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Inverse Electron Demand Diels-Alder Reactions of Indole IV. A New Route to β–Carbolines

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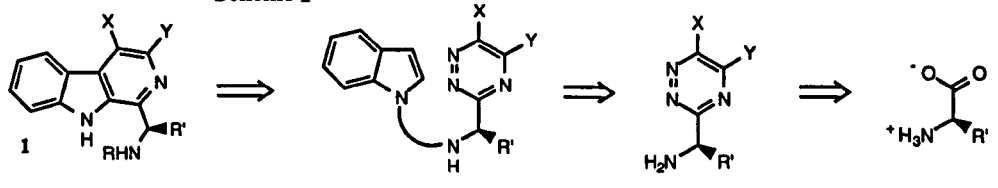
Abstract: β-Carbolines have been prepared by the intramolecular cycloaddition of indole with 1,2,4-triazines tethered from C3 with the indolyl nitrogen using a thiourea linkage. Subsequent to the cycloaddition, reductive cleavage of the thiourea subunit provides the β-carboline.

β-Carbolines are an important class of alkaloids expressing a variety of pharmacologically relevant biological responses.[1] Past syntheses of these molecules have usually relied upon Pictet-Spengler[2] or Bischler-Napieralski[3] strategies to heteroannulate the C-ring onto an existing indole system of tryptamine or tryptophan.[4] While these procedures provide tetrahydro-β-carbolines in excellent yields, aromatization can be capricious and incompatible with ring substituents.[5] As the role of bioactive natural products has evolved from that of drug candidates to that of lead structures for further development, synthetic strategies easily adaptable to the preparation of a variety of analogues are increasingly desirous. A conceptually simple pathway to β-carbolines which accesses a variety of C-ring derivatives employs the cycloaddition of indole with substituted 1,2,4-triazines. Unfortunately, the occurrence of three different regiochemical pathways for this intermolecular chemistry limited the practicality of this approach.[6] Intramolecular cycloadditions of indole with the triazines using a trimethylene tether linking the indole nitrogen and triazinyl C3 positions were successfully used in the syntheses of canthin-6-one alkaloids.[7] We now report preliminary results utilizing a thiourea linkage as a removeable tether to prepare β-carbolines without the canthine D-ring. Our immediate goal was to incorporate an amino acid carboxylate group into the triazinyl C3 position in order to develop a general route to the antileukemic eudistomidin series of marine alkaloids, which possess the basic skeleton **1** (X = Y = H),[8] and their analogues (Scheme 1). To test this strategy with the simplest amino acid, work began with glycine (R' = H).

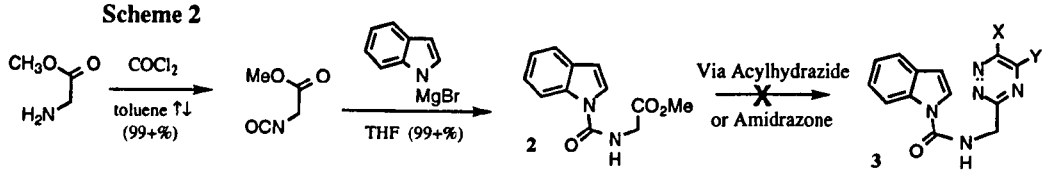
Scheme 1



Initial work focused on a urea tether. Kraus had previously used this linkage to achieve intramolecular cycloadditions between indole and tethered dienes.[9] Preliminary experiments established that the triazine ring could not be constructed from the amino acid carboxylate with the indolylurea linkage already in place (Scheme 2). Attempts to form the urea tethered triazine **3** from indolylurea **2** by converting the ester group to either the

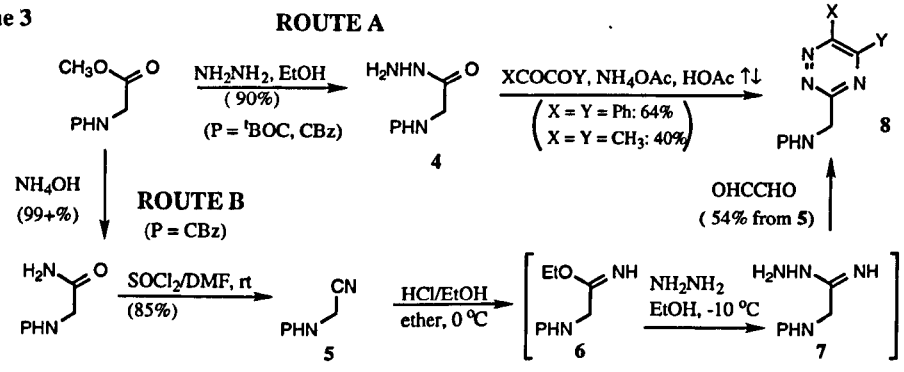
corresponding amidrazone[10] or acyl hydriazide,[11] as previously described in the canthine work, met only with failure due to deacylation of the indole.[12]

