Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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September 2014: The paragraphs above replace the section “Handling and Disposal of Hazardous Chemicals” in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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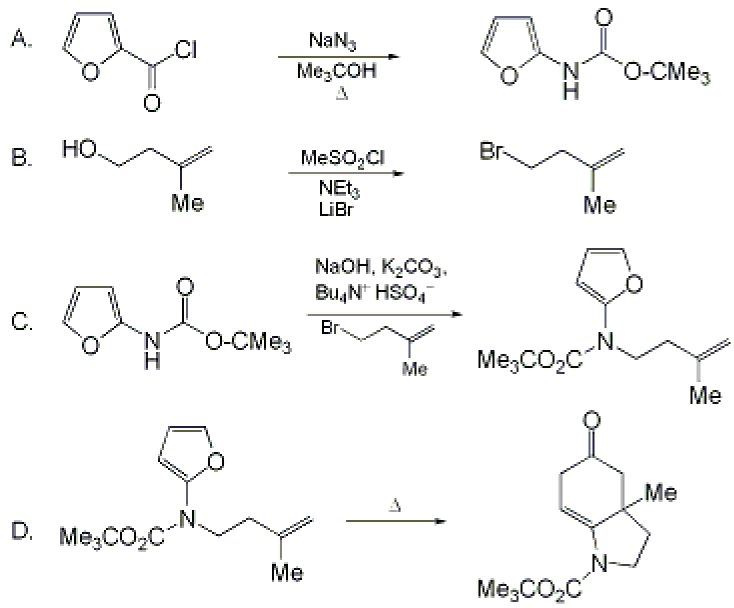
PREPARATION AND DIELS-ALDER REACTION OF A 2-AMIDO SUBSTITUTED FURAN: tert-BUTYL 3a-METHYL-5-OXO-2,3,3a,4,5,6-HEXAHYDROINDOLE-1-CARBOXYLATE

[1H-Indole-1-carboxylic acid, 2,3,3a,4,5,6-hexahydro-3a-methyl-5-oxo-, 1,1-dimethylethyl ester]



Submitted by Albert Padwa[1] , Michael A. Brodney, and Stephen M. Lynch.
Checked by Sivaraman Dandapani and Dennis P. Curran.

1. Procedure

A. Furan-2-ylcarbamic acid tert-butyl ester . In a 250-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar are placed 10 g (0.07 mol) of 2-furoyl chloride (Note 1), 80 mL of tert-butyl alcohol (Note 2), and 5.1 g (0.08 mol) of sodium azide (Note 3). After the flask is stirred at 25°C for 20 hr under an argon atmosphere, it is placed behind a protective shield (Note 4) and the solution is heated at reflux for 15 hr under a constant flow of argon. The solvent is removed with a rotary evaporator at aspirator vacuum to provide a white solid that is purified by flash silica gel chromatography (10% ethyl acetate/hexane) to give 10.8 g (81%) of furan-2-ylcarbamic acid tert-butyl ester as a white solid: mp 98-99°C (Note 5).

B. 4-Bromo-2-methyl-1-butene. In a 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, reflux condenser, and a dropping funnel are placed 20 g (0.23 mol) of 3-methyl-3-buten-1-ol (Note 6), 160 mL of freshly distilled dichloromethane (Note 7) and 36 mL (0.24 mol) of triethylamine (Note 8). The reaction mixture is cooled to −5°C and 14.4 g (0.24 mol) of freshly distilled methanesulfonyl chloride (Note 9) is added dropwise from the dropping funnel. After the reaction mixture is stirred at 0°C for an additional 2 hr, it is quenched with 80 mL of water and the aqueous phase is extracted three times with 40-mL portions of dichloromethane . The combined organic phase is dried over magnesium sulfate and the solvent is removed with a rotary evaporator at aspirator vacuum. The crude yellow oil is taken up in 25 mL of dry acetone and added dropwise from a dropping funnel to a slurry of 60 g (0.68 mol) of lithium bromide in 115 mL of dry acetone in a 250-mL round-bottomed flask fitted with the dropping funnel and a reflux condenser. The solution is slowly warmed to 35°C and is stirred at this temperature for 18 hr, at which time the reaction is quenched with 120 mL of water. The aqueous phase is extracted three times with 40-mL portions of ether. The combined organic phase is dried over magnesium sulfate and the solvent is removed with a rotary evaporator at aspirator vacuum. The resulting oil is distilled at aspirator pressure to provide 17.7 g (51%) of 4-bromo-2-methyl-1-butene as a colorless oil: bp 41-42°C at 34-39 torr (Note 10).

