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Lewis Acid Mediated Addition of Indoles and Alcohols to Tetronic Acid and Tetramic Acids

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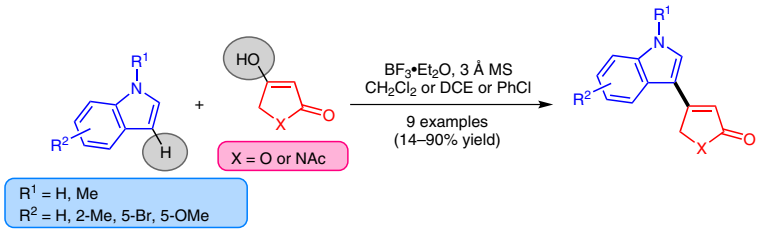

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Abstract The electrophilic substitution of indoles with tetronic acid and *N*-acetyltetramic acid mediated by $BF_3{\cdot}OEt_2$ was investigated. This strategy allowed for the preparation of nine indole-substituted furan-2-ones (indolyl-γ-lactones) and 3-pyrrolin-2-ones (indolyl-γ-lactams) and is more straightforward than previously reported synthetic methods. During the course of our investigation, we also discovered a facile synthesis of tetronates and a tetramate via a BF_3-mediated addition of alcohols to tetronic acid and *N*-acetyltetramic acid, respectively.

Key words lactams, lactones, indoles, heterocycles, cycloadditions

Indolylmaleimides (parent = **1**)[1,2] and indolylmaleic anhydrides (parent = **2**)[2] are heterocyclic molecules that have interesting physical properties, reactivity, and utility in the preparation of polycyclic heterocycles (Figure 1). Indolylmaleimides have been used as a structural platform to study chemiluminescence and fluorescence.[3] A bromo-substituted indolylmaleimide demonstrated antibacterial activity,[4] while chloro-substituted indolylmaleimides showed anticancer activity.[5] The Diels–Alder reactivity of **1** and **2** and substituted variants have been exploited in the preparation of a variety of biologically active heterocycles.[1,2]

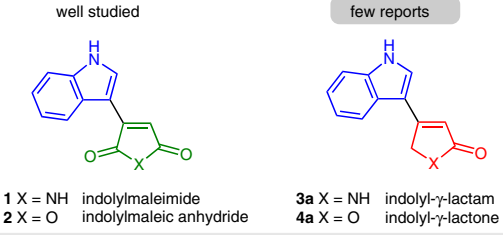
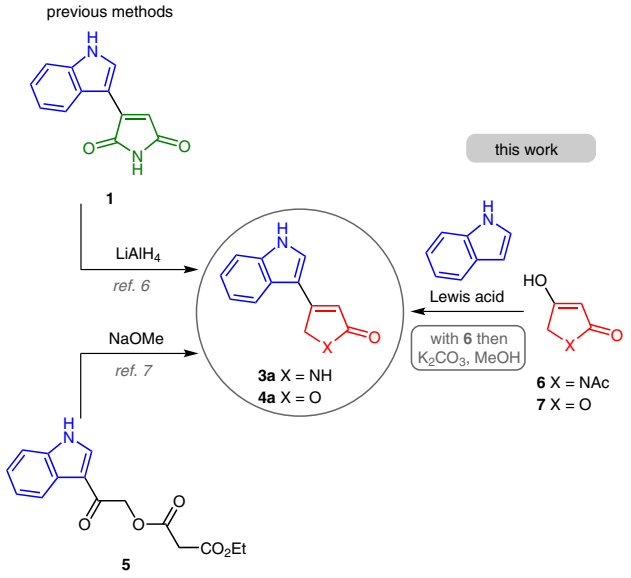


Figure 1 Structures of indolyl-substituted heterocycles

Much less attention has been given to the corresponding monocarbonyl γ-lactams (e.g., **3a**)[6] and γ-lactones (e.g., **4a**).[7] To our knowledge, there is just one reported synthesis of **3a**. Prudhomme and co-workers studied the reduction of **1** with various reducing agents.[6] Lactam **3a** was the major product when **1** was treated with $LiAlH_4$. Baron and co-workers reported the synthesis of furanone **4a** via the Dieckmann condensation of 3-acylindole **5**.[7] Given the lack of synthetic methods, it is not surprising that neither the biological activity nor the cycloaddition chemistry of **3** or **4** has ever been reported.

