

Intramolecular cycloaddition reaction of bromo and nitro substituted furanyl amides

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Dedicated to Waldemar Adam on the occasion of his 70th anniversary

Abstract

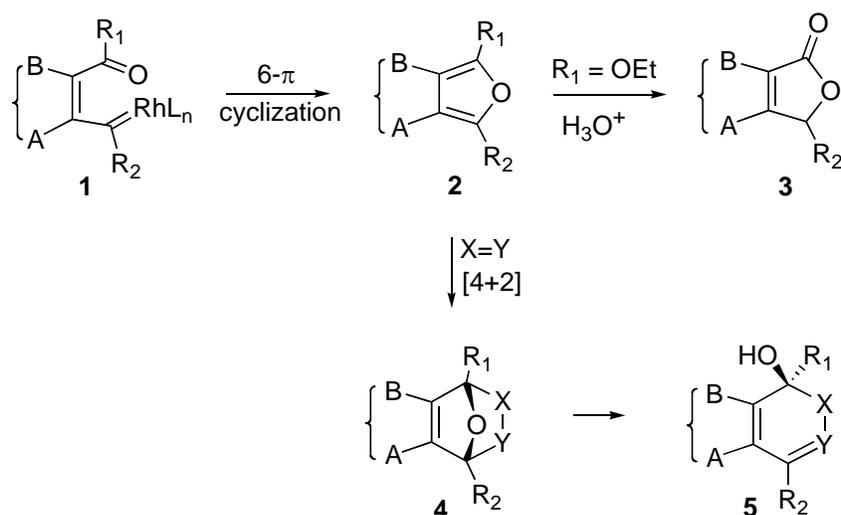
The intramolecular Diels-Alder reaction (IMDAF) of an *N*-alkenyl substituted furanyl amide was investigated. Upon thermolysis at 80-110 °C, a smooth IMDAF reaction occurred to provide a stable aza-7-oxabicyclo[2.2.1]heptane cycloadduct in high yield. The intramolecular cyclization of the related 5-bromo substituted furanyl amide was found to proceed at a much faster rate and in higher yield than the unsubstituted variant. The rate enhancement observed by incorporating a bromine in the 5-position of the furan ring appears to be general. The origin of the increased rate of cycloaddition for the 5-bromo substituted furan when compared to the unsubstituted example can be attributed to an increase in reaction exothermicity; this both decreases the activation enthalpy, and increases the barrier to retrocycloaddition. Bromine substitution on furan also increases reactant energy and stabilizes the product due to the preference of the electronegative bromine atom to be attached to a more highly alkylated, and therefore more electropositive framework. An unusual isomerization-cyclization reaction of a 5-nitro substituted furanyl amide was also found to occur under microwave conditions and provided a 1,4-dihydro-2*H*-benzo[4.5]furo[2,3-*c*]pyridin-3-one derivative.

Keywords: Furans, intramolecular, [4+2], Diels-Alder, cycloaddition, synthesis

Introduction

The rhodium(II)-catalyzed reaction of α -diazo ketones bearing tethered alkyne units represents a powerful method for the construction of a variety of polycyclic skeletons.¹ Exposure of the starting α -diazo ketone to a rhodium(II) catalyst results in cyclization of the α -keto carbenoid to an intermediate in which carbene-like reactivity has been transferred to one of the original alkyne carbon atoms. A neighboring functional present on the backbone then traps the cyclized intermediate *via* known carbenoid chemistry to give various products.² During the course of our studies in this area, we reported on a novel construction of bicyclic furans by coupling a metal

carbenoid cyclization onto a tethered alkyne with an electrocyclization reaction (Scheme 1).³ Transformations of this type are of considerable synthetic utility, since the vast majority of furano-sesquiterpenes are functionalized at the C₃ and C₄ position of the furan ring.^{4,5} Use of an ester group (R₁=OEt) also allows for transformation of **2** to the corresponding butenolide system **3**. Formation of five-membered rings by 6 π -electrocyclization is a well-precedented process in heterocyclic chemistry.⁶⁻¹⁰ Several different synthetic approaches to alkenone carbenes have been developed over the years, producing intermediates that display common trends in their reactivity.¹¹⁻¹⁷ The utility of this cyclization approach to ring construction would be significantly expanded if the resulting bicyclic furan **2** was to undergo a subsequent [4+2]-cycloaddition, since a cyclohexane annulation would then result (*i.e.*, **2**→**4**→**5**). As part of our broader interest in using furan-cycloaddition products for the synthesis of natural products,^{18,19} we examined the strategic incorporation of several functional groups into the furan moiety that could be leveraged for the further transformation.



