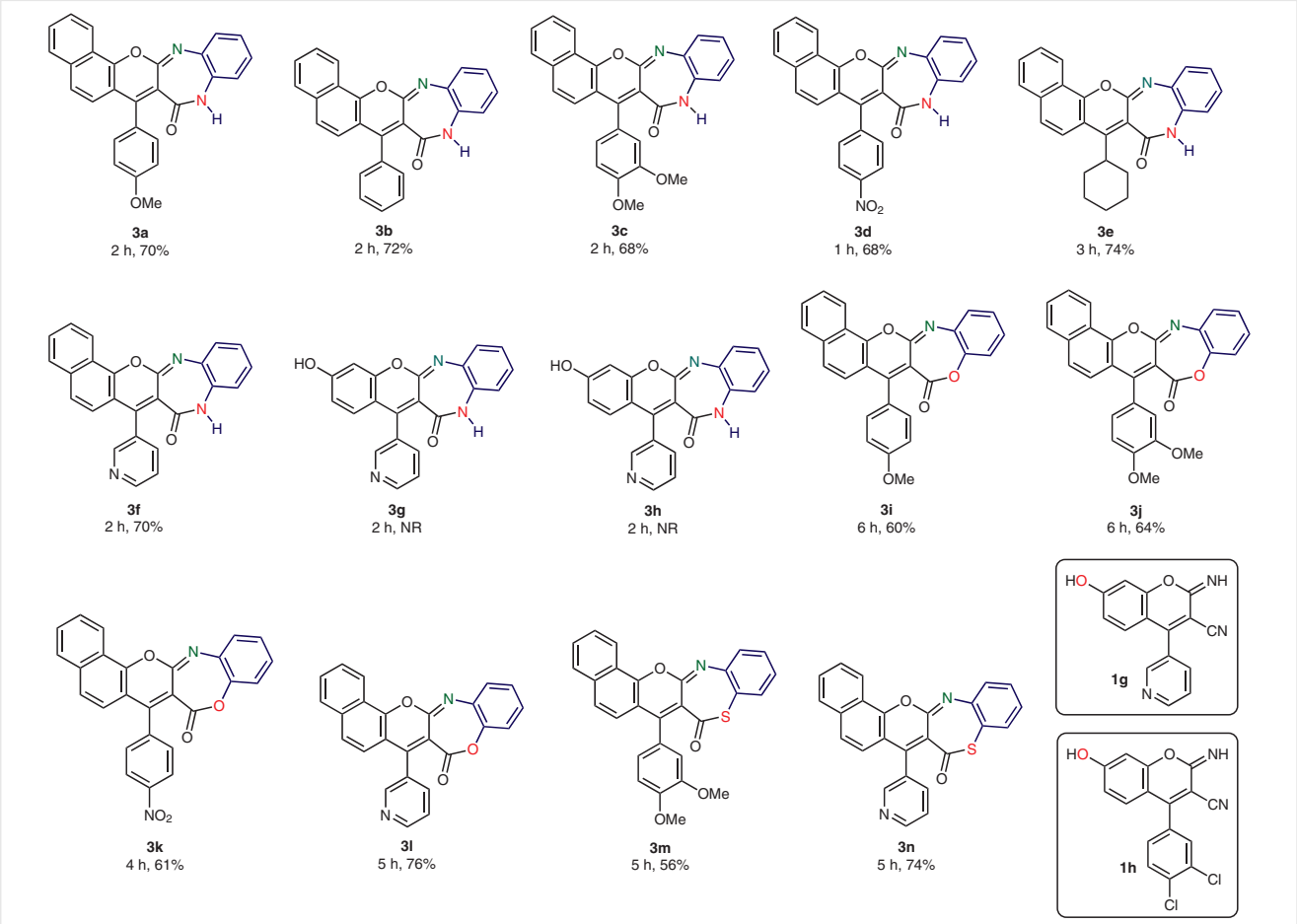
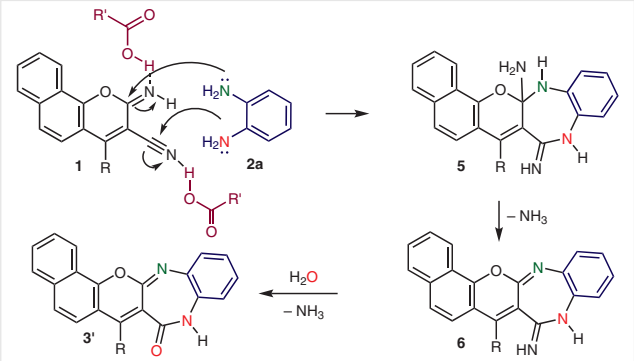