In continuation of our work aimed at the synthesis of aryl-substituted 3-pyrrolin-2-ones[8] and aryl-fused 3-pyrrolin-2-ones,[9] we became interested in developing a new approach to **3** and **4**. We hypothesized that these materials could be obtained directly by treating the corresponding tetramic acids and tetronic acids with indole nucleophiles in the presence of a Lewis acid (Scheme 1). Lobo and Prabhakar and co-workers reported a single example of an indole substitution reaction involving a tetramic acid and 2,2′-biindole, which was mediated by $BF_3{\cdot}OEt_2$.[10–12] This transformation proceeds via a Lewis acid mediated addition–elimination of the hydroxy moiety of the tetramic acid with the indole nucleophile.[13] The use of tetramic acids and tetronic acids as electrophiles would also further build on the work of others who have investigated the electrophilic substitution of other 1,3-dicarbonyl electrophiles with indoles in the presence of transition metals,[14] Lewis acids,[15] and Brønsted acids.[16]

We started this work by systematically studying the BF_3-mediated arylation of commercially available tetronic acid (**7**) and *N*-methylindole (**8b**). We charged a 20 mL vial fitted with a Teflon cap with a stir bar, **7**, **8b**, and a solvent. $BF_3{\cdot}OEt_2$ was then added, and the reaction mixtures were either stirred at room temperature or heated at the specified temperatures as noted (Table 1). We estimated the rela-



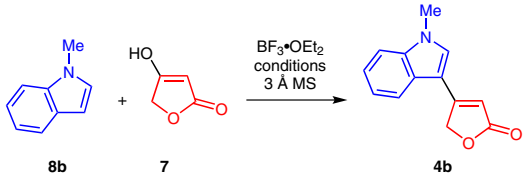
Scheme 1 Synthetic approaches to indolyl-substituted heterocycles

tive conversion of each reaction by analysis of the relative integrations of the methylene protons in the crude ^{1}H NMR spectra (δ = 4.65 ppm for **7** vs. δ = 5.34 ppm for **4b** in DMSO-d_6). In selected cases, we repeated the reaction conditions two to four times and purified the reaction mixtures by flash chromatography to determine the isolated yields.

The indolylation reaction worked well and was amenable to improvement (Table 1). Running the reaction in CH_2Cl_2 for 30 minutes at room temperature led to a 42% relative conversion of starting material to product (Table 1, entry 1). The isolated yield using these reaction conditions proved to be 38%, which indicates that the relative conversion we determined using ^{1}H NMR analysis of the crude mixture is a good predictor of the efficacy of the reaction. Running the reaction for longer periods of time (Table 1, entry 2) or at 40 °C (Table 1, entry 3) improved the relative conversion to 84% and 73%, respectively. Running the reaction at 40 °C for four hours (Table 1, entry 5) elevated the relative conversion to 100%; these conditions then gave an isolated yield of 77% (average of four runs).[17,18] Running the reaction in other chlorinated solvents at 65 °C, 1,2-dichloroethane (DCE) and chlorobenzene (PhCl), also allowed for full conversion (Table 1, entries 8 and 14). Isolated yields in DCE and PhCl conditions were 90% and 87%, respectively. A longer reaction time in PhCl led to a slight erosion in the isolated yield (Table 1, entry 15). Non-chlorinated solvents, tetrahydrofuran (THF) and toluene (PhMe), gave incomplete conversions over the same range of temperatures and times. We briefly investigated the effect of leaving out the molecular sieves (Table 1, entry 6), and we found a slight erosion of the yield. This result surprised us as earlier experiments in a related system suggested that molecular sieves were necessary for an efficient reaction.[11]