C. tert-Butyl N-(3-methyl-3-butenyl)-N-(2-furyl)carbamate. In a flame-dried, 500-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and reflux condenser are placed 4.0 g (21.8 mmol) of furan-2-ylcarbamic acid tert-butyl ester and 150 mL of toluene (Note 11) under an argon atmosphere. To this solution are added 3.1 g (76.4 mmol) of freshly ground powdered sodium hydroxide , 6.04 g (43.7 mmol) of potassium carbonate , and 1.48 g (4.4 mmol) of tetrabutylammonium hydrogen sulfate (Note 12). The solution is heated at 80°C for 25 min with vigorous stirring and then 3.9 g (26.2 mmol) of freshly distilled 4-bromo-2-methyl-1-butene is added as a solution in 10 mL of toluene over a 30-min period. After being heated at 80°C for 30 min, the solution is charged with an additional 0.98 g (6.6 mmol) of 4-bromo-2-methyl-1-butene . The mixture is heated at 80°C for an additional 1 hr. After the reaction is cooled to room temperature, it is quenched by the addition of 200 mL of water and the aqueous phase is extracted three times with 100-mL portions of dichloromethane . The combined organic phase is dried over magnesium sulfate and the solvent is removed with a rotary evaporator at aspirator vacuum. The crude residue is purified by silica gel chromatography (10% ethyl acetate-hexane) to give 5.0 g (91%) of tert-butyl N-(3-methyl-3-butenyl)-N-(2-furyl)carbamate as a colorless oil (Note 13).

D. tert-Butyl 3a-methyl-5-oxo-2,3,3a,4,5,6-hexahydroindole-1-carboxylate. Into an oven-dried, 35-mL heavy-wall, high pressure tube (Note 14) equipped with a magnetic stirring bar and rubber septum are placed 3.7 g (14.7 mmol) of tert-butyl N-(3-methyl-3-butenyl)-N-(2-furyl)carbamate and 20 mL of toluene under an argon atmosphere. Argon is vigorously bubbled through the solution for 30 min at which time the septum is replaced with a threaded plunger valve equipped with an O-ring seal (Note 14). The vessel is placed behind a protective shield (Note 4) and immersed into a preheated oil bath at 160°C for 14 hr. After the solution is cooled to room temperature, solvent is removed with a rotary evaporator at aspirator vacuum and the crude residue is purified by silica gel chromatography (40% ethyl acetate-hexane) to give 2.8 g (70-75%) of tert-butyl 3a-methyl-5-oxo-2,3,3a,4,5,6-hexahydroindole-1-carboxylate as a white solid: mp 112-113°C (Note 15).