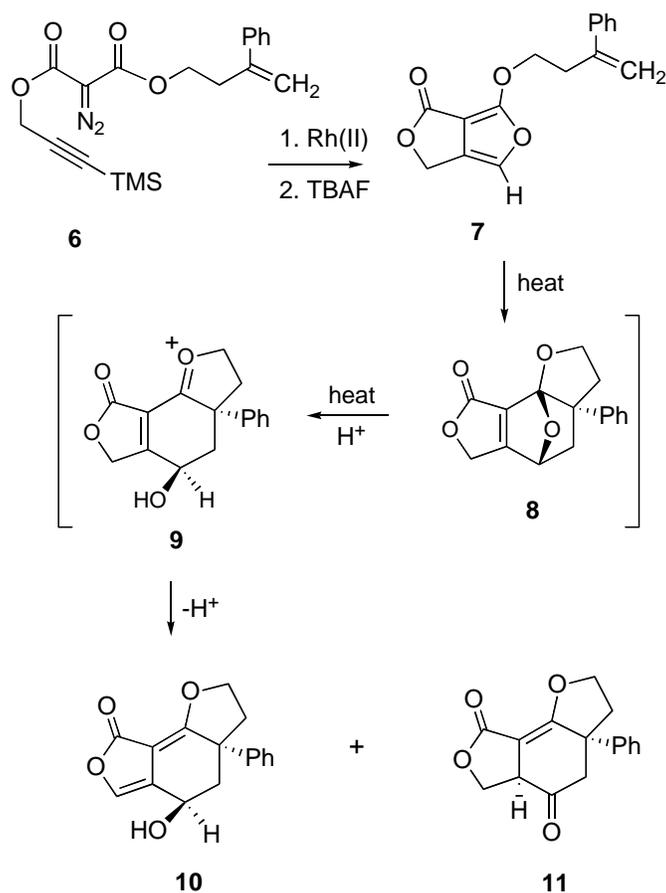
Scheme 1

Results and Discussion

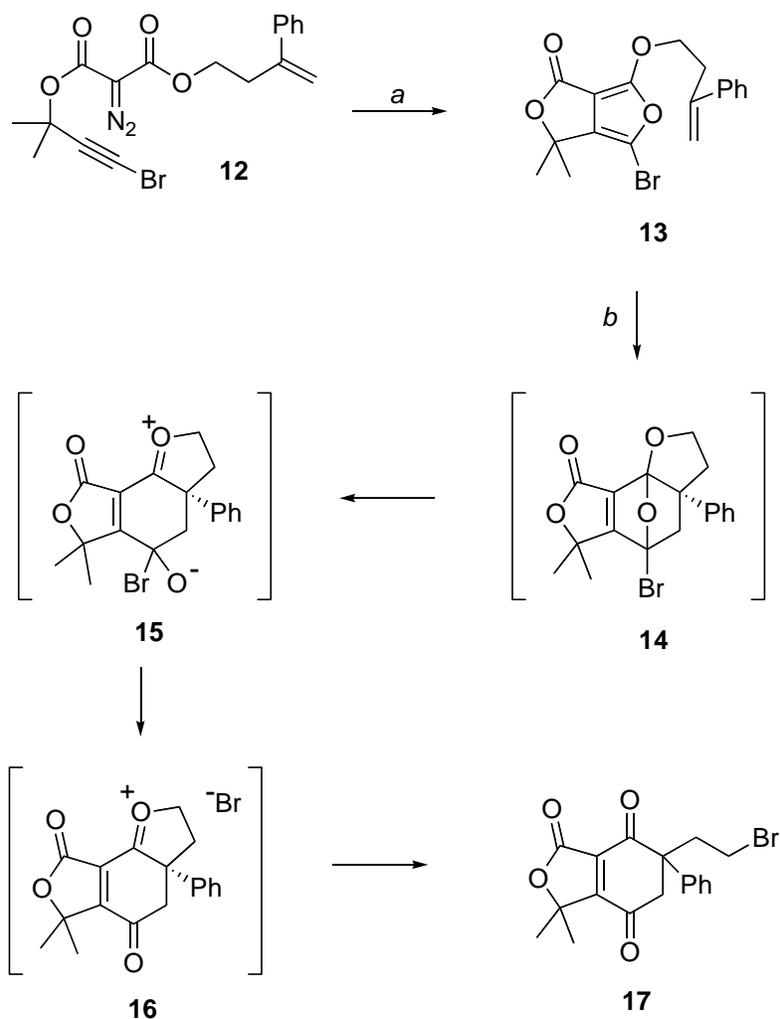
Our initial studies focused on an intramolecular variation of the Rh(II)-catalyzed cyclization/Diels-Alder cycloaddition sequence of a propargyl diazo malonic ester system. The reaction of diazo ester **6** with Rh₂(OAc)₄ followed by protidesilylation with TBAF produced furan **7** in good yield. Heating a sample of **7** at 145 °C in xylene furnished indacene dione **10** (36%) and the dienol- substituted lactone **11** (63%) (Scheme 2). These products are presumably derived by an initial IMDAF reaction (intramolecular Diels-Alder of furan)²⁰ followed by