Scheme 2



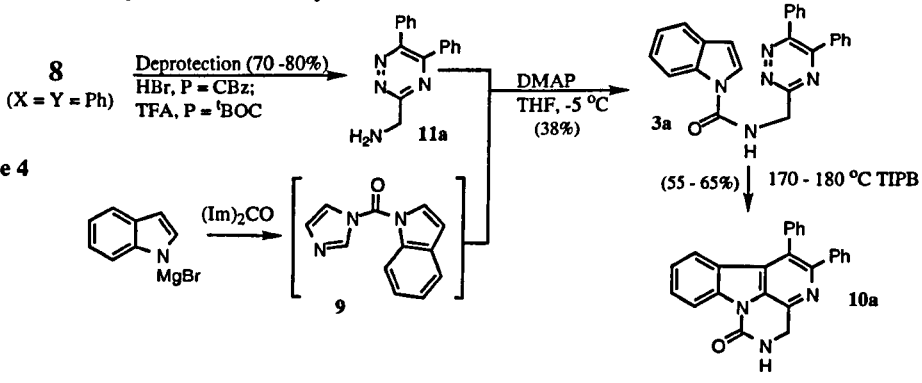
Formation of triazines **8** (X = Y = Ph, CH_3, H) from the protected glycine ester prior to urea linkage proceeded routinely by either the acyl hydrazide **4** or amidrazone **7** in comparable overall yields (Scheme 3, Routes A and B, respectively). In the latter route, the intermediate imidate **6** and amidrazone **7** were carried through to triazine **8** without purification; the sequence from nitrile **5** to **8** proceeding in 54% yield for R = H.

Scheme 3



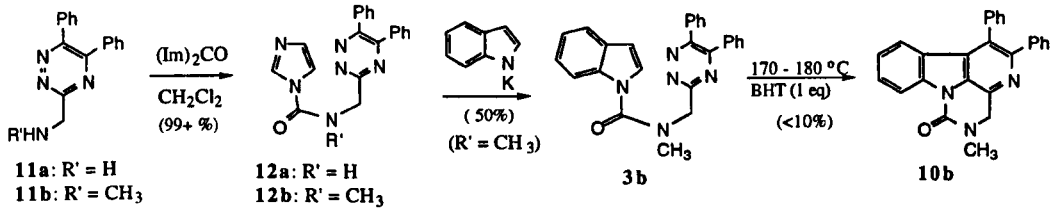
The diphenyl triazine **8**, X = Y = Ph, was used to examine the urea and thiourea linkages due to ease of preparation and isolation. Deprotection of **8** followed by reaction with the unstable indolylimidazolylurea **9**, generated in situ from carbonyl diimidazole[13] (Im_2CO) and indole Grignard salt, gave the desired urea-tethered triazine **3a** albeit in poor yield (38%, Scheme 4). Heating the urea **3a** in triisopropylbenzene (TIPB) produced cycloadduct **10** in 65% yield. The main drawback to this route was the poor yield of the urea-tethered triazine **3a** presumably stemming from the instability of **9**.[14]

Scheme 4



The reverse urea formation, initial acylation of the glycine derived triazines **11a** and **11b** (prepared from Cbz-protected N-methylglycine methyl ester according to Route A, Scheme 3) with carbonyl diimidazole, also met with only limited success (Scheme 5); the stable imidazoylureas **12** were produced in near quantitative yield. Subsequent indolyl urea formation (**12** → **3**) by reaction with the indole potassium salt worked only with N-methylated urea **12b** (50%); all attempts to prepare the corresponding nonmethylated urea-tethered triazine from **12a** failed. In a single trial, heating **3b** in TIPB (170 - 180 °C) produced the cycloadduct **10b** in poor yield (<10%). The addition of 2,6-di-*t*-butyl-4-methylphenol (BHT, 1 eq) did not significantly improve the yield of cycloadduct. While further work undoubtedly would have improved the yield of cycloadduct, the limitation of urea formation to fully N-substituted imidazole ureas such as **12b** led us to examine the thiourea alternative.

