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Synthesis of bis(indole)-1,2,4-triazinones

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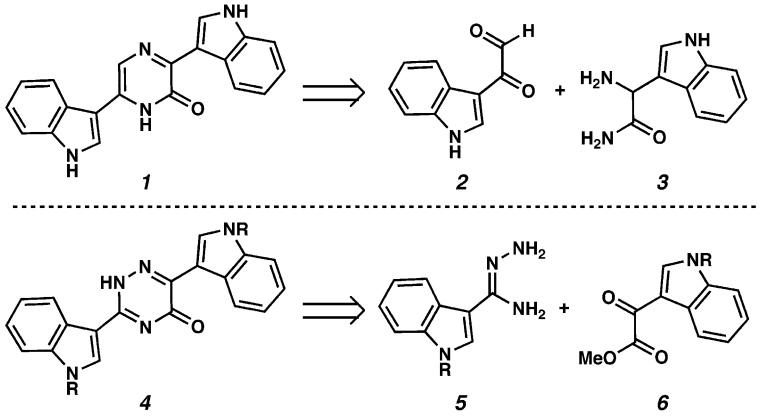
Abstract—A facile method for the synthesis of *para*- and *meta*-substituted bis(indole)-1,2,4-triazinones is presented. Our approach to access these triazinones involves a cyclocondensation reaction between amidrazone and ketoester functionalities. The structures of these interesting compounds were established unambiguously by X-ray crystallography.

Over the past several decades, the search for natural products in marine environments has led to the discovery of a number of biologically active bis(indole) alkaloids.[1] These compounds, as well as many unnatural analogs, have shown promise as leads for the development of novel cancer therapies. In conjunction with an ongoing research program involving the synthesis of bis(indole) natural products, in 2002 we reported a simple method for the preparation of bis(indole)pyrazinone **1**[2] via the cyclocondensation of ketoaldehyde **2** with aminoamide **3** (Scheme 1).[3] We then wondered if a similar approach involving the cyclization of amidrazones (**5**) and ketoesters (**6**) could be used to prepare bis(indole)triazinone derivatives (**4**), which, to the best of our knowledge, have not yet appeared in the literature. Herein, we report the successful implementation of this strategy to access both *para*- and *meta*-substituted bis(indole)triazinone scaffolds.

Although indole-ketoesters are well known in the literature, indole-amidrazones are not. Therefore, our initial goal was to develop a simple synthesis of indole-amidrazones, and then utilize those amidrazones to access bis(indole)triazinones. The preparation of unsubstituted indole-amidrazones turned out to be relatively straightforward (Scheme 2). Beginning from commercially



Scheme 1.

Keywords: Heterocycle synthesis; Triazinone; Bis(indole).
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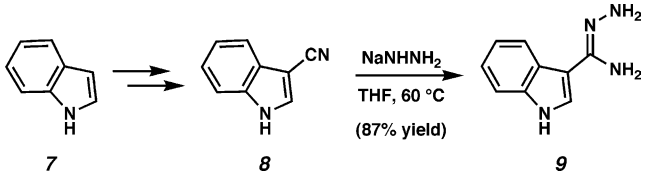
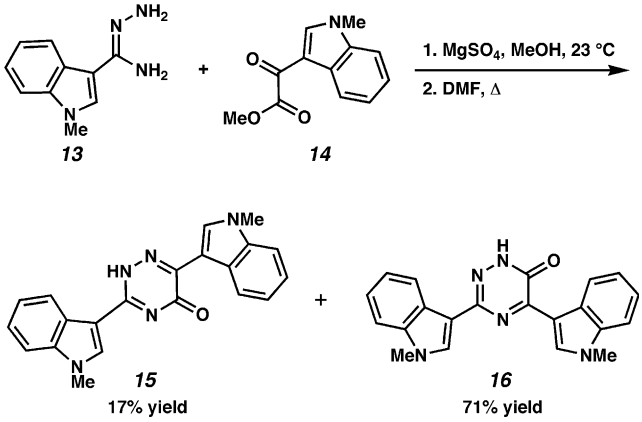