2. Notes

1. 2-Furoyl chloride was purchased from Aldrich Chemical Company, Inc. , and used without further purification.
2. 2-Methyl-2-propanol (HPLC grade; tert-butyl alcohol) was purchased from Aldrich Chemical Company, Inc. , and used without further purification.
3. Sodium azide (99%) was purchased from Aldrich Chemical Company, Inc. ; a Teflon spatula was used when handling this reagent. *Caution: avoid contact with metal and heat when using sodium azide* .
4. The protective shield was purchased from Lab-Line, Inc. and was used for protection when heating at high temperatures.
5. The product has the following spectralcharacteristics: IR (neat) cm^{-1}: 3267, 2980, 1700, and 1546 ; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.50 (s, 9 H), 6.04 (brs, 1 H), 6.34 (m, 1 H), 6.63 (brs, 1 H), and 7.06 (m, 1 H) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 28.2, 81.3, 95.1, 111.2, 136.0, 145.4, 151.9 . Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.64. Found: C, 59.09; H, 7.13; N, 7.67.
6. 3-Methyl-3-buten-1-ol was purchased from Aldrich Chemical Company, Inc. , and used without further purification.
7. Dichloromethane was distilled from calcium hydride prior to use.
8. Triethylamine was purchased from Aldrich Chemical Company, Inc. , and used without further purification.
9. Methanesulfonyl chloride was purchased from Aldrich Chemical Company, Inc. , and was distilled before use.
10. The product has the following spectral characteristics: IR (neat) cm^{-1}: 3075, 1652, 1445, and 890 ; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.75 (s, 3 H), 2.58 (t, 2 H, J = 7.4), 3.47 (t, 2 H, J = 7.4), 4.77 (s, 1 H), and 4.86 (s, 1 H) ; ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 22.1, 31.0, 41.1, 112.9, and 142.6
11. Toluene was distilled from calcium hydride prior to use.
12. Tetrabutylammonium hydrogen sulfate (97%) was purchased from Aldrich Chemical Company, Inc.

, and used without further purification.

13. The product has the following spectral characteristics: IR (neat) cm^{-1}: 2975, 1711, 1606, and 1369 ; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.45 (s, 9 H), 1.74 (s, 3 H), 2.27 (t, 2 H, J = 7.2), 3.67 (dd, 2 H, J = 9.2 and 6.0), 4.71 (s, 1 H), 4.76 (s, 1 H), 6.33 (brs, 1 H), 7.14 (t, 1 H, J = 1.2), and 6.0 (brs, 1 H) ; ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 22.2, 28.0, 36.6, 46.9, 80.7, 100.9, 110.7, 111.8, 137.8, 142.3, 148.3, and 153.5 . Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.93; H, 8.38; N, 5.60. The broad resonance at δ 6.0 in the ^{1}H NMR spectrum merges into a sharp multiplet when the spectrum is recorded at 50°C.

14. The 35-mL heavy-wall high pressure tube, Teflon plug, and O-ring were purchased from Ace Glass and were oven dried prior to use.

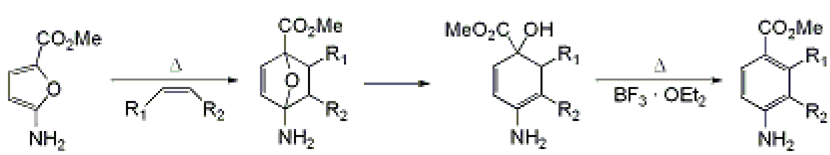
15. The product has the following spectral characteristics: IR (KBr) cm^{-1}: 2961, 1709, and 1388 ; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 0.94 (s, 3 H), 1.42 (s, 9 H), 1.72 (m, 2 H), 2.35 (d, 1 H, J = 14.6), 2.49 (d, 1 H, J = 14.6), 2.63 (dd, 1 H, J = 14.6 and 2.8), 2.89 (dd, 1 H, J = 14.6 and 4.8), 3.51 (m, 1 H), 3.66 (m, 1 H), and 5.78 (brs, 1 H) ; ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 22.8, 27.7, 35.2, 36.7, 42.5, 46.1, 51.6, 79.6, 96.4, 143.7, 151.5, and 208.3 . Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.99; H, 8.38; N, 5.49.