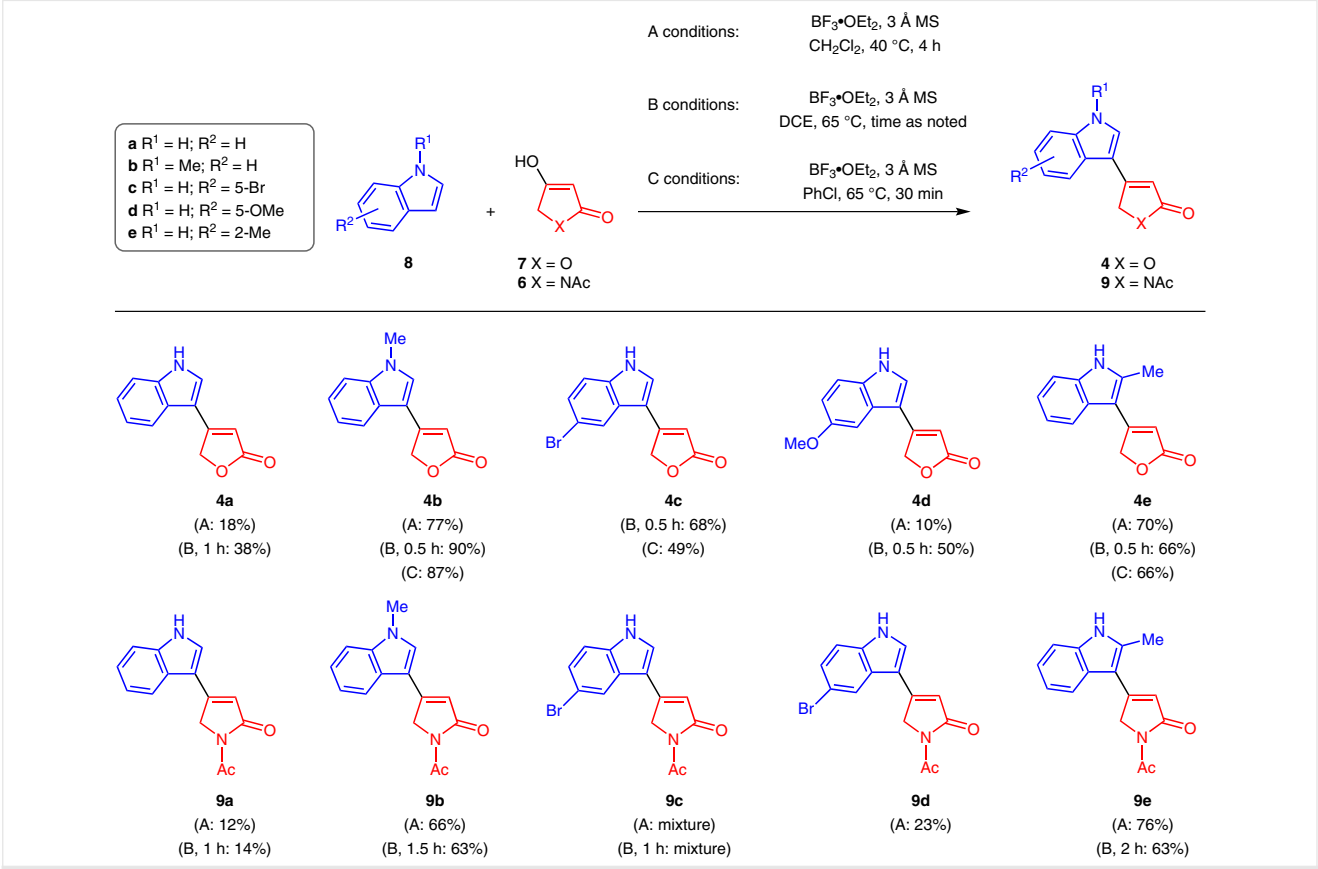
We next explored the scope of the reaction using different indole nucleophiles and using both tetronic acid (**7**) and known *N*-acetyltetramic acid (**6**)[19] as electrophiles (Scheme 2). To help with systematic comparisons, we chose to use three different reaction conditions: (A) CH_2Cl_2, 40 °C, 4 h; (B) DCE, 65 °C, time as noted; (C) PhCl, 65 °C, 30 min. With tetronic acid (**7**) as the electrophile, good yields (>65% yield) were obtained with *N*-methylindole (**8b**), 2-methylindole (**8e**), and 5-bromoindole (**8c**). Lower yields were obtained with indole (**8a**) and 5-methoxyindole (**8d**). We observed that the choice of reaction conditions made a significant difference in the yields with the latter two indole substrates; DCE at 65 °C often proved to be better than CH_2Cl_2 at 40 °C.