Figure 2 [4+3]-Annulation of 2-iminochromenes with 1,2-diaminobenzene, 2-aminophenol and 2-aminothiophenol. All reactions were carried out using iminochromene **1** (1.0 equiv), **2** (1.0 equiv) in toluene-AcOH mixture (4:1, 0.25 M); NR = no reaction; ND = yield not determined.

chromenobenzodiazepine **3f** in good yield (70%). Iminochromene **1g**, generated from the resorcinol-derived chromene, failed to undergo condensation to generate the chromenobenzodiazepine **3g** the under the standard conditions. When the condensation reaction was carried out at higher temperature (150 °C), a complex reaction mixture was obtained. Similarly, iminochromene **1h**, generated from the resorcinol-derived chromene, also failed to give measurable amounts of compound **3h**. The successful annulations of iminochromenes generated from chromenes derived from α-naphthol[11] encouraged us to test the reaction with 2-aminophenol and 2-aminothiophenol under the standard conditions. To our satisfaction, annulation reactions with 2-aminophenol and 2-aminothiophenol were also effective and produced chromenobenzoazepines in moderate to good yields. These reactions usually required longer reaction time, presumably due to the lower nucleophilicity of the phenol and thiophenol groups. The iminochromene having a *p*-methoxyphenyl group at the 4-position required six hours for completion of condensation with 2-aminophenol, producing chromenobenzoazepine **3i** in moderate yield (60%). The iminochromene possessing a 3,4-dimethoxyphenyl group at the 4-position produced chromenobenzoazepine **3j** in 64% yield. Chromenobenzoazepine **3k**, having a *p*-nitrophenyl group at the 4-position, was obtained in 61% yield and iminochromene incorporating a 3-pyridyl group at the 4-position also generated chromenobenzoazepine **3l** in good yield (76%). Annulation reactions of 2-aminothiophenols containing a 3,4-dimethoxyphenyl group and a 3-pyridyl group at the 4-position furnished the corresponding chromenobenzoazepines **3m** and **3n** in 56% and 74% yields, respectively.

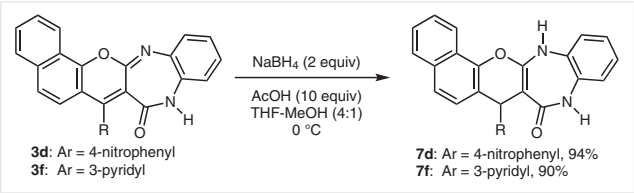
The mechanism of chromenobenzoazepine synthesis is depicted in Scheme 2. Concomitant nucleophilic addition of 1,2-diaminobenzene to the imino and cyano group of 2-iminochromene **1** activated by the carboxylic acid via weak coordination generates intermediate **5**, which liberates a molecule of ammonia to be converted into intermediate **6**. Hydrolysis of the unstable intermediate **6** leads to the chromenobenzodiazepine **3′**. In case of resorcinol-derived iminochromenes (**1g**, **1h**), the phenolic hydroxyl group in-



Scheme 2 Mechanism of chromenodiazepine synthesis

creases the electron density in the aromatic ring and presumably decreases the reactivity of the imino group towards nucleophiles.

Our efforts to convert the synthesized chromenobenzodiazepines into the corresponding 4*H*-chromenobenzodiazopines by reduction with $NaBH_4$ met with difficulties. Reduction with $NaBH_4$ in THF-MeOH (4:1) at 0 °C was not clean and generated several spots on TLC analysis. However, upon careful optimization, we were pleased to observe that addition of 10 equivalents of AcOH was necessary for clean reduction of the chromenobenzodiazepines to obtain 4*H*-chromenobenzodiazopines in excellent yields (Scheme 3).



Scheme 3 Reduction of chromenobenzodiazepines

In summary, a general method for annulation of 2-iminochromenes with 1,2-diaminobenzene, 2-aminophenol and 2-aminothiophenol has been developed to generate biologically important 1,4-chromenobenzodiazepines and chromenobenzoazepines in good yields. The chromenobenzodiazepines can be conveniently reduced to the corresponding 4*H*-chromenobenzodiazepines in the presence of AcOH. The reduced 4*H*-chromenobenzodiazepines offer opportunity for further structural elaboration.