Scheme 2.

available indole (**7**), we were able to access cyanoindole **8** in three steps using a known protocol.[4] Then, simply treating **8** with sodium hydrazide in refluxing THF afforded the desired amidrazone (**9**)[5] in good yield.[6]

In the cyclocondensation reaction, exposure of amidrazone **9** to ketoester **10**[7] in the presence of $MgSO_4$ in methanol,[6] followed by reflux in DMF, afforded the desired *p*-triazinone product (**11**) in 68% yield (Scheme 3). *m*-Triazinone **12** was also formed, although in low yield.[8] After separation by silica gel chromatography, the C–C connectivity of each of the triazinone products (**11** and **12**) was determined by single crystal X-ray diffraction studies.[9]

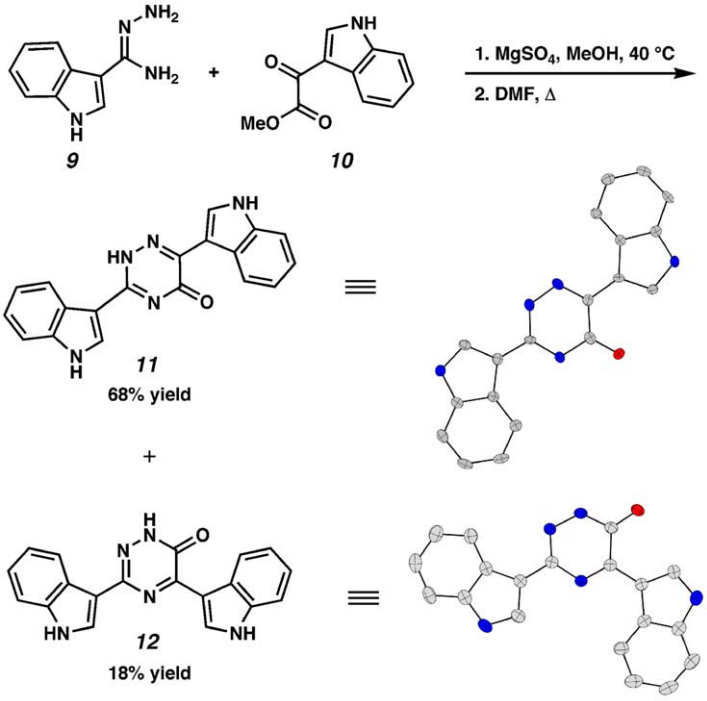
We also prepared the corresponding 1-methylated cyclization starting materials, methylamidrazone **13**[10] and methylketoester **14** (Scheme 4).[11] When these compounds were reacted under similar conditions to those described above, triazinone formation proceeded readily. However, the product distribution favoured *m*-methyltriazinone **16** over *p*-methyltriazinone **15**.[12] This reversal in selectivity is presumably due to the electron donating effect of the *N*-Me group on the ketone functionality of **14**, thereby altering its reactivity.



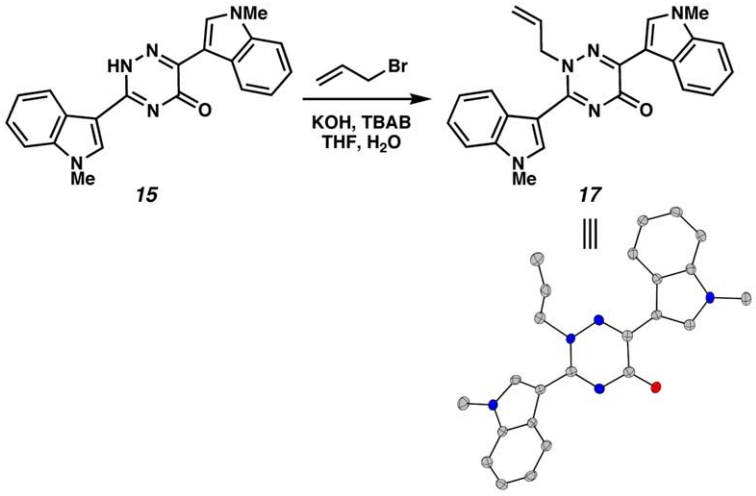
Scheme 4.