Scheme 5



11a: R' = H
11b: R' = CH_3

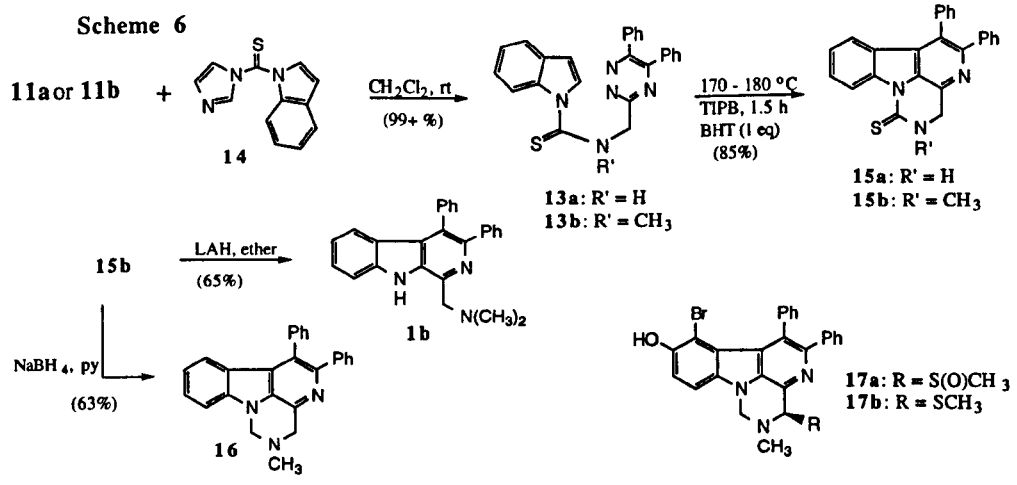
12a: R' = H
12b: R' = CH_3

3b

10b

Thioureas **13** (Scheme 5) were easily prepared in near quantitative yields from the triazines **11** and the stable indolyl-imidazolylurea **14** (prepared from thiocarbonyl 1,1'-diimidazole[13] and one equivalent of indole potassium salt, 85%[15]). Cycloadditions proceeded smoothly in TIPB in the presence of BHT (170 - 180 °C) in excellent yields (minimum 85%) to provide cycloadducts **15**. With adequate quantities of cycloadduct **15b** in hand, cleavage of the thiourea linkage was briefly probed. Reduction of **15b** with LAH[16] gave β-carboline **1b** in 65% yield. Alternatively, $NaBH_4$ reduction in refluxing pyridine[17] reduced the thiocarbonyl yet retains the tetrahydropyrimidine D-ring (**15b** → **16b**, 63%). This latter reduction is of interest due to the recently reported eudistomidins E and F [**17a** and **17b**, respectively) which have the tetrahydropyrimidine D-ring.[18]

Scheme 6



14

13a: R' = H
13b: R' = CH_3

15a: R' = H
15b: R' = CH_3

1b

16

17a: R = $S(O)CH_3$
17b: R = SCH_3

These prelimiary studies with glycine have served to validate the cycloaddition strategy to prepare β-carbolines and indicate the utility of the thiourea grouping to function as a removal tether. Current work is in progress to expand the scope of both the triazine substituents X and Y as well as the amino acid synthon. In particular, initial work with alanine has indicated that triazines analogous to **8** can be prepared by the imidate route (Scheme 3, Route B) without racemization of the chiral center. Triazine preparation from alanine through the acyl hydrazide (Route A, Scheme 3) however leads to complete racemization.