Table 1 Screen of Reaction Conditions



Entry	Solvent	Temp (°C)	Time (h)	Conv. (%)[a]	Isolated yield (%)[b]
1	CH_2Cl_2	r.t.	0.5	42	38
2	CH_2Cl_2	r.t.	4	84	–
3	CH_2Cl_2	40	0.5	73	–
4	CH_2Cl_2	40	2	86	–
5	CH_2Cl_2	40	4	100	77
6[c]	CH_2Cl_2	40	4	–	71
7	DCE	40	0.5	82	–
8	DCE	65	0.5	100	90
9	THF	40	0.5	22	–
10	THF	40	2	20	–
11	THF	65	0.5	39	–
12	PhMe	40	0.5	57	–
13	PhMe	65	0.5	88	–
14	PhCl	65	0.5	100	87
15	PhCl	65	2	–	80

[a] Determined by ^{1}H NMR analysis of **4b**/**7** ratio (average of 2+ runs).
[b] 1.0 mmol scale (average of 2+ runs).
[c] No molecular sieves added.

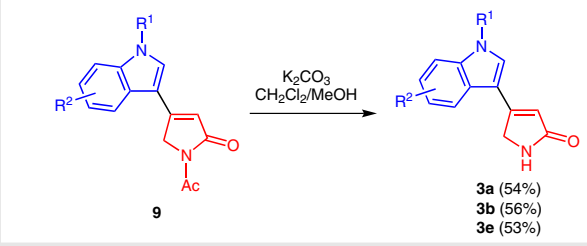


Scheme 2 Reaction scope for Lewis acid mediated indole-substitution of tetronic acid (**7**) and tetramic acid (**6**)

Moving on to tetramic acid **6** as the electrophile, the reactions leading to 3-pyrrolin-2-ones **9** tended to be lower yielding than the corresponding reactions with tetronic acid (**7**) leading to furan-2-ones **4**. For example, the yield was 66% for the preparation of **9b** compared to 77% for **4b** under the identical conditions (CH_2Cl_2, 40 °C, 4 h). Potentially, the lower yields can be explained by the lower electrophilicity of **6** and/or by the fact that the acetyl group has the potential to partially fall off during the reaction. Analysis of crude reaction mixtures did reveal that small amounts of deprotected products **3** were being formed (methylene protons δ = 4.5 ppm). Using **6** and indole (**8a**), the highest yield obtained was just 14%. The reaction of **6** with 5-bromoindole (**8c**) led to an inseparable mixture of materials that we believe to be indole substitution regioisomers. Further regarding the reactions between **6** and **8c**, we consistently observed and were able to isolate a relatively nonpolar byproduct. We will return to this result later in the discussion.

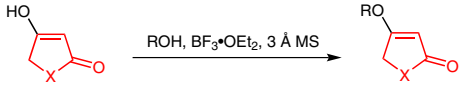
We next pursued the synthesis of the *N*-unsubstituted 3-pyrrolin-ones **3** starting from the *N*-acetyl-3-pyrrolin-2-ones **9** (Scheme 3). Treatment of **9** with K_2CO_3 in 1:1 CH_2Cl_2–MeOH smoothly gave the corresponding deprotected 3-pyrrolin-2-ones **3** in moderate yields (53–56%). We did not attempt to improve upon the reaction.

As mentioned earlier in the case of the reaction between **6** and **8c**, we observed the formation of a nonpolar byproduct. We determined that the byproduct was the known methyl tetramate, *N*-acetyl-4-methoxy-3-pyrrolin-2-one (**10**).[20] This material was obtained in about ca. 10% yield in this case[21] and arose from the BF_3-mediated addition of methanol to tetramic acid; methanol was introduced to the reaction mixture as part of the workup. This result struck us as having potential for providing a mild and direct approach to alkyl tetronates and alkyl tetramates from the corresponding tetronic acids and tetramic acids.



Scheme 3 Deprotection of *N*-acetyltetramic acids

Table 2 Synthesis of Tetronates **10** and Tetramate **11**



6 X = NAc
7 X = O

10 X = NAc
11 X = O

Entry	Starting material	Solvent	Temp (°C)	Time (h)	R	Product	Yield (%)[a]
1	**6**	CH_2Cl_2	40	4	Me	**10**	35
2	**7**	CH_2Cl_2	40	4	Me	**11a**	50
3	**7**	CH_2Cl_2	40	4	*i*-Pr	**11b**	69
4	**7**	CH_2Cl_2	40	4	Bn	**11c**	54
5	**7**	CH_2Cl_2	40	4	4-$MeOC_6H_4$	**11d**	0
6	**7**	PhCl	100	2	4-$MeOC_6H_4$	**11d**	4
7	**7**[b]	PhCl	100	2	4-$MeOC_6H_4$	**11d**	17

[a] Isolated yield.
[b] Used 3.0 equiv of BF_3·OEt_2.

