Regiospecific Syntheses of 3-Aza-α-carbolines via Inverse Electron-Demand Diels–Alder Reactions of 2-Aminoindoles with 1,3,5-Triazines

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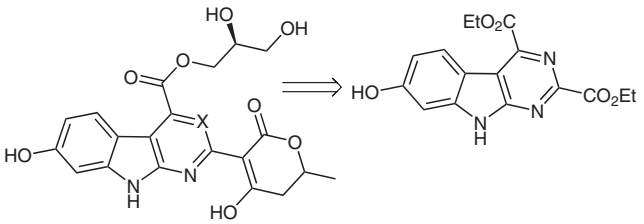
Abstract: The scope of 1,3,5-triazine inverse electron-demand Diels–Alder (IDA) reactions was expanded to include 2-aminoindoles as productive dienophiles leading to various 3-aza-α-carbolines in excellent yields. Furthermore, the two ester groups of the IDA product were differentiated via reduction of the C4-ester to its corresponding alcohol. This new IDA reaction could be potentially applied to the synthesis of various 3-aza-mescengrincin analogues that may possess neuroprotective activities.

Key words: 2-aminoindoles, inverse electron-demand Diels–Alder reactions, heterocycles, 3-aza-α-carbolines, regiospecific syntheses

Diels–Alder reactions have long been recognized as one of the most efficient methods in organic synthesis since multiple bonds are formed simultaneously. Subsequently, hetero Diels–Alder reactions were developed to prepare various heterocycles efficiently and have found wide applications in total synthesis of natural products[1,2] and the preparation of biologically active compounds.[3] For instance, the Boger group investigated the scope of inverse electron-demand Diels–Alder (IDA) reactions between 1,3,5-triazines and various electron-rich dienophiles such as enamines, ynamines, and amidines.[4,5]



mescengricin (**1**) X = CH
3-aza-mescengrincin (**2**) X = N

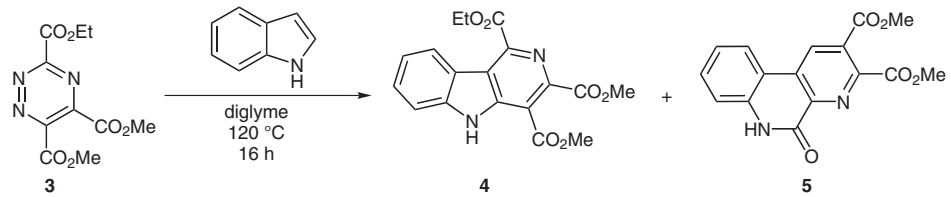
Scheme 1 Retrosynthetic strategy to 3-aza-mescengrincin

α-Carbolines are an interesting class of heterocycles with intriguing biological activities.[6–11] For example, mescengrincin is an alkaloid natural product with neuroprotective activities against L-glutamate toxicity.[12,13] However, α-carbolines are less frequently studied compared to β-carbolines, possibly due to the relatively few available synthetic methodologies to access α-carbolines.[14] We envision that an efficient entry to 3-aza-α-carbolines via IDA reactions of indoles with 1,3,5-triazines is feasible, which should enable rapid exploration of biological activities of 3-aza-α-carboline analogues. Moreover, this IDA strategy should be applicable to the synthesis of 3-aza-mescengrincin analogues (Scheme 1), which could be explored for their potential neuroprotective activities.

Various examples of indoles as dienophiles in IDA reactions were reported. For instance, the Seitz group reported the IDA reactions of indoles with 1,2,4,5-tetrazines.[15,16] The Haider group reported the IDA reactions of indoles with pyridazines,[17,18] and the Snyder group reported their seminal work on IDA reactions of indoles with both 1,2,4,5-tetrazines and 1,2,4-triazines.[19,20] For example, Snyder et al. reported that indole reacted with 1,2,4-triazine **3** to produce the IDA product **4** in 89% yield, along with 6% of a rearrangement product **5** (Scheme 2).[21]

Herein we report our investigations of indoles as dienophiles for IDA reactions with 1,3,5-triazines and the development of this new method to prepare various 3-aza-α-carbolines.

Given the structural similarity between 1,2,4-triazine **3** and 2,4,6-tris(ethoxycarbonyl)-1,3,5-triazine (**6a**), we decided to explore the IDA reactions of indole with 1,3,5-triazine **6a** using the Snyder conditions. Treatment of 1,3,5-triazine **6a** with four equivalents of indole in diglyme at



Scheme 2 IDA reaction of indole and a 1,2,4-triazine[21]

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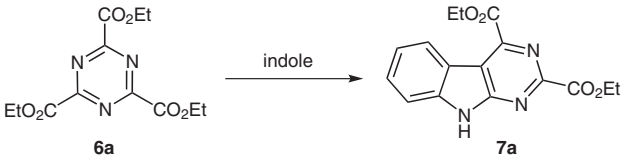
120 °C did not produce any IDA product after 48 hours, and only starting materials were recovered (entry 2, Table 1). Other solvents and conditions were also explored (entries 3–6, Table 1), but none produced any IDA product, and only starting materials remained after prolonged heating. This observation indicated that there are significant differences in reactivity between 1,2,4-triazine **3** and 1,3,5-triazine **6a**, thus caution should be used when generalizations of results obtained with one azadiene are made to another azadiene.