opening of the oxybridge of cycloadduct **8** to give oxonium ion **9**. A subsequent loss of a proton from either of the two available positions nicely accounts for the products formed.

In contrast to this result, thermolysis of the related bromofuran **13**, derived from the Rh(II)-catalyzed reaction of diazo ester **12**, gave the unusual rearranged bromide **17** as the major product in 43% yield (Scheme 3). Presumably, **17** arises from an initial intramolecular Diels-Alder reaction of furan **13** to give oxabicyclo **14**. Fragmentation of the oxabridge results in a zwitterionic intermediate **15**, which can ketonize with the expulsion of a bromide ion, producing oxonium ion **16**. The ejected bromide ion then attacks the oxonium ion at the adjacent methylene position, leading to the observed product.



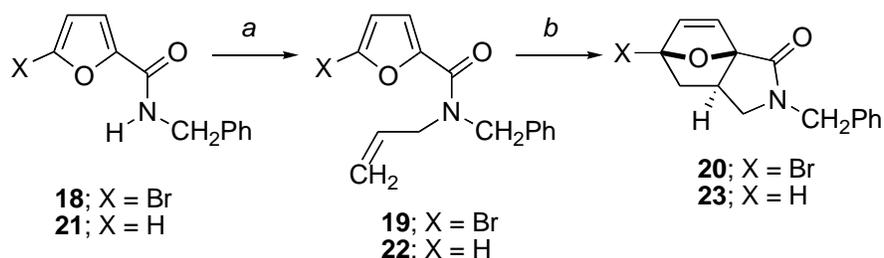
Scheme 2



Reagents: (a) $\text{Rh}_2(\text{OAc})_4$, PhH, heat; (b) xylene, 145°C , 43%.

Scheme 3

Intrigued by these results and considering the importance of 7-oxabicyclo [2.2.1]heptanes as valuable synthetic intermediates, we decided to examine some related systems that could provide polyfunctional oxabicycles. 5-Bromo-2-furoyl amide **19** was prepared by *N*-allylation of the secondary amide **18** under phase transfer conditions (Scheme 4). Heating a sample of furan **19** at 110°C for 90 min provided the stable oxatricycle **20** as a single diastereomer. The stereochemistry of **20** is consistent with preferred *exo*-orientation of the tether in the Diels-Alder cycloaddition reaction and is analogous with that reported by others for related furanyl systems possessing short tethers.²¹ In marked contrast to this finding, it was necessary to heat the unsubstituted amidofuran (X = H) for one week at 110°C in order to complete the cycloaddition of **22** to **23**.

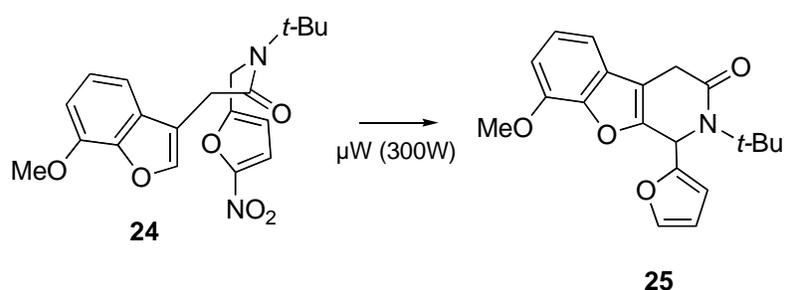


Reagents: (a) NaOH, K₂CO₃, *n*-Bu₄NHSO₄, allyl bromide (b) PhCH₃, heat.