Structural assignments for *N*-methyl derivatives **15** and **16** were made by correlating ^{1}H NMR and TLC data with data for the corresponding *N*–H compounds (**11** and **12**, respectively). In addition, *p*-methyltriazinone **15** was treated with allyl bromide under phase transfer conditions to afford allyl derivative **17** (Scheme 5).[13] X-ray diffraction analysis of a single crystal revealed the C–C connectivity of allyl species **17** and confirmed that triazinone **15** was *para*-substituted.[9]

In summary, we have developed a facile approach to prepare bis(indole)triazinones via cyclocondensation reactions between indole-amidrazones and indole-ketoesters. By altering the protective group on the indole nitrogen, it is possible to favour either *para*- or *meta*-substituted products. Biological evaluation of the bis(indole)triazinone products is currently underway.



Scheme 3.



Scheme 5.

Acknowledgements

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References and notes

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2. Pyrazinone **1** was evaluated by the National Cancer Institute, and was shown to display strong inhibitory effects against a variety of tumor cell lines. See: Jiang, B.; Gu, X.-H. *Bioorg. Med. Chem.* **2000**, *8*, 363–371.
3. Garg, N. K.; Sarpong, R.; Stoltz, B. M. *J. Am. Chem. Soc.* **2002**, *124*, 13179–13184.
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5. To a suspension of NaH (60% dispersion in mineral oil, 167 mg, 4.16 mmol) in Et_2O (3.5 mL) at 0 °C was added anhydrous hydrazine (131 μL, 4.15 mmol). After stirring for 1 h, a solution of cyanoindole **8**[4] (200 mg, 1.39 mmol) in THF (7 mL) was added dropwise over 10 min. The reaction mixture was heated to 60 °C for 6 h, cooled to 23 °C, quenched by the addition of H_2O (5 mL), and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (15 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was triturated with Et_2O (2 mL) and dried under vacuum to afford amidrazone **9** (213 mg, 87% yield), which was used immediately in the subsequent reaction. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.10 (br s, 1H), 8.15 (d, J = 7.7 Hz, 1H), 7.69 (s, 1H), 7.33 (d, J = 8.1 Hz, 1H), 7.10–7.03 (m, 1H), 7.01–6.93 (m, 1H), 5.48 (br s, 2H), 4.83 (br s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 145.3, 136.3, 124.8, 123.6, 122.2, 121.2, 119.0, 111.3, 111.1.