Table 1 Attempted IDA Reactions of Indole with 1,3,5-Triazine **6a**[a]



6a **7a**

Entry	Dienes	Conditions	Product	Yield (%)
1	**3**	diglyme, 120 °C, 16 h	**4**	89[b]
2	**6a**	diglyme, 120 °C, 48 h	**7a**	0[c]
3	**6a**	diglyme, 50 °C, 48 h	**7a**	0[c]
4	**6a**	MeOH, reflux, 48 h	**7a**	0[c]
5	**6a**	CH_2Cl_2, reflux, 48 h	**7a**	0[c]
6	**6a**	DMSO, 100 °C, 33 h	**7a**	0[d]

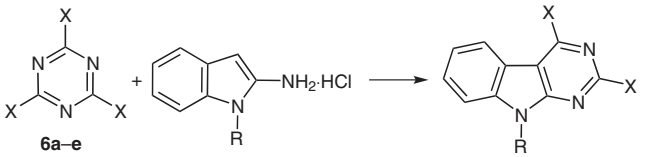
[a] All reactions were conducted using 4 equiv of indole under nitrogen, and monitored by LC-MS, checked after 12, 24, and 48 h.
[b] A yield of 6% of **5** was also obtained (Scheme 2, ref. 21).
[c] Both starting materials remained.
[d] Mostly **6a** remained, trace indole left, reaction was messy.

To address the lack of reactivity for indole toward 1,3,5-triazine **6a**, we envisioned that 2-aminoindoles could serve as productive dienophiles. The amino group should increase the HOMO energy for 2-aminoindoles due to the strong electron-donating capability of the amino group,[22] which should enhance their reactivity as dienophiles in IDA reactions.

The 2-aminoindoles **8a**–**c** were prepared and used as hydrogen chloride salts using reported procedures with minor modifications.[23] Initially, 2-aminoindole **8a** was tested with 1,3,5-triazine **6a** in DMSO at room temperature, which gave the desired 9*H*-pyrimido[4,5-*b*]indole **7a** in excellent yield (entry 1, Table 2). This observation indicated that 2-aminoindole **8a** was indeed capable of functioning as a productive dienophile in the IDA reaction. In contrary to most IDA reactions, which often require thermal conditions (medium to elevated temperatures), the IDA reactions with compound **8a** proceeded rapidly at room temperature, which indicated that compound **8a** had a higher propensity as a dienophile in IDA reactions.

Encouraged by the initial success, the scope of this new IDA reaction was then explored with 2-aminoindoles **8a**–**c** and various 1,3,5-triazines **6a**–**e**. Results from this study are summarized in Table 2.

Table 2 IDA Reactions of **8a**–**c** with **6a**–**e**[a]



6a–e

8a R = H
8b R = Me
8c R = Bn

7 R = H
9 R = Me
10 R = Bn

Entry	**6**	X	**8**	Conditions	Product	Yield (%)
1	**6a**	CO_2Et	**8a**	25 °C, 4.5 h[b]	**7a**	99
2	**6a**	CO_2Et	**8a**	50 °C, 11 h[d,c]	**7a**	82
3	**6a**	CO_2Et	**8b**	50°C, 18 h[d]	**9a**	94
4	**6a**	CO_2Et	**8c**	50 °C, 18 h	**10a**	97
5	**6b**	CF_3	**8a**	50 °C, 7.5 h	**7b**	94
6	**6b**	CF_3	**8b**	50 °C, 17 h	**9b**	97
7	**6b**	CF_3	**8b**	50 °C, 18 h[c]	**9b**	79
8	**6b**	CF_3	**8c**	50 °C, 18 h	**10b**	93
9	**6c**	CO_2Bu	**8a**	50 °C, 4 h[e]	**7c**	94
10	**6d**	H	**8a**	50 °C, 19 h	**7d**	78
11	**6e**	Ph	**8a**	50 °C, 84 h[d]	**7e**	0

[a] All reactions were conducted using 1 equiv of indoles and 2 equiv of 1,3,5-triazines in MeOH unless noted.
[b] DMSO as the solvent.
[c] Et_3N (2 equiv) was added.
[d] DMSO–MeOH (1:1) as the solvent.
[e] *i*-PrOH as the solvent.