Scheme 4

The rate enhancement observed by incorporating a bromine or another halogen group at the 5-position appears to be general.²² The origin of the increased bimolecular cycloaddition rate for the 5-bromo-substituted furans was recently investigated by Houk and Pieniazek using quantum mechanical calculations.²³ The origin of the increased rate of cycloaddition for the 5-bromo substituted furan when compared to the unsubstituted example can be attributed to an increase in reaction exothermicity; this both decreases the activation enthalpy, and increases the barrier to retrocycloaddition. Bromine substitution on furan also increases reactant energy and stabilizes the product due to the preference of the electronegative bromine atom to be attached to a more highly alkylated, and therefore more electropositive framework.

The remarkable enhancement in the rate of the cycloaddition involving bromo furans, combined with our recent success with cycloadditions across heteroaromatic π -systems,²⁴ also prompted us to examine the IMDAF reaction using the electron withdrawing nitro group, rather than the bromo-substituent. Accordingly, we prepared the 5-nitro-furan variant **24** and found that when nitrofurans **24** was exposed to microwave irradiation for 15 min in *N*-methyl-2-pyrrolidinone (NMP), furan **25** was isolated as the major product (Scheme 5). Compound **25** was unequivocally assigned by a single crystal X-ray analysis (Figure 1).



Scheme 5

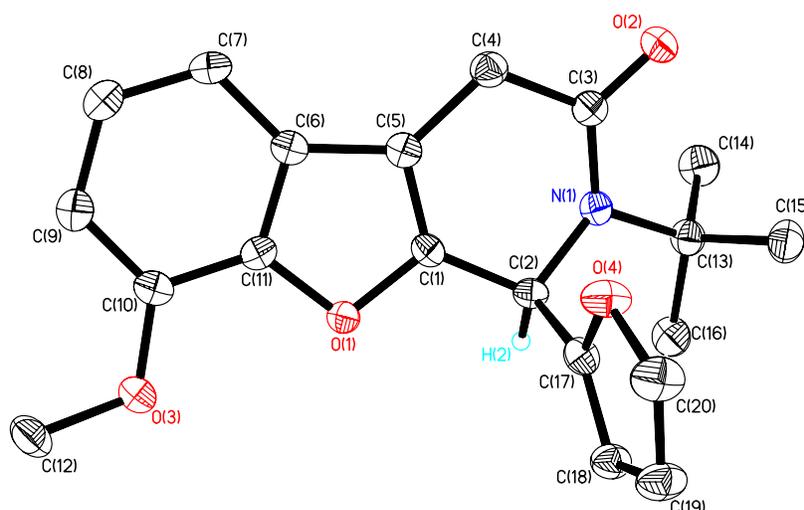
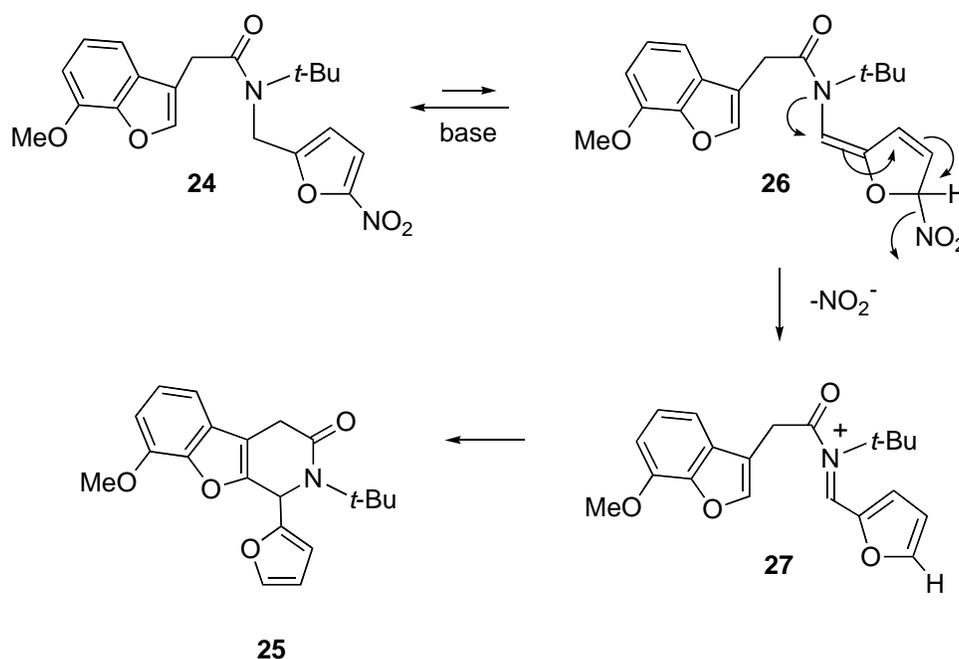


Figure 1. Ortep drawing of compound **25**.