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7. Faul, M. M.; Winneroski, L. L.; Krumrich, C. A. *J. Org. Chem.* **1999**, *64*, 2465–2470.
8. To crude amidrazone **9** (100 mg, 0.568 mmol) and $MgSO_4$ (171 mg, 1.42 mmol) in MeOH (2 mL) at 23 °C was added a solution of ester **10** (105 mg, 0.516 mmol) in MeOH (5 mL). The reaction mixture was heated to 40 °C for 24 h, then cooled to 23 °C. After removal of solvent under vacuum, DMF (5 mL) was added. The resulting suspension was refluxed for 24 h, then cooled to 23 °C. The solvent was removed under vacuum and the crude product was purified by flash column chromatography (1:1 hexanes/EtOAc eluent) to afford *p*-triazinone **11** (115 mg, 68% yield) and *m*-triazinone **12** (30 mg, 18% yield) as yellow solids. For **11**, suitable crystals for X-ray diffraction were grown by the slow diffusion of hexanes into a saturated solution of **11** in DMF/MeOH (1:1). For **12**, single crystals suitable for X-ray diffraction were obtained by the slow diffusion of hexanes into a saturated solution of **12** in MeOH. *p*-Triazinone **11**: R_f 0.28 (4:1 EtOAc/hexanes); mp > 250 °C dec; ^{1}H NMR (500 MHz, DMSO-d_6): δ 13.66 (br s, 1H), 12.03 (s, 1H), 11.67 (s, 1H), 8.83 (s, 1H), 8.52 (d, J = 7.6 Hz, 1H), 8.50–8.45 (m, 1H), 8.44 (d, J = 2.5 Hz, 1H), 7.55–7.51 (comp. m, 2H), 7.28–7.17 (comp. m, 4H); ^{13}C NMR (125 MHz, DMSO-d_6, 16/19 C): δ 136.7, 136.3, 131.6, 129.0, 125.3, 125.2, 122.7, 122.3, 122.1, 121.9, 121.1, 120.5, 112.2, 112.0, 108.1, 106.2; IR (film) 3350, 1520, 1421, 1187 cm^{-1}; HRMS-FAB (*m/z*): $[M+H]^+$ calcd for $C_{19}H_{14}N_5O$, 328.1198; found, 328.1185. *m*-Triazinone **12**: R_f 0.61 (4:1 EtOAc/hexanes); mp > 250 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.12 (s, 1H), 12.13 (s, 1H), 11.54 (s, 1H), 9.12 (d, J = 2.9 Hz, 1H), 8.77 (d, J = 7.3 Hz, 1H), 8.26 (d, J = 7.7 Hz, 1H), 8.14 (d, J = 2.6 Hz, 1H), 7.60–7.47 (comp. m, 2H), 7.39–7.26 (comp. m, 2H), 7.25–7.12 (comp. m, 2H).
9. Molecular structures are shown with 50% probabililty ellipsoids and hydrogen atoms have been omitted for clarity. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number; *p*-triazinone **11**: 259291; *m*-triazinone **12**: 161494; allyl triazinone **17**: 259195.
10. Methylamidrazone **13** was prepared in a manner analogous to the preparation of **9**. To a suspension of NaH (60% dispersion in mineral oil, 779 mg, 19.48 mmol) in Et_2O (16.2 mL) at 0 °C was added anhydrous hydrazine