All electron-deficient 1,3,5-triazines **6a**–**c** reacted with 2-aminoindoles **8a**–**c** productively leading to desired pyrimido[4,5-*b*]indoles **7a**–**c**, **9a**,**b**, and **10a**,**b** in excellent yields (>90%). On the other hand, the reactions in the presence of triethylamine (entries 2 and 6) produced the same products without base (entries 1 and 5), but with lower yields. One likely cause for the lower yield under basic conditions was the poor stability of the 2-aminoindole free bases. The other was that acids were beneficial for the second step of the cascade reactions by promoting the elimination of ammonia as the ammonium salt. As expected the unsubstituted 1,3,5-triazine **6d** was much less reactive but still gave the desired product in good yield, albeit at a much slower reaction rate (entry 10). The 2,4,6-triphenyl-1,3,5-triazine **6e** was not reactive enough to participate in the IDA reaction, and when reaction temperature was raised to >120 °C the 2-aminoindole **8a** decomposed before any desired IDA product could be detected. The experimentally observed reactivity of 1,3,5-triazines **6a**–**e** was consistent with previous reports, but the large differences in reaction rates for indoles **8a**–**c** were somewhat unexpected. The N^1-unsubstituted 2-aminoindole **8a** was much more reactive compared to 2-aminoindoles **8b**,**c**, even though the calculated HOMO

energies were very similar among the three compounds.[24] One possible explanation is that the steric hindrance of the N^1-substituents slowed down the [4+2] cycloaddition reaction.

The regiochemical outcome of IDA reactions were relatively predictable, and recent theoretical studies further delineated that the electronic effect of both 1,3,5-triazines and dienophiles controlled the regiochemical selectivity of IDA reactions.[25,26] Theoretical calculations suggested that the strong electron-donating amino group of five-membered aromatic dienophiles dictated the regiochemistry of IDA products. Analogously, 2-aminoindoles should react with 1,3,5-triazines in a similar fashion as 2-aminopyrroles and produce IDA products **7**, **9**, and **10**. However, to unambiguously determine the regiochemistry of these new IDA products, an X-ray structure of compound **9b** was obtained (Figure 1), which confirmed the predicted regiochemistry.[27]

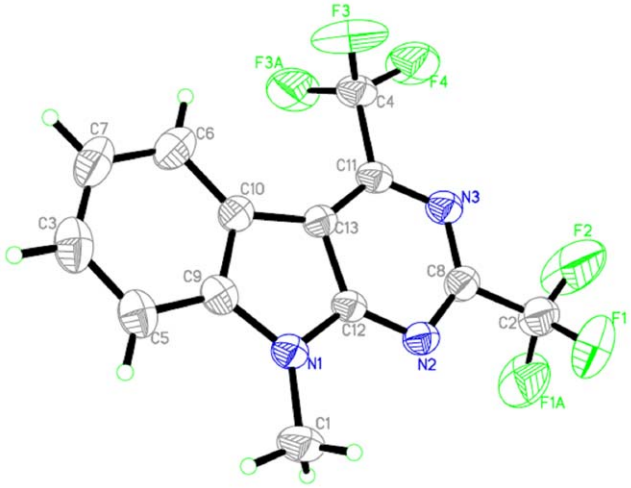
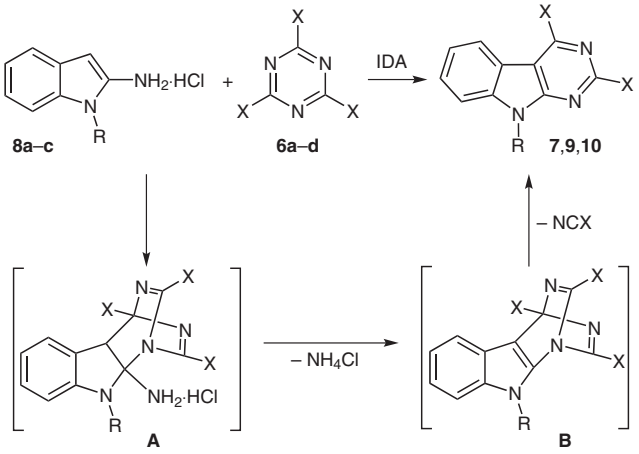


Figure 1 X-ray structure of IDA product **9b**

The IDA reactions of 2-aminoindoles **8a–c** with 1,3,5-triazines should also proceed as a cascade reaction in a similar manner as the previously reported 2-aminopyrrole IDA reactions (Scheme 3).[28] The [4+2] cycloaddition of 1,3,5-triazines with 2-aminoindoles produces a bicyclic intermediate **A**, which is likely going through a zwitterionic transition state as revealed by theoretical studies.[25] Compound **A** undergoes elimination of ammonium chloride to give intermediate **B**, and a final retro Diels–Alder reaction with the loss of NC–X to produce pyrimido[4,5-*b*]indoles **7**, **9**, and **10**.