Examination of the literature revealed three common methods for preparing alkyl tetramates from tetramic acids: treatment with diazomethane (to methyl tetronates);[22] treatment with base followed by alkyl halides;[23] and via the Mitsunobu reaction.[24] Similarly, there are three general methods for preparing alkyl tetronates from tetronic acids: treatment with diazomethane;[25] treatment with base followed by alkyl halides;[26] and via the Mitsunobu reaction.[27] There also is a report by Zimmer and co-workers of the use of a Brønsted acid (H_2SO_4) to promote the condensation of acids with tetronic acid (**7**).[28] In their report, isopropyl alcohol gave the best yield (65%) of the corresponding tetronate and benzyl alcohol gave the lowest yield (11%).

We briefly investigated the use of BF_3·OEt_2 in the transformation of tetramic acid (**6**) and tetronic acid (**7**) into alkyl tetramates and alkyl tetronates (Table 2). We chose to run the reactions in CH_2Cl_2 at 40 °C for four hours. With tetramic acid (**6**) and methanol, we obtained a 35% yield of **10** (Table 2, entry 1). Higher yields of alkyl tetronates were obtained with tetronic acid (**7**) and methanol (50%, Table 2, entry 2), isopropanol (69%, Table 2, entry 3), and benzyl alcohol (54%, Table 2, entry 4). The result with benzyl alcohol is a significant improvement over the literature yield with H_2SO_4. On the other hand, the reaction failed with *p*-methoxyphenol as the nucleophile under the standard reaction conditions (CH_2Cl_2, 40 °C). When we ran the reaction in PhCl at 100 °C, we did manage to obtain a 4% yield of the desired aryl tetronate **11d** (Table 2, entry 6). It is notable that the preparation of **11d** would not be possible using standard alkylation or Mitsunobu conditions. Finally, the yield of **11d** was improved to 17% when the number of equivalents of BF_3·OEt_2 was increased from 1.5 to 3.0 (Table 2, entry 7).

In conclusion, we have demonstrated a one-step transformation of tetronic acids and tetramic acids into indolyl-substituted furan-2-ones and 3-pyrrolin-2-ones, respectively. During the course of our work, we also discovered a facile transformation of tetronic acids and tetramic acids into alkyl tetronates and alkyl tetramates. These two types of reactions make use of a BF_3-mediated substitution of the latent ketone functionality of tetronic and tetramic acids by indole and alcohol nucleophiles, respectively. This work provides direct access to indolyl-γ-lactones, and indolyl-γ-lactams, alkyl tetronates, and alkyl tetramates from readily available starting materials, tetronic acids and tetramic acids.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588335.

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(17) **General Procedure**
A reaction vial fitted with a septa-bonded cap was charged with a stir bar, indole **8** (1.00 mmol or 1.20 mmol), tetronic acid (**7**, 1.00 mmol) or tetramic acid (**6**, 1.00 mmol), and anhydrous solvent (10 mL) as noted. Neat $BF_3{\cdot}OEt_2$ (185 µL, 1.50 mmol) was added through the septum via syringe. The reaction vial was heated to the specified temperature for the specified time and then allowed to cool to r.t. MeOH (1 mL) was added to the reaction mixture, and the solvent was removed in vacuo. The crude materials obtained were purified by flash chromatography (EtOAc–PE).

(18) Compound **4b** (0.194 g, 0.910 mmol, 91% yield): white powder; mp 204–205 °C. IR (ATR, neat): 1717 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 8.01 (s, 1 H), 7.92–7.94 (m, 1 H), 7.57–7.59 (m, 1 H), 7.30–7.34 (m, 1 H), 7.22–7.26 (m, 1 H), 6.40 (t, *J* = 1.6 Hz, 1 H), 5.34 (d, *J* = 1.6 Hz, 2 H), 3.86 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.6, 158.7, 138.0, 130.2, 126.0, 123.8, 122.4, 120.5, 110.6, 107.5, 107.2, 71.5, 33.8. HMRS (ESI-FTICR): *m/z* calcd for $C_{13}H_{11}NO_2{\cdot}Na$: 236.0682; found: 236.0679.

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