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REFERENCES

1. For reviews of psychopharmacological properties: (a) Gardner, C. R. *Prog. Neurobiol* **1988**, *31*, 425. (b) Allen, M. S.; Tan, Y.-C; Trudell, M. L.; Narayanan, K.; Schindler, L. R.; Martin, M. J.; Schultz, C.; Hagen, T. J.; Koehler, K. F.; Codding, P. W.; Skolnick, P.; Cook, J. M. *J. Med. Chem.* **1990**, *33*, 2343. (c) Dodd, R. H. *Europ. Bull. Cogn. Psychol.* **1992**, *12*, 484.
2. (a) Whaley, W. M.; Govindachari, T. R. *Org. React.* **1951**, *6*, 151. (b) Abramovitch, R. A.; Spenser, I. D. *Adv. Heterocycl. Chem.* **1964**, *3*, 79. (c) Stuart, K.; Woo-Ming, R. *Heterocycles* **1975**, *3*, 223. (d) Ungemach, F.; Cook, J. M. *Heterocycles* **1978**, *9*, 1089.
3. (a) Whaley, W. M.; Govindachari, T. R. *Org. React.* **1951**, *6*, 74. (b) Fodor, G.; Nagubandi, S. *Tetrahedron* **1980**, *36*, 1279. Also, see ref. 2b.
4. Other recently reported routes to β-carbolines: (a) Biere, H.; Russe, R.; Seelen, W. *Liebigs Ann. Chem.* **1986**, 1749. (b) Suzuki, H.; Yokoyama, Y.; Miyagi, C.; Murakami, Y. *Chem. Pharm. Bull.* **1991**, *39*, 2170. (c) Rocca, P.; Marsais, F.; Godard, A.; Queguiner, G. *Tetrahedron* **1993**, *49*, 3325. (d) Dekhane, M.; Dodd, R. H. *Tetrahedron* **1994**, *50*, 6299. (e) Love, B. E.; Raje, P. S. *J. Org. Chem.* **1994**, *59*, 3219. For earlier alternative routes, see ref. 2c.
5. For example: (a) Hamaguchi, F.; Ohki, S. *Heterocycles* **1977**, *8* 383. (b) Soerens, D.; Sandrin, J.; Ungemach, F.; Mokry, P.; Wu, G. S.; Yamanaka, E.; Hutchins, L.; DiPierro, M.; Cook, J. M. *J. Org. Chem.* **1979**, *44*, 535. (c) Murakami, Y.; Takahashi, H.; Nakazawa, Y.; Koshimizu, M.; Watanabe, T.; Yokoyama, Y. *Tetrahedron Lett.* **1989**, *30*, 2099. (d) Van Wagenen, B. C.; Cardellina, J. H. *Tetrahedron Lett.* **1989**, *30*, 3605.
6. Benson, S. C.; Gross, J. L.; Snyder, J. K. *J. Org. Chem.* **1990**, *55* , 3257.
7. (a) Benson, S. C.; Li, J.-H.; Snyder, J. K. *J. Org. Chem.* **1992**, *57*, 5285. (b) Li, J.-H.; Snyder, J. K. *Tetrahedron Lett.* **1994**, *35*, 1485.
8. Kobayashi, J.; Cheng, J.-F.; Ohta, T.; Nozoe, S.; Ohizumi, Y.; Sasaki, T. *J. Org. Chem.* **1990**, *55*, 3666.
9. (a) Kraus, G. A., Raggon, J.; Thomas, P. J.; Bougie, D. *Tetrahedron Lett.* **1988**, *29*, 5605. (b) Kraus, G. A.; Bougie, D.; Jacobsen, R. A.; Su, Y. *J. Org. Chem.* **1989**, *54*, 2425.
10. (a) Kauffman, T.; Spaude, S.; Wolf, D. *Angew. Chem. Int. Ed. Eng.* **1963**, *2*, 217. (b) Kauffman, T.; Spaude, S.; Wolf, D. *Chem. Ber.* **1964**, *97*, 3436. (c) Case, F. H. *J. Org. Chem.* **1965**, *30*, 931.
11. (a) Laasko, P. V.; Robinson, R.; Vandrewala, H. P. *Tetrahedron* **1957**, *1*, 103. (b) Atkinson, C. M.; Cossey, H. D. *J. Chem. Soc.* **1962**, 1805. (c) Taylor, E. C.; French, L. G. *J. Org. Chem.* **1989**, *54*, 1245. (d) Taylor, E. C.; Macor, J. E.; French, L. G. *J. Org. Chem.* **1991**, *56*, 1807.
12. For reviews of 1,2,4-triazine preparations: (a) Neunhoeffer, H. In *Chemistry of 1,2,3-Triazines and 1,2,4-Triazines, Tetrazines, and Pentazines*; 1978, Wiley-Interscience: New York, pp 194 - 220. (b) Neunhoeffer, H. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W.; Boulton, A. J.; McKillop, A., Eds.; Pergamon: Oxford, 1984; Vol. 3, pp 385 - 456.
13. Staab, H. A. *Angew. Chem. Int. Ed. Eng.* **1962** *1*, 351.
14. Attempts to prepare **3a** from carbonyl diindole and **11a** failed
15. In contrast to the urea, this thiourea was stable to chromatography.
16. Larizza, A.; Brancaccio, G.; Lettieri, G. *J. Org. Chem.* **1964**, *29*, 3697.
17. Kikugawa, Y.; Yamada, S. *Tetrahedron Lett.* **1969**, 699.
18. Murata, O.; Shigemori, H.; Ishibashi, M.; Sugama, K.; Hayashi, K.; Kobayashi, J. *Tetrahedron Lett.* **1991**, *32*, 3539.

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