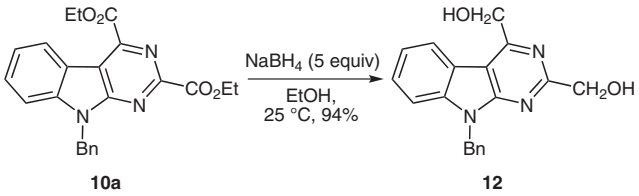
To synthesize 3-aza-mescengrincin and its analogues, the two ester groups in compounds **10a** have to be differentiated, preferably leaving the C4 ester group intact since mescengrincin has an ester group at the C4-position. Boger et al. reported selective reduction of pyrimidine-2,4-diesters as part of their seminal work on the application of 1,3,5-triazine IDA reactions to the synthesis of bleomycin and related natural products.[29,30] Therefore, we set out to



Scheme 3 Proposed mechanism of the IDA reaction

explore the selective reduction of diester **10a**, and results from this investigation are summarized in Table 3.

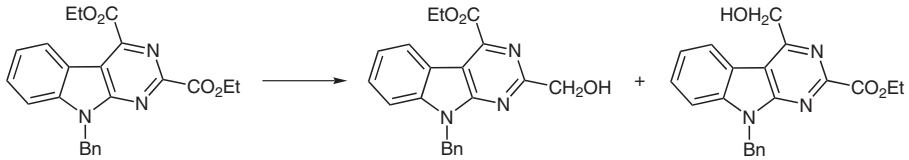
The reduction of **10a** using the Boger conditions preferentially produced one major isomer but the selectivity was moderate (entries 1–3, Table 3). The major isomer was isolated, and unexpectedly all spectral data indicated that it was the C4-reduced product **11b**. The initial structural assignment of **11b** was based on the comparison of ^{1}H NMR spectra between **10a** and **11b**. One of the aromatic peaks in **10a** (δ = 8.88 ppm) was significantly shifted in **11b** (to δ = 8.2 ppm), which was consistent with reduction of the C4 ester since reduction of the C2 ester (compound **11a**) should have minimal effect on the aromatic peaks. Preliminary optimization led to a condition (entry 7, Table 3) that gave compound **11b** in 62% yield. Thus, the two ester groups in compound **10a** could be differentiated with 95% selectivity for the reduction of the C4 ester vs. the C2 ester.



Scheme 4

To determine the structure of **11b** unambiguously, both esters in compound **10a** were reduced to give the diol **12** in excellent yield (Scheme 4). 1D ROESY NMR studies were performed on both compounds **11b** and **12**. Both $HOCH_2$ groups in compound **12** were irradiated in separate 1D ROESY experiments, but only one of them produced a NOE with an aromatic proton (C5–H) and this $HOCH_2$ group was assigned as C4 CH_2OH group. The $HOCH_2$ group in compound **11b** has the same chemical shift as the C4 CH_2OH group in **12**, and it also produced a NOE with an aromatic proton in a 1D ROESY experiment. These results further confirmed the structural assignment for **11b**.

Table 3 Selective Reduction of Diester **10a**[a]



Entry	Conditions	**11a/11b**[b]	Yield of **11b** (%)
1	EtOH, –10 °C, 1 h	1:4.4	NI[c]
2	THF, –10 °C, 1 h	1:2.9	NI[c]
3	*i*-PrOH, –10 °C, 4 h	1:6.8	9
4	EtOH–THF, –10 °C, 2 h	1:10.0	33
5	EtOH–THF, –30 °C, 4 h	1:7.3	NI[c]
6	EtOH–THF, –20 °C, 3.5 h	1:9.5	55
7	EtOH–THF, –20 °C, 24 h[d]	1:18.7	62

[a] All reactions were conducted under anhyd conditions using 2 equiv of $NaBH_4$ except entry 7.
[b] The ratio of compounds **11a** and **11b** was determined by LC-MS analysis;
[c] NI denotes no isolation was performed.
[d] Conditions: 1 equiv of $NaBH_4$ was used.

In summary, 2-aminoindoles **8a–c** were introduced as productive dienophiles in IDA reactions with various 1,3,5-triazines, which produced highly substituted 3-aza-α-carbolines in excellent yields. Unlike most IDA reactions that often require thermal conditions (moderate to elevated temperatures), the 2-aminoindoles **8a–c** are highly reactive, and its IDA reactions proceeded smoothly at room temperature. This methodology represents a new entry to 3-aza-α-carboline synthesis and should complement existing methods to readily access the 3-aza-α-carboline scaffold. Furthermore, the two ester groups of the IDA product **10a** were differentially reduced with 95% selectivity toward the C4 ester group. The application of this new IDA reaction to the synthesis of various 3-aza-mescengrincin analogues and exploration of their neuroprotective activities are in progress and will be reported in due course.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

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