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Synthesis of a novel series of 10-oxa-3-aza-tricyclo[5.2.1.0^{1,5}]dec-8-en-4-ones through an intramolecular Diels–Alder reaction

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Abstract—The synthesis of a novel series of 10-oxa-3-aza-tricyclo[5.2.1.0^{1,5}]dec-8-en-4-ones through the use of the intramolecular Diels–Alder reaction is presented. The use of this reaction allows for the synthesis of functionalized polycyclic systems in a stereocontrolled manner.

The Diels–Alder reaction provides a facile route to the synthesis of complicated multicyclic structures. Several heterocycles undergo this reaction, but the most extensively studied five-membered heterocycle for this cycloaddition is furan. In many cases, however, this reaction is difficult, due to the low reactivity of furan.[1] Many times, the cyclization requires high pressure or the employment of Lewis Acid catalysis to proceed. The intramolecular Diels–Alder reaction holds great advantage in that even sterically hindered and less reactive dienophiles can be made to react through thermal cyclization.[2] This reaction can be used for the generation of highly functionalized polycyclic systems[3] and often proceeds at a lower temperature than its intermolecular counterpart.[4,5] Another advantage to the intramolecular Diels–Alder reaction is its stereocontrol, as four potential stereocenters are created in one step. When the furan is connected to a dienophile through a tether, the triene undergoes the intramolecular Diels–Alder reaction to stereospecifically provide a tricylic system. For the 10-oxa-3-aza-tricyclo[5.2.1.0^{1,5}]dec-8-en-4-ones, only the *exo* transition state is geometrically possible due to the length and hybridization of the tether. 2D NOESY experiments[3] have confirmed the stereo- and regiochemistry of the resulting cycloadduct is *exo* (Fig. 1). The stereochemistry at position 6 is determined by the *cis* or *trans* nature of the dienophile.

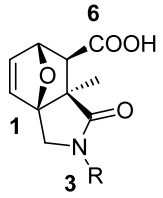

Figure 1. *exo*-Configuration of 5-methyl-4-oxo-10-oxa-3-aza-tricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid.

Herein we describe the synthesis of a novel series of 10-oxa-3-aza-tricyclo[5.2.1.0^{1,5}]dec-8-en-4-ones through the use of the intramolecular Diels–Alder reaction. Compounds of this general structure have been used for the treatment of physiological and/or drug-induced psychosis, as antidyskinetic agents[6] and as HMG-CoA reductase inhibitors.[7]

The general synthetic procedure is illustrated by the synthesis of compound **4**. The first step of the synthesis involved a reductive amination[8] of 4-bromo-2-furaldehyde with aniline to afford **1**. The resulting product was treated with phenylboronic acid in a Suzuki coupling[9] to give the desired product **2**. Compound **2** was acylated with methacryloyl chloride to afford **3**, which was thermally cyclized by an intramolecular Diels–Alder reaction,[10,11] resulting in compound **4**, containing the desired stereochemistry. A complicated tricyclic compound with three stereocenters was thereby obtained in four steps with a 63% overall yield (Scheme 1).

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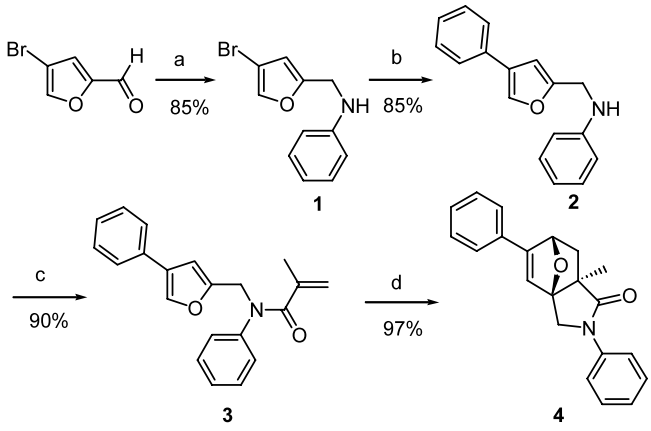


Scheme 1. *Reagents and conditions*: (a) aniline (1.05 equiv.), $NaBH(OAc)_3$ (1.6 equiv.), $C_2H_4Cl_2$, 2 h, rt; (b) phenylboronic acid (2.0 equiv.), $Pd(PPh_3)_4$ (0.05 equiv.), 1 M KOH/THF 1/1, 65°C, 18 h; (c) methacryloyl chloride (1.2 equiv.), TMEDA (1.2 equiv.), CH_2Cl_2, 0°C, 15 min; (d) anhyd. toluene, 100°C, 1 h.

To determine whether the intramolecular Diels–Alder reaction could proceed in the presence of heterocycles, similar compounds were synthesized in which phenylboronic acid was replaced with 2-thiopheneboronic acid or 2-furanboronic acid in the Suzuki couplings. It was found that the Diels–Alder reaction proceeded smoothly in both cases (Fig. 2).

Compounds **5** and **6** also illustrate that alkyl amines can be used in place of anilines. These compounds were synthesized as in Scheme 1, with cyclopentylamine replacing aniline in the reductive amination.

