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Synthesis of a novel series of tetra-substituted furan[3,2-*b*]pyrroles

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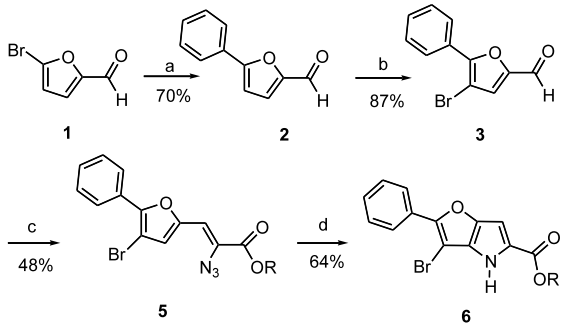
Abstract—Furan[3,2-*b*]pyrroles are important isosteres for the indole scaffold in which the benzene ring is replaced by the furan ring. A series of novel tetra-substituted furan[3,2-*b*]pyrroles was synthesized from a simple furaldehyde. The divergent synthesis allows for substitution on multiple positions on the scaffold, creating the potential for the formation of large libraries.

Furan[3,2-*b*]pyrroles are isosteres for the indole ring system in which the benzene ring is replaced by the furan ring. Efficient synthetic routes to these heterocycles are of great interest,[1] as the core scaffold has been found in compounds with diverse biological activities, including analgesic,[2] anti-inflammatory,[2] and anti-allergy[3] activities. The furan[3,2-*b*]ring system is electron-rich, and amenable to multiple chemical reactions.[4] These scaffolds are ideal for synthesis of a large library of compounds, as they contain five potential diversity sites. Herein we describe a synthesis of the core scaffold, along with the formation of a small series of diverse compounds. One attractive feature of this synthetic method is its use of simple commercially available starting materials.

Our synthesis of the furo[3,2-*b*]pyrrole scaffold began with commercially available 5-bromo-furan-2-carbaldehyde (**1**), which was converted into 5-phenyl-furan-2-carbaldehyde (**2**) through Suzuki coupling.[5] Bromination with NBS in acetonitrile led exclusively to the desired isomer[6] (**3**) in good yield. The furo[3,2-*b*]pyrrole ring system was formed through a modified Hemetsberger indole synthesis,[7] in which the furan ring replaces the more typical phenyl ring. Condensation with methyl or ethyl azidoacetate[8] (**4**) in the presence of sodium methoxide or ethoxide gave the azide (**5**), which led to the desired furo [3,2-*b*]pyrrole (**6**) upon thermolysis[9,10] (Scheme 1).

To elaborate on this core scaffold, **6** was subjected to a Suzuki coupling with 4-chlorophenylboronic acid to form **7**. At this point, it was desired to incorporate diversity at the pyrrole nitrogen. Compound **7** was treated with a variety of alkylating agents to afford **8a–j** (Table 1). Finally, these esters were saponified to the corresponding acids (**9a–j**) (Scheme 2).



Scheme 1. *Reagents and conditions*: (a) Phenylboronic acid (2.0 equiv.), $Pd(PPh_3)_4$ (0.02 equiv.), Na_2CO_3 (2.5 equiv.), toluene/EtOH (6/1), 80°C, 2 h; (b) NBS (1.1 equiv.), acetonitrile, rt, 16 h; (c) ethyl azidoacetate (8.0 equiv.), Na (4.0 equiv.), EtOH, 0°C, 2 h; (d) toluene reflux, 16 h.

Alternatively, it was found that the order of reactions may be reversed, with the nitrogen alkylation performed prior to the second Suzuki reaction. This allows diversity in the 3 position while keeping the 4 position constant. In this way, compounds **11a** and **11b** were synthesized (Scheme 3). The esters were saponified in the same manner as in the previous scheme.