A more detailed study of the reaction showed that catalytic amounts of 2,6-lutidine enhanced the formation of **25**, suggesting a mechanism involving a base catalyzed tautomerization of the furfuryl moiety to give intermediate **26** as a transient species. The lone pair of electrons on the amide nitrogen facilitates the loss of the nitro group to furnish acyl iminium ion **27** which then undergoes a subsequent cyclization with the adjacent benzofuran as shown in Scheme 6.



Scheme 6

In conclusion, the results presented herein demonstrate the versatility of the intramolecular [4+2]-cycloaddition reaction of substituted furans. Different rearrangement pathways of the resulting oxabicyclo adducts become available depending on the nature of the substituent group attached to the furan. We are currently investigating application of the methodology outlined here toward the synthesis of several alkaloid natural products.

Experimental Section

2-Diazo-malonic acid 3-bromo-1,1-dimethyl-prop-2-ynyl-3-phenyl-but-3-enyl ester (12). To a solution containing 4.2 mmol of malonic acid mono-(3-bromo-1,1-dimethyl-prop-2-ynyl) ester¹⁹ in 25 mL of CH₂Cl₂ at 0 °C under Ar was added 0.4 mmol of DMAP, 8.3 mmol of 3-phenyl-3-buten-1-ol and 4.6 mmol of 1,3-dicyclo-hexylcarbodiimide. The reaction mixture was allowed to stir at room temperature for 3 h. The resulting suspension was filtered, the filtrate concentrated under reduced pressure and the crude residue was subjected to silica gel chromatography to give malonic acid 3-bromo-1,1-dimethyl-prop-2-ynyl-3-phenyl-but-3-enyl ester (97%) as a light yellow oil; IR (neat) 2117, 1755, 1736, 1254, and 1123 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 1.68 (s, 6H), 2.87 (dt, 2H, *J* = 7.2 and 1.2 Hz), 3.30 (s, 2H), 4.26 (t, 2H, *J* = 7.2 Hz), 5.15 (dd, 1H, *J* = 1.2 and 1.2 Hz), 5.39 (d, 1H, *J* = 1.2 Hz), and 7.26-7.42 (m, 5H); ¹³C-NMR (100 MHz, CDCl₃) d 28.8, 34.4, 42.4, 45.9, 64.3, 74.2, 76.9, 114.8, 126.2, 127.9, 128.7, 140.5, 144.1, 164.8, and 166.6; HRMS Calcd. for C₁₈H₁₉BrO₄: 378.0467. Found: 378.0462.

To a solution containing 2.1 mmol of the above malonic acid ester and 3.1 mmol of 4-nitrobenzenesulfonyl azide in 20 mL of CH₂Cl₂ at 0 °C under Ar was added 6.7 mmol of triethyl amine. After stirring the solution for 12 h, the solvent was removed to give diazo ester **12** (95%) as a yellow oil; IR (neat) 2203, 2138, 1758, 1736, 1695, and 1328 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) d 1.72 (s, 6H), 2.90 (dt, 2H, *J* = 6.8 and 0.8 Hz), 4.34 (t, 2H, *J* = 6.8 Hz), 5.14 (dd, 1H, *J* = 0.8 and 0.8 Hz), 5.38 (d, 1H, *J* = 0.8 Hz), and 7.27-7.42 (m, 5H); ¹³C-NMR (100 MHz, CDCl₃) d 29.2, 34.7, 46.3, 64.4, 74.8, 80.3, 115.0, 126.2, 127.9, 128.7, 140.4, 144.2, 159.2, and 160.9.

Diazo ester **12** was used in the next step without further purification.

6-(2-Bromo-ethyl)-3,3-dimethyl-6-phenyl-5,6-dihydro-3H-isobenzofuran-1,4,7-trione (17).

To a solution of 1.6 g (0.4 mmol) of diazo ester **12** in 5 mL of dry benzene at 80 °C was added 5 mg of Rh₂(OAc)₄. The reaction mixture was heated at 80 °C for 15 min. The solvent was removed under reduced pressure to give furan **13** as a clear oil which was used in the next step without further purification; ¹H-NMR (400 MHz, CDCl₃) d 1.60 (s, 6H), 3.00 (t, 2H, *J* = 6.0 Hz), 4.50 (t, 2H, *J* = 6.0 Hz), 5.20 (s, 1H), 5.43 (s, 1H), and 7.26-7.42 (m, 5H).