Further substitution was incorporated in both the 5 and 6 positions of the 10-oxa-3-aza-tricyclo[5.2.1.$0^{1,5}$]dec-8-en-4-one system through the use of alternative acylating agents (Scheme 2). Compound **8** was formed by acylation of **7** with commercially available cinnamoyl chloride. The intramolecular Diels–Alder reaction affords compound **9**. Stereospecificity was confirmed by comparing the predicted NMR coupling constants to the actual using dihedral angles obtained from a model. Compound **11** was formed by acylation of **10** with 2-benzyl-acryloyl chloride (synthesis shown in Scheme 3), followed by thermal cyclization to compound **12**.

The increased steric bulk of these systems (as compared to compound **4**) may account for the decreased yields in the cylization reaction.

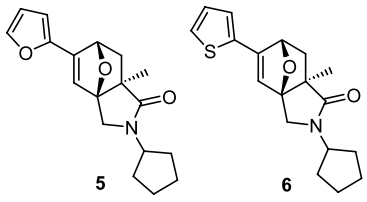
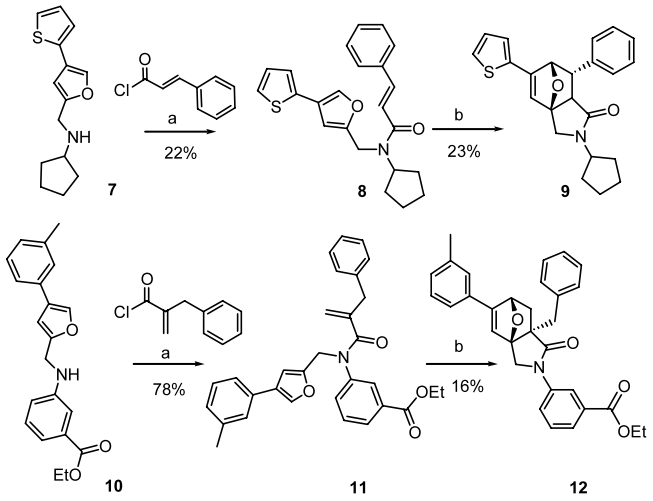
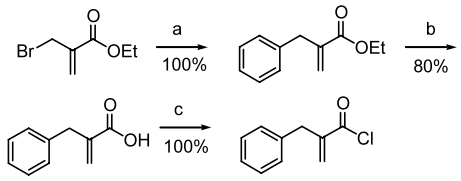


Figure 2. Representative products containing heterocycles in the 8-position.



Scheme 2. *Reagents and conditions*: (a) acylating agent (1.2 equiv.), TMEDA (1.2 equiv.), 30 min, CH_2Cl_2, 0°C; (b) anhyd. toluene, 100°C, 1 h.



Scheme 3. *Reagents and conditions*: (a) benzene (excess), $AlCl_3$, 0°C–rt, 1 h; (b) MeOH, KOH (2 equiv.), 18 h; (c) oxalyl chloride (1.1 equiv.), CH_2Cl_2, DMF (cat.), 1.5 h.

In an alternative route, the Diels–Alder reaction was performed prior to the Suzuki couplings. This allows diversification at the R_1 position while maintaining R_2, R_3, and R_4 constant (see Fig. 3). Scheme 4 illustrates this route of synthesis. Compound **13** was formed from

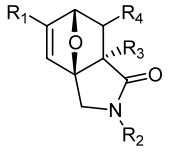
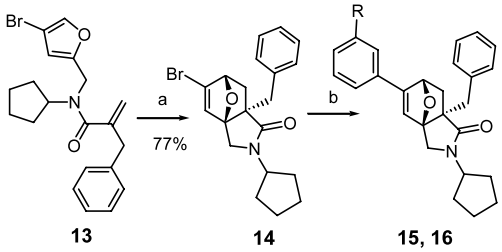


Figure 3. Generic structure of cyclization product.



Scheme 4. *Reagents and conditions*: (a) 100°C, toluene; (b) boronic acid (2.0 equiv.), $Pd(PPh_3)_4$ (0.5 equiv.), KOH, THF, 65°C; **15**: R = CH_3, 66% yield; **16**: R = Cl, 44% yield.

a reductive amination and acylation in a similar manner to compound **11**.

In conclusion, we have synthesized a diverse series of 10-oxa-3-aza-tricyclo[5.2.1.0^{1,5}]dec-8-en-4-ones. The selected compounds shown incorporate both heterocyclic and phenyl rings, and alkyl and aryl amides. The intramolecular Diels–Alder reaction provides a facile method for the creation of complicated molecules with 3–4 chiral centers and predictable regio- and stereochemistry. Through altering the order of synthetic steps, one can easily diversify at multiple positions on the scaffold. The ease of synthesis and the incorporation of four diversity sites lend themselves to the formation of large chemical libraries.