Extension of the Suzuki couplings to heterocyclic rings allowed for greater diversity in the 3-position. Com-

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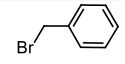
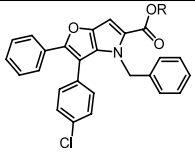
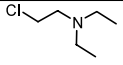
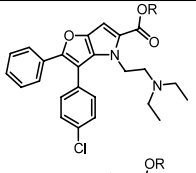
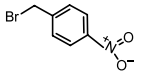
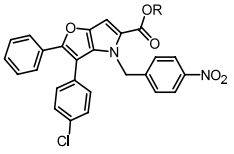
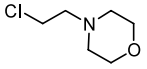
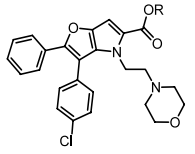
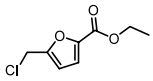
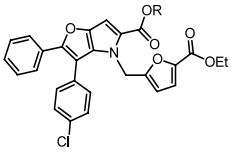
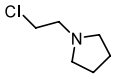
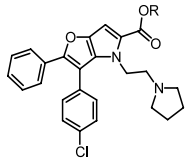
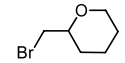
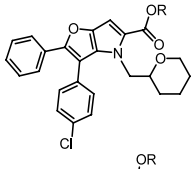
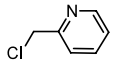
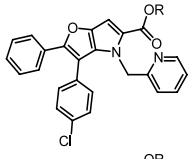
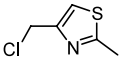
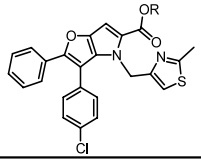
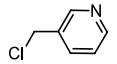
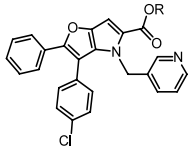
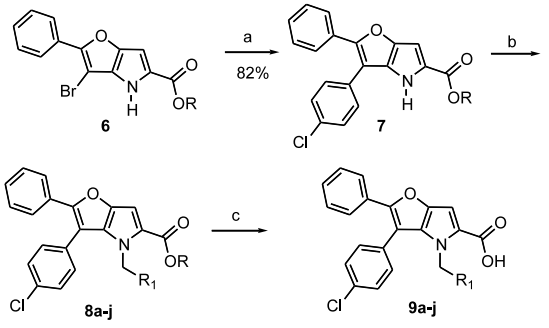
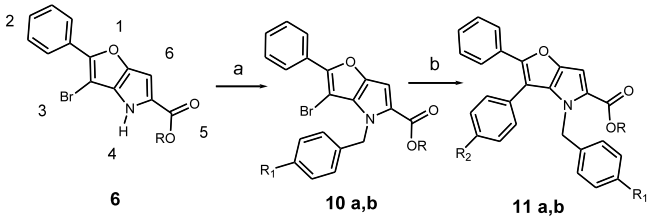
Table 1. Reaction of furo[3,2-*b*]pyrrole scaffold with alkylating agents

Cmpd #	Alkylating Agent	Product	Yield	Cmpd #	Alkylating Agent	Product	Yield
8a			73	**8f**			16
8b			81	**8g**			56
8c			87	**8h**			9
8d			16	**8i**			16
8e			44	**8j**			44



Scheme 2. *Reagents and conditions*: (a) 4-Chlorophenyl boronic acid (2.0 equiv.), $Pd(PPh_3)_4$ (0.02 equiv.), Na_2CO_3 (2.5 equiv.), toluene/EtOH (6/1); (b) alkyl bromide or chloride, (2.0 equiv.), NaH, (2.0 equiv.), NaI (2.0 equiv.), 60°C, 16 h; (c) NaOH, EtOH, 50°C, 4 h.



Scheme 3. *Reagents and conditions*: (a) Alkyl bromide or chloride (2.0 equiv.), NaH (2.0 equiv.), NaI (2.0 equiv.), 60°C, 16 h; (b) phenylboronic acid (2.0 equiv.), $Pd(PPh_3)_4$ (0.02 equiv.), Na_2CO_3 (2.5 equiv.), toluene/EtOH (6/1). **10a**, **11a**: R_1 = Cl, R_2 = Cl, **10b**, **11b**: R_1 = H, R_2 = H. Yields: **10a** = 44%, **10b** = 77%, **11a** = 79%, **11b** = 78%.

pounds **12**–**14** are examples of heterocycles at the 3-position (Fig. 1).