Chemicals received from commercial sources were used without purification. The 2-iminochromenes were synthesized by following a reported procedure.[11] All commercial grade solvents were used without purification. Column chromatography was performed on 60–120 mesh silica gel using a gradient mixture of EtOAc in petroleum ether (60–80 °C) as eluent. Mass spectra were recorded with a Waters Xevo G2-SQ TOF mass spectrometer. ^1H and ^{13}C NMR spectra were recorded with a Jeol JNM-ECS spectrometer at operating frequencies of 400 MHz (^1H) or 100 MHz (^{13}C), as indicated in the individual spectrum, using TMS as an internal standard. Multiplicities in the ^1H NMR spectra are presented as s for singlet, d for doublet, dd for doublet of doublet, t for triplet, and m for multiplet. Thin-layer chromatography was performed on aluminum plates (silica gel 60 PF_{254}, 0.25 mm) purchased from Merck.

Typical Procedure

A mixture of 3-cyano-4-(*p*-methoxyphenyl) 2-iminochromene **1a** (200 mg, 0.61 mmol) and 1,2-diaminobenzene (66 mg, 0.61 mmol) in toluene-AcOH (4:1, 2.5 mL) was stirred in a pre-heated oil bath at 100 °C under a nitrogen atmosphere. After 2 hours, TLC analysis indicted complete consumption of starting material. The reaction mixture was cooled to r.t. and solvent was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography using a gradient mixture of 10→30% EtOAc in hexane as eluent to obtain **3a** (180 mg, 70%) as a pale-yellow solid.

7-(4-Methoxyphenyl)benzo[*b*]benzo[7,8]chromeno[2,3-*e*][1,4]diazepin-8(9*H*)-one (3a)

Yield: 180 mg (70%); pale-yellow solid; mp 220–222 °C.

^1H NMR (DMSO-d_6, 400 MHz): δ = 12.49 (br s, 1 H, NH), 8.51–8.45 (m, 1 H), 8.07–8.01 (m, 1 H), 7.81 (d, *J* = 8.6 Hz, 1 H), 7.79–7.74 (m, 2 H), 7.48 (d, *J* = 8.0 Hz, 1 H), 7.44 (d, *J* = 7.8 Hz), 7.26 (d, *J* = 8.7 Hz, 2 H), 7.21 (d, *J* = 8.8 Hz, 1 H), 7.17–7.05 (m, 2 H), 6.91 (d, *J* = 8.7 Hz, 2 H), 3.69 (s, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 160.0, 159.8, 156.6, 150.7, 146.3, 143.6, 135.2, 134.5, 130.7, 130.1, 128.6, 128.4, 126.1, 124.9, 123.6, 123.0, 122.7, 122.4, 121.8, 119.6, 117.9, 115.4, 114.2, 112.0, 55.6.

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{27}H_{19}N_2O_3$: 419.1396; found: 419.1410.

7-(Pyridin-3-yl)-8*H*-benzo[*b*]benzo[7,8]chromeno[2,3-*e*][1,4]oxazepin-8-one (3l)

Yield: 200 mg (76%); dark-brown solid; mp 198–200 °C.

^1H NMR ($CDCl_3$, 400 MHz): δ = 8.74–8.65 (m, 2 H), 8.62 (s, 1 H), 7.93–7.87 (m, 1 H), 7.78–7.71 (m, 3 H), 7.69–7.63 (m, 2 H), 7.45–7.36 (m, 2 H), 7.35–7.26 (m, 2 H), 7.16 (d, *J* = 8.6 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 158.2, 156.9, 155.2, 152.0, 150.6, 148.7, 141.1, 136.3, 135.7, 130.2, 130.1, 128.0, 127.9, 125.9, 125.0, 124.7, 123.3, 123.0, 122.4, 120.7, 115.3, 114.3, 110.9.

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{25}H_{15}N_2O_3$: 391.1083; found: 391.1141.

7-(Pyridin-3-yl)-9,14-dihydrobenzo[*b*]benzo[7,8]chromeno[2,3-*e*][1,4]diazepin-8(7*H*)-one (7f)

Yield: 45 mg (90%); yellow solid; mp 235–236 °C.

^1H NMR (DMSO-d_6, 400 MHz): δ = 10.25 (br s, 1 H, NH), 8.14 (br s, 1 H), 7.86 (d, *J* = 8.2 Hz), 7.71–7.54 (m, 1 H), 7.54–7.21 (m, 7 H), 7.18–6.89 (m, 4 H), 6.11 (d, *J* = 11.8 Hz, 1 H), 5.87 (d, *J* = 11.8 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 153.4, 153.0, 150.3, 150.2, 147.7, 143.2, 142.6, 138.4, 136.0, 134.7, 133.5, 127.9, 126.3, 126.0, 125.5, 123.9, 123.7, 122.7, 121.9, 121.7, 120.2, 118.9, 118.7, 111.9, 44.5.

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{25}H_{18}N_3O_2$: 392.1399; found: 392.1405.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591573.

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