Data for selected compounds:

4: ^{1}H NMR (400 MHz, $CDCl_3$ δ): 7.71–7.65 (m, 2H), 7.42–7.36 (m, 6H), 7.20–7.15 (m, 2H), 6.64 (s, 1H), 5.36 (d, $J=4.8$ Hz, 1H), 4.39 (d, $J=11.2$ Hz, 1H), 4.16 (d, $J=11.6$ Hz, 1H), 2.72 (dd, $J=4.8$ Hz, 4.8 Hz, 1H), 1.35 (d, $J=11.6$ Hz, 1H), 1.17 (s, 3H). MS (ESI) m/z 318.00 (MH$^+$).

5: ^{1}H NMR (400 MHz, $CDCl_3$ δ): 7.51–7.50 (m, 1H), 7.44–7.43 (m, 1H), 6.49–6.48 (m, 1H), 6.32 (s, 1H), 5.04 (d, $J=4.4$ Hz, 1H), 4.59–4.50 (m, 1H), 3.81–3.78 (d, $J=11.6$ Hz, 1H), 3.66–3.63 (m, $J=12.0$ Hz, 1H), 2.51 (dd, $J=4.8$ Hz, 4.8 Hz, 1H), 1.97–1.80 (m, 3H), 1.77–1.60 (m, 4H), 1.57–1.45 (m, 2H), 1.05 (s, 3H). MS (ESI) m/z 300.1 (MH$^+$).

6: ^{1}H NMR (400 MHz, $CDCl_3$ δ): 7.37–7.32 (m, 1H), 7.25–7.21 (m, 1H), 7.21–7.17 (m, 1H), 6.39 (s, 1H), 5.18 (d, $J=5.2$ Hz, 1H), 4.61–4.50 (m, 1H), 3.81 (d, $J=11.6$ Hz, 1H), 3.65 (d, $J=12.0$ Hz, 1H), 2.54 (dd, $J=5.2$ Hz, 5.2 Hz, 1H), 1.95–1.83 (m, 3H), 1.76–1.59 (m, 4H), 1.56–1.45 (m, 2H), 1.05 (s, 3H). MS (ESI) m/z Found: 316.12 (MH$^+$).

9: ^{1}H NMR (400 MHz, $CDCl_3$ δ): 7.07–7.05 (m, 5H), 6.82 (m, 1H), 6.62 (s, 1H), 6.34–6.31 (m, 1H), 5.22 (d, $J=4.8$ Hz, 1H), 4.64–4.54 (m, 1H), 3.99–3.93 (m, 2H), 3.71 (d, $J=12.0$ Hz, 1H), 2.96 (d, $J=4.4$ Hz, 1H), 1.98–1.84 (m, 2H), 1.79–1.49 (m, 6H), 1.13–1.15 (m, 1H). MS (ESI) m/z 378.12 (MH$^+$).

12: ^{1}H NMR (400 MHz, $CDCl_3$ δ): 7.85–7.79 (m, 1H), 7.77–7.70 (m, 2H), 7.54–7.36 (m, 6H), 7.25–7.11 (m, 5H), 6.84 (s, 1H), 5.38 (d, $J=4.8$ Hz, 1H), 4.42–4.33 (m, 2H), 3.71 (d, $J=10.8$ Hz, 1H), 3.30 (d, $J=14$ Hz, 1H), 3.20 (d, $J=11.2$ Hz, 1H), 2.88–2.77 (m, 1H), 2.39 (d, $J=14$ Hz, 1H), 1.50 (d, $J=12$ Hz, 1H), 1.41 (t, $J=7.2$ Hz, 3H). MS (ESI) m/z 466.09 (MH$^+$).

15: ^{1}H NMR (400 MHz, $CDCl_3$ δ): 7.33–7.23 (m, 6H), 7.21–7.13 (m, 3H), 6.77 (s, 1H), 5.27 (d, $J=4.9$ Hz, 1H), 4.49–4.40 (m, 1H), 3.25 (d, $J=11.2$ Hz, 1H), 3.20 (d, $J=11.2$ Hz, 1H), 2.72 (d, $J=11.2$ Hz, 1H), 2.70–2.65 (dd, $J=4.9$ Hz, 11.2 Hz, 1H), 2.41 (s, 3H), 2.26 (d, $J=13.9$ Hz, 1H), 1.84–1.74 (m, 1H), 1.58–1.24 (m, 8H). MS (ESI) m/z 400.10 (MH$^+$).

16: ^{1}H NMR (400 MHz, $CDCl_3$ δ): 7.47–7.41 (m, 1H), 7.37–7.23 (m, 6H), 7.20–7.14 (m, 2H), 6.83 (s, 1H), 5.24 (d, $J=4.9$ Hz, 1H), 3.25 (d, $J=11.2$ Hz, 1H), 3.20 (d, 13.9 Hz, 1H), 2.72 (d, $J=11.2$ Hz, 1H), 2.68 (dd, $J=4.8$ Hz, 11.2 Hz, 1H), 2.24 (d, $J=13.9$ Hz, 1H), 1.84–1.73 (m, 1H), 1.57–1.24 (m, 8H), 0.80–0.91 (m, 1H). MS (ESI) m/z 420.10 (MH$^+$).

Acknowledgements

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