(611 μL, 19.48 mmol). After stirring for 1 h, a solution of *N*-methyl-3-cyanoindole (910 mg, 6.49 mmol) in THF (32.5 mL) was added dropwise over 10 min. The reaction mixture was heated to 60 °C for 6 h, cooled to 23 °C, quenched by the addition of H_2O (17 mL), and extracted with EtOAc (4 × 25 mL). The combined organic extracts were washed with brine (2 × 25 mL), dried over $MgSO_4$, and evaporated under reduced pressure to afford crude amidrazone **13** (880 mg, 79% yield), which was used immediately in the subsequent reaction without further purification. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.16 (d, J = 8.0 Hz, 1H), 7.65 (s, 1H), 7.39 (d, J = 8.2 Hz, 1H), 7.18–7.11 (m, 1H), 7.07–6.99 (m, 1H), 5.43 (br s, 2H), 4.81 (br s, 2H), 3.76 (s, 3H).

11. Faul, M. M.; Winneroski, L. L.; Krumrich, C. A. *J. Org. Chem.* **1998**, *63*, 6053–6058.
12. To crude amidrazone **13** (65 mg, 0.378 mmol) and $MgSO_4$ (159 mg, 1.32 mmol) in MeOH (2 mL) at 23 °C was added a solution of ester **14** (75 mg, 0.343 mmol) in MeOH (3.4 mL). The reaction mixture was stirred at 23 °C for 24 h. After removal of solvent under vacuum, DMF (5 mL) was added. The resulting suspension was refluxed for 24 h, then cooled to 23 °C. The solvent was removed under vacuum and the crude product was purified by flash chromatography (1:1 hexanes/EtOAc eluent) to afford *p*-bis(methyl)triazinone **15** (20 mg, 16% yield) as a yellow solid and impure *m*-bis(methyltriazinone) **16**. The crude *m*-triazinone was repurified by flash chromatography (1:1 hexanes/EtOAc eluent) to afford pure **16** (86 mg, 71% yield) as a yellow solid. *p*-Bis(methyl)triazinone **15**: R_f 0.10 (1:1 hexanes/EtOAc); mp > 250 °C dec; ^{1}H NMR (500 MHz, DMSO-d_6): δ 13.60 (br s, 1H), 8.79 (s, 1H), 8.57–8.49 (comp. m, 2H), 8.34 (s, 1H), 7.60–7.52 (comp. m, 2H), 7.33–7.20 (comp. m, 4H), 3.91 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6, 19/21 C): δ 153.9, 137.2, 136.8, 135.1, 132.5, 125.9, 125.7, 122.6, 122.4, 122.2, 122.1, 121.1, 120.6, 110.5, 110.1, 107.6, 106.3, 33.3, 32.9; IR (film) 3600, 1567, 1539, 1370 cm^{-1}; HRMS-FAB (*m*/*z*): $[M+H]^+$ calcd for $C_{21}H_{18}N_5O$, 356.1511; found, 356.1520. *m*-Bis(methyl)triazinone **16**: R_f 0.43 (1:1 hexanes/EtOAc); mp > 250 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.15 (br s, 1H), 9.14 (s, 1H), 8.83 (d, J = 7.3 Hz, 1H), 8.28 (d, J = 7.8 Hz, 1H), 8.14 (s, 1H), 7.62 (d, J = 7.0 Hz, 1H), 7.54 (d, J = 7.7 Hz, 1H), 7.47–7.32 (comp. m, 2H), 7.31–7.16 (comp. m, 2H), 3.96 (comp. m, 6H); ^{13}C NMR (75 MHz, DMSO-d_6, 20/21 C): δ 157.7, 153.2, 148.0, 140.0, 137.6, 137.2, 131.4, 126.3, 124.9, 123.2, 122.4, 122.1, 121.6, 120.3, 111.2, 110.7, 110.3, 109.2, 33.3, 32.9; IR (film) 3600, 1646, 1465, 1373 cm^{-1}; HRMS-FAB (*m*/*z*): $[M+H]^+$ calcd for $C_{21}H_{18}N_5O$, 356.1511; found, 356.1521.
13. To *p*-triazinone **15** (25 mg, 0.070 mmol) in THF at 23 °C, was added allyl bromide (6.7 μL, 0.078 mmol), H_2O (150 μL), powdered KOH (20 mg, 0.35 mmol), and tetrabutylammonium bromide (0.2 mg, 0.0007 mmol) in H_2O (10 μL). The resulting solution was stirred for 24 h, diluted with H_2O (5 mL), and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and evaporated under reduced pressure to afford allyl triazinone **17** (17 mg, 61% yield). Single crystals suitable for X-ray diffraction were obtained by the slow diffusion of hexanes into a saturated solution of **17** in acetone. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.85 (s, 1H), 8.42 (d, J = 7.7 Hz, 1H), 8.14 (d, J = 8.1 Hz, 1H), 8.02 (s, 1H), 7.62–7.51 (comp. m, 2H), 7.37–7.18 (comp. m, 4H), 6.30–6.15 (m, 1H), 5.400–5.28 (comp. m, 2H), 5.07 (d, J = 5.1 Hz, 2H), 3.92 (s, 3H), 3.91 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 160.3, 154.4, 145.6, 136.9, 136.6, 136.0, 133.3, 133.2, 126.4, 125.8, 122.6, 122.5, 122.4, 121.2, 121.1, 121.0, 118.3, 110.6, 110.3, 106.4, 105.8, 58.3, 33.1, 33.0.