Furan **13** was taken up in xylene, placed in a sealed tube, the tube was sealed and the mixture was heated at 145 °C for 15 h. The solution was concentrated under reduced pressure, and the residue was subjected to silica gel chromatography to give 0.07 g (43%) of the titled compound **17** as a pale yellow oil; IR (neat) 1780, 1796, 1446, 1390, and 1300 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) d 1.31 (s, 3H), 1.74 (s, 3H), 2.49 (ddd, 1H, *J* = 14.4, 10.4 and 6.0 Hz), 2.73 (ddd, 1H, *J* =

16.0, 10.4 and 6.0 Hz), 3.08-3.19 (m, 2H), 3.27 (d, 1H, $J = 16.8$ Hz), 3.72 (d, 1H, $J = 16.8$ Hz), 7.12-7.15 (m, 2H) and 7.32-7.40 (m, 3H); ^{13}C -NMR (100 MHz, CDCl_3) d 23.9, 25.7, 26.6, 41.0, 47.8, 60.1, 84.2, 126.0, 129.3, 129.5, 130.3, 136.0, 164.5, 168.5, 188.8, and 194.2; Anal. Calcd. for $\text{C}_{18}\text{H}_{17}\text{BrO}_4$: C, 57.31; H, 4.54. Found: C, 57.04; H, 4.26.

5-Bromo-furan-2-carboxylic Acid Benzylamide (18). To a solution of 5-bromo-2-furoic acid (10 g, 52 mmol) in CH_2Cl_2 (65 mL) at 0 °C was added $(\text{COCl})_2$ (6.8 mL, 79 mmol) and DMF (50 μL). The flask was fitted with a drying tube containing CaSO_4 and the resulting solution was warmed to rt for 1.5 h. Concentration under reduced pressure afforded the crude acid chloride as a yellow solid that was used directly in the next step without further purification. A solution of this acid chloride in THF (20 mL) was added slowly to solution of benzylamine (6.2 mL, 57 mmol) and Et_3N (15 mL, 100 mmol) in THF (20 mL) at 0 °C. The solution was warmed to rt over 1 h and then H_2O was added. The layers were separated and the aqueous layer was extracted with ether. The combined organic layer was dried (MgSO_4), filtered, and concentrated under reduced pressure. The yellow oil obtained was subjected to flash silica gel chromatography to give furanyl amide **18** (15 g, 100%) as a white solid. All of its spectroscopic properties were identical to those reported previously.²⁵

5-Bromo-furan-2-carboxylic Acid Allyl-benzylamide (19). A mixture of furan **18** (1.0 g, 3.6 mmol), powdered NaOH (0.6 g, 14 mmol), K_2CO_3 (0.5 g, 3.6 mmol), and $(n\text{-Bu}_4)\text{NHSO}_4$ (0.01 g, 0.01 mmol) in benzene (20 mL) was stirred for 1 h at rt. Allyl bromide (0.6 mL, 7.2 mmol) was added, and the reaction mixture was stirred at rt for 22 h. The mixture was diluted with water and the layers were separated. The aqueous layer was extracted with EtOAc, and the combined organic layers were dried (MgSO_4) and concentrated under reduced pressure. The resulting crude oil was subjected to flash silica gel chromatography to give 1.1 g (99%) of **19** as a colorless oil; IR (neat) 1711, 1624, 1572, 1478, 1414, 1261, and 1013 cm^{-1} ; ^1H -NMR (400 Hz, CDCl_3) d 4.08 (brs, 2H), 4.59-4.88 (m, 2H), 5.08-5.35 (m, 2H), 5.79-5.95 (m, 1H), 6.39 (brs, 1H), 6.83-7.10 (m, 1H), and 7.16-7.45 (m, 5H); ^{13}C -NMR (100 Hz, CDCl_3) d 48.8, 49.7, 113.2, 117.8, 118.7, 124.5, 127.5, 128.6, 132.9 (br), 134.2, 136.7, 149.2, and 159.1; HRMS Calcd. for $\text{C}_{15}\text{H}_{14}\text{BrNO}_2$: 319.0208. Found: 319.0208.