Compounds **12** and **13** were synthesized by the alkylation of **6** with 4-chlorobenzyl chloride and 3-trifluoromethylbenzyl bromide, respectively. They were both coupled to pyridine-3-boronic acid 1,3-propanediol ester in a Suzuki coupling. Saponification with aqueous sodium hydroxide and heat led to the desired acids **12** and **13**. Compound **14** was synthesized in a manner similar to **8a**–**j**. First, **6** was subjected to a Suzuki coupling with *N*-(BOC)indole-2-boronic acid, followed by alkylation of the furan pyrrole nitrogen with benzyl bromide. The BOC protecting group was removed through treatment with 10% TFA/CH_2Cl_2 at rt for 2 h. This product was saponified as above to form the desired acid **14**.

Finally, compound **9a** was converted to the acid chloride with thionyl chloride, followed by coupling to N^1,N^1-dimethyl-ethane-1,2-diamine to form compound **15**, thus illustrating another position for diversity (Scheme 4).

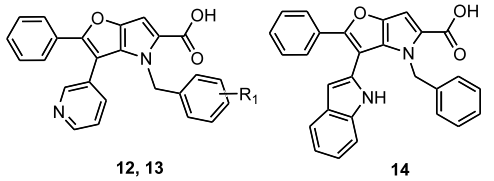
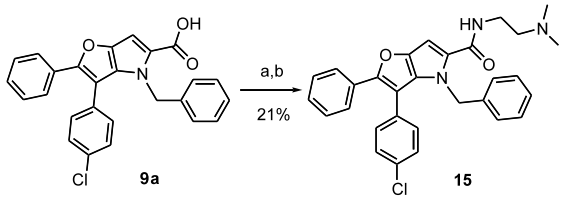


Figure 1. **12**: $R_1 = 4\text{-Cl}$, **13**: $R_1 = 3\text{-}CF_3$.



Scheme 4. *Reagents and conditions*: (a) Thionyl chloride (5 equiv.), CH_2Cl_2, 5 min; (b) *N*,*N*-DMEDA (2.5 equiv.), TEA (2.5 equiv.), –20°C, 20 h.

In conclusion, we have synthesized a diverse series of novel furan[3,2-*b*]pyrroles, exploiting four different diversity sites, including aromatic rings, heteroaromatic rings, and aminoalkyl substituents. This chemistry can be further extended to synthesize large libraries of furan[3,2-*b*]pyrroles.

Data for selected compounds:

9a: ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$ δ): 7.34–7.30 (m, 2H), 7.22–7.13 (m, 5H), 7.13–7.08 (m, 3H), 7.05–7.01 (m, 2H), 6.95 (s, 1H), 6.63–6.60 (m, 2H), 5.40 (s, 2H). MS (ESI): m/z 428.35 (MH$^+$).

9b: ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$ δ): 8.06 (d, $J=8.8$ Hz, 2H), 7.45–7.38 (m, 2H), 7.31 (d, $J=8.4$ Hz, 2H), 7.28–7.25 (m, 3H), 7.12 (d, $J=7.6$ Hz, 2H), 7.11 (s, 1H), 6.83 (d, $J=8.4$ Hz, 2H), 5.54 (s, 2H). MS (ESI): m/z 473.41 (MH$^+$)

9c: ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$ δ): 7.37–7.29 (m, 6H), 7.22–7.14 (m, 3H), 6.96–6.89 (m, 2H), 5.90–5.85 (m, 1H), 5.34 (s, 2H). MS (ESI): m/z 462.10 (MH$^+$).

9d: ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$ δ): 7.40–7.36 (m, 4H), 7.36–7.31 (m, 2H), 7.20–7.12 (m, 3H), 6.85 (s, 1H), 4.21–4.14 (m, 1H), 4.07–3.97 (m, 1H), 3.74–3.68 (m, 1H), 3.35–3.27 (m, 1H), 3.11–3.02 (m, 1H), 1.67–1.59 (m, 1H), 1.35–1.16 (m, 5H). MS (ESI): m/z 436.29 (MH$^+$).

9e: ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$ δ): 7.42–7.39 (m, 2H), 7.32–7.28 (m, 2H), 7.26–7.22 (m, 3H), 7.18–7.15 (m, 2H), 7.00 (s, 1H), 6.27 (s, 1H), 5.53 (s, 2H), 2.62 (s, 3H). MS (ESI): m/z 448.77 (MH$^+$).

9f: ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$ δ): 7.51–7.46 (m, 2H), 7.45–7.36 (m, 5H), 7.24–7.22 (m, 2H), 6.90 (s, 1H), 4.57–4.50 (m, 2H), 2.86–2.81 (m, 2H), 2.77 (q, $J=7.2$ Hz, 4H), 1.07 (t, $J=7.2$ Hz, 6H). MS (ESI): m/z 437.16 (MH$^+$).

9g: ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$ δ): 7.54–7.45 (m, 5H), 7.43–7.40 (m, 2H), 7.28–7.25 (m, 2H), 6.93 (s, 1H), 4.47–4.41 (m, 2H), 3.73 (t, $J=4.8$ Hz, 4H), 2.75–2.69 (m, 2H), 2.50–2.45 (m, 4H). MS (ESI): m/z 451.07 (MH$^+$).

9h: ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$ δ): 7.62–7.34 (m, 9H), 6.93 (s, 1H), 4.75–4.56 (m, 2H), 3.19–3.06 (m, 2H), 2.04–1.88 (m, 4H), 1.00–0.78 (m, 4H). MS (ESI): m/z 435.12 (MH$^+$).

9i: ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$ δ): 8.50–8.46 (m, 1H), 7.63–7.57 (m, 1H), 7.42–7.39 (m, 2H), 7.31–7.29 (m, 1H), 7.28–7.11 (m, 7H), 7.08 (s, 1H), 6.56 (d, $J=8.0$ Hz, 1H), 5.53 (s, 2H). MS (ESI): m/z 428.89 (MH$^+$).

9j: ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$ δ): 8.46 (d, $J=4.4$ Hz, 1H), 8.25 (s, 1H), 7.44–7.36 (m, 4H), 7.28–7.18 (m, 4H), 7.09 (d. $J=8.0$ Hz, 1H), 7.07 (s, 1H), 5.51 (s, 2H). MS (ESI): m/z 429.27 (MH$^+$).

11a: ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$ δ): 7.41–7.37 (m, 2H), 7.25–7.22 (m, 3H), 7.15–7.10 (m, 4H), 7.00 (s, 1H), 6.61 (d, $J=8.4$ Hz, 2H), 5.42 (s, 2H). MS (ESI): m/z 462.21 (MH$^+$).

11b: ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$ δ): 7.44–7.29 (m, 5H), 7.17–7.13 (m, 3H), 7.06 (s, 1H), 6.70–6.66 (m, 2H), 5.44 (s, 2H). MS (ESI): m/z 394.27 (MH$^+$).

12: ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$ δ): 8.69–8.37 (m, 2H), 7.55 (d, $J=8.0$ Hz, 1H), 7.39 (s, 1H), 7.35–7.31 (m, 2H), 7.27–7.22 (m, 3H), 7.12 (d, $J=8.8$ Hz, 2H), 7.05 (s, 1H), 6.58 (d, $J=8.4$ Hz, 2H), 5.49 (s, 2H). MS (ESI): m/z 429.25 (MH$^+$).

13: ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$ δ): 8.82–8.76 (m, 1H), 8.72–8.65 (m, 1H), 7.91 (d, $J=7.6$ Hz, 1H), 7.77–7.69 (m, 1H), 7.43 (d, $J=7.6$ Hz, 1H), 7.37–7.25 (m, 6H), 7.10 (s, 1H), 6.93–6.87 (m, 2H), 5.72 (s, 2H). MS (ESI): m/z 463.13 (MH$^+$).

14: ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$ δ): 8.64 (s, 1H), 7.55 (d, $J=8.8$ Hz, 1H), 7.47–7.42 (m, 2H), 7.23–7.05 (m, 9H), 6.97 (s, 1H), 6.71–6.63 (m, 2H), 6.43 (d, $J=1.2$ Hz, 1H), 5.52 (s, 1H). MS (ESI): m/z 433.30 (MH$^+$).

15: ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$ δ): 7.38–7.33 (m, 2H), 7.25–7.11 (m, 8H), 7.08 (d, $J=8.4$ Hz, 2H), 6.81–6.75 (bt, 1H), 6.70–6.65 (m, 2H), 6.64 (s, 1H), 5.47 (s, 2H). MS (ESI): m/z: 498.23 (MH$^+$).

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