3-Benzyl-7-bromo-10-oxa-3-aza-tricyclo[5.2.1.0^{1,5}]dec-8-en-2-one (20). A solution of furan **19** (0.2 g, 0.66 mmol) in toluene (7 mL) was heated at 110 °C for 1.5 h. The mixture was concentrated under reduced pressure and the crude oil was subjected to flash silica gel chromatography to give **20** (0.21 g, 99%) as a white solid, mp 120-121 °C; IR (film) 1702, 1485, 1435, and 1283 cm^{-1} ; ^1H -NMR (300 MHz, CDCl_3) d 2.13-2.25 (m, 2H), 2.33-2.42 (m, 1H), 3.26 (dd, 1H, $J = 9.9$ and 8.4 Hz), 3.47 (dd, 1H, $J = 9.9$ and 8.4 Hz), 4.46 (d, 1H, $J = 15$ Hz), 4.57 (d, 1H, $J = 15$ Hz), 6.50 (d, 1H, $J = 5.4$ Hz), 6.66 (d, 1H, $J = 5.4$ Hz), and 7.24-7.38 (m, 5H); ^{13}C -NMR (75 MHz, CDCl_3) d 42.1, 42.9, 47.3, 51.5, 90.8, 90.9, 128.1, 128.3, 129.1, 134.5, 135.7, 141.5, and 166.1; Anal. Calcd. for $\text{C}_{15}\text{H}_{14}\text{BrNO}_2$: C, 56.27; H, 4.41; N, 4.37. Found: C, 56.19; H, 4.20; N, 4.16.

Furan-2-carboxylic Acid Allyl-benzylamide (22). A mixture of furan-2-carboxylic acid benzylamide (**21**),²⁶ (0.72 g, 3.6 mmol) of powdered NaOH (0.6 g, 14 mmol), K₂CO₃ (0.5 g, 3.6 mmol), and (*n*-Bu₄)NHSO₄ (0.02 g, 0.06 mmol) in toluene (20 mL) was stirred for 1 h at rt. Allyl bromide (0.86 g, 7.1 mmol) was added, and the reaction mixture was heated at 110 °C for 48 h. The mixture was cooled, diluted with water, and extracted with EtOAc. The combined organic layer was dried (MgSO₄) and concentrated under reduced pressure. The crude oil was subjected to flash silica gel chromatography to give 0.34 g (40%) of **22** as a yellow oil; IR (neat) 1633, 1574, 1487, 1177, and 1015 cm⁻¹; ¹H-NMR (400 Hz, CDCl₃) δ 4.07 (brs, 2H), 4.74 (brs, 2H), 5.05-5.35 (m, 2H), 5.76-5.98 (m, 1H), 6.43 (s, 1H), 7.02 (brs, 1H), 7.16-7.40 (m, 5H), and 7.44 (s, 1H); ¹³C-NMR (100 Hz, CDCl₃) δ 48.5, 49.5, 106.3, 111.1, 116.2, 117.6, 127.3, 128.5, 133.2, 136.8, 143.9, 147.6, and 160.2; Anal. Calcd. for C₁₅H₁₅NO₂: C, 74.67; H, 6.27; N, 5.80. Found: C, 74.49; H, 6.08; N, 5.63.

This reaction also produced 0.42 g (48%) of cycloadduct **23**.

3-Benzyl-10-oxa-3-aza-tricyclo[5.2.1.0_{1,5}]dec-8-en-2-one (23). A 0.16 g sample of **22** (0.66 mmol) in toluene (7 mL) was heated at 125 °C for 7 days. The mixture was concentrated under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 0.16 g (98%) of **23** as a white solid: mp 140-141 °C; IR (film) 1690, 1446, 1282, 1158 and 1020 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 1.47 (dd, 1H, *J* = 11.7 and 7.5 Hz), 1.75-1.90 (m, 1H), 2.21 (ddd, 1H, *J* = 16.1, 8.1 and 3.0 Hz), 3.11 (dd, 1H, *J* = 9.5 and 8.5 Hz), 3.40 (dd, 1H, *J* = 9.5 and 8.5 Hz), 4.48 (s, 2H), 5.10-5.20 (m, 1H), 6.37-6.45 (m, 1H), 6.54-6.62 (m, 1H), and 7.16-7.35 (m, 5H); ¹³C-NMR (75 MHz, CDCl₃) δ 31.0, 38.7, 46.7, 51.4, 81.4, 91.8, 127.4, 127.8, 128.6, 133.0, 135.8, 137.1, and 168.1; Anal. Calcd. for C₁₅H₁₅NO₂: C, 74.67; H, 6.27; N, 5.81. Found: C, 74.51; H, 6.11; N, 5.74.

***N*-tert-Butyl-2-(7-methoxy-benzofuran-3-yl)-*N*-(5-nitro-furan-2-ylmethyl)-acetamide (24).** Following the procedure used for reductive amination as described by Abdel-Magid,²⁷ 5-nitro-2-furfural (3.0 g, 21 mmol), *tert*-butylamine (2.2 mL, 21 mmol), and NaBH(OAc)₃ (6.8 g, 32 mmol), and dichloroethane (72 mL) gave *tert*-butyl-(5-nitro-furan-2-ylmethyl)amine as an orange solid that was used in the next step without any further purification; mp 25-26 °C; IR (neat) 1593, 1529, 1356, 1229, and 739 cm⁻¹; ¹H-NMR (400 Hz, CDCl₃) δ 1.16 (s, 9H), 1.62 (brs, 1H), 3.82 (s, 2H), 6.46 (d, 1H, *J* = 3.6 Hz), and 7.24 (d, 1H, *J* = 3.6 Hz); ¹³C-NMR (100 Hz, CDCl₃) δ 28.8, 40.1, 50.9, 109.9, 112.8 (br), and 159.5.

A mixture of (7-methoxy-benzofuran-3-yl)-acetic acid²⁸ (0.21 g, 1.0 mmol), (COCl)₂ (0.26 mL, 3.0 mmol), in CH₂Cl₂ (80 mL) was treated with DMF (0.1 mL). A drying tube (CaSO₄) was added, and the mixture was stirred for 3 h. The mixture was then concentrated under reduced pressure to give the crude acid chloride. A cooled solution of the above amide (2.8 g, 12.1 mmol) and pyridine (1.8 mL, 24.2 mmol) in CH₂Cl₂ (80 mL) was added. After stirring for 1 h at rt, the reaction mixture was subjected to aqueous workup, and the residue was chromatographed on a silica gel column to give the title compound **24** (0.16 g, 41%) as a pale yellow solid: mp 140-142 °C; IR (film) 1654, 1629, 1625, 1497, and 1359 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 1.48 (s,

9H), 3.75 (d, 1H, $J = 1.2$ Hz), 3.99 (s, 3H), 4.65 (s, 2H), 6.41 (d, 1H, $J = 3.6$ Hz), 6.82 (dd, 1H, $J = 6.0, 1.5$ Hz), 7.05-7.20 (m, 2H), 7.22-7.31 (m, 1H), and 7.55 (s, 1H); ^{13}C -NMR (75 MHz, CDCl_3) δ 28.7, 32.5, 42.9, 56.1, 58.5, 106.8, 110.2, 111.9, 112.3, 114.5, 123.5, 129.2, 142.4, 144.5, 145.5, 156.4, and 170.7; Anal. Calcd. for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_6$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.30; H, 5.71; N, 5.65.

2-tert-Butyl-1-furan-2-yl-8-methoxy-1,4-dihydro-2H-benzo[4,5]furo[2,3-c]pyridin-3-one

(**25**). A 10 mL glass microwave reaction vessel containing furanyl amide **24** (0.07 g, 0.18 mmol), dry 1-methyl-2-pyrrolidinone (NMP, 2 mL) and a magnetic stir bar was sealed with a septum and irradiated for 15 min using a power of 300 W with continuous cooling (60 psi of compressed air). After cooling to rt, the mixture was subjected to the normal aqueous workup, and the residue was purified by preparative silica gel chromatography to give **25** (0.022 g, 36%) as a yellow solid: mp 164-166 °C; IR (film) 1678, 1654, 1620, 1498, 1207, and 731 cm^{-1} ; ^1H -NMR (600 Hz, CDCl_3) δ 1.44 (s, 9H), 3.70 (d, 1H, $J = 20.4$ Hz), 3.98 (dd, 1H, $J = 20.4$ and 1.8 Hz), 3.98 (s, 3H), 6.04 (s, 1H), 6.27-6.31 (m, 1H), 6.33 (d, 1H, $J = 3.6$ Hz), 6.80 (d, 1H, $J = 7.8$ Hz), 7.06 (d, 1H, $J = 7.2$ Hz), 7.17 (t, 1H, $J = 7.8$ Hz), and 7.30 (s, 1H); ^{13}C -NMR (150 Hz, CDCl_3) δ 28.3, 31.7, 50.7, 56.0, 58.9, 106.7, 107.7, 110.3, 110.5, 111.6, 123.9, 128.2, 142.6, 144.3, 145.4, 148.4, 152.0, and 170.0; Anal. Calcd. for $\text{C}_{20}\text{H}_{21}\text{NO}_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.63; H, 6.13; N, 4.06.

Acknowledgements

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