Waste Disposal Information

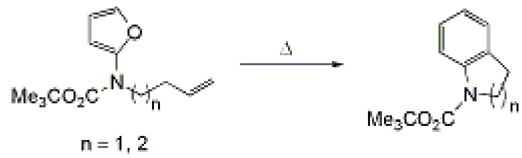
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

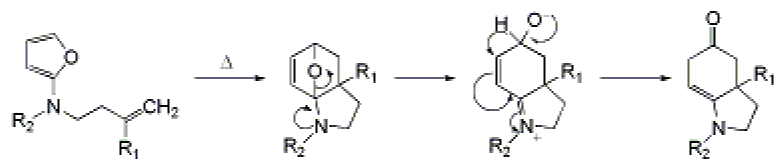
3. Discussion

Heterocycles such as furan, thiophene, and pyrrole undergo Diels-Alder reactions despite their stabilized 6p-aromatic electronic configuration.[2] By far the most extensively studied five-ring heteroaromatic system for Diels-Alder cycloaddition is furan and its substituted derivatives.[3] The resultant 7-oxabicyco[2.2.1]heptanes are valuable synthetic intermediates that have been further elaborated to substituted arenes, carbohydrate derivatives, and various natural products.[4] [5] [6] A crucial synthetic transformation employing these intermediates involves the cleavage of the oxygen bridge to produce functionalized cyclohexene derivatives.[7,8] While the bimolecular Diels-Alder reaction of alkyl-substituted furans has been the subject of many reports in the literature,[9] much less is known regarding the cycloaddition behavior of furans that contain heteroatoms attached directly to the aromatic ring.[10] In this regard, we have become interested in the Diels-Alder reaction of 2-aminofurans as a method for preparing substituted aniline derivatives since these compounds are important starting materials for the preparation of various pharmaceuticals.[11] Many furan Diels-Alder reactions require high pressure or Lewis acid catalysts to give satisfactory yields of cycloadduct.[12] In contrast to this situation, 2-amino-5-carbomethoxyfuran readily reacted with several monoactivated olefins by simply heating in benzene at 80°C. The initially formed cyclohexadienol underwent a subsequent dehydration when treated with 1 equiv of boron trifluoride etherate ($BF_3·OEt_2$) to give the substituted aniline derivative.[13] In each case, the cycloaddition proceeded with complete regioselectivity, with the electron-withdrawing group being located ortho to the amino group. The regiochemical results are perfectly consistent with FMO theory.[14] The most favorable FMO interaction is between the HOMO of the furanamine and the LUMO of the dienophile. The atomic coefficient at the ester carbon of the furan is larger than at the amino center, and this nicely accommodates the observed regioselectivity.



The intramolecular Diels-Alder reaction of furans, often designated as IMDAF,[15] helps to overcome the sluggishness of this heteroaromatic ring system toward [4+2]-cycloaddition. Not only do IMDAF reactions allow for the preparation of complex oxygenated polycyclic compounds, but they also often proceed at lower temperatures than their intermolecular counterparts.[9] Even more significantly, unactivated p-bonds are often suitable dienophiles for the internal cycloaddition. Indeed, the submitters discovered that the IMDAF reaction of a series of furanamide derivatives occurred smoothly to furnish cyclized aromatic carbamates as the only isolable products in high yield.[16] When the alkenyl group possesses a substituent at the 2-position of the p-bond, the thermal reaction furnishes a rearranged hexahydroindolinone.[17] With this system, the initially formed cycloadduct cannot aromatize. Instead, ring opening of the oxabicyclic intermediate occurs to generate a zwitterion that undergoes hydride transfer to give the rearranged ketone. The procedure described here provides a simple and general approach for the construction of various hexahydroindolinones. This strategy can be cleanly applied toward the synthesis of more complex octahydroindole-based alkaloids.





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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

tert-Butyl 3a-methyl-5-oxo-2,3,3a,4,5,6-hexahydroindole-1-carboxylate:
1H-Indole-1-carboxylic acid, 2,3,3a,4,5,6-hexahydro-3a-methyl-5-oxo-, 1,1-dimethylethyl ester (14);
(212560-98-0)

Furan-2-ylcarbamic acid tert-butyl ester:
Carbamic acid, 2-furanyl-, 1,1-dimethylethyl ester (9); (56267-47-1)

2-Furoyl chloride (8):
2-Furancarbonyl chloride (9); (527-69-5)

tert-Butyl alcohol (8):
2-Propanol, 2-methyl- (9); (75-65-0)

Sodium azide (8,9); (26628-22-8)

4-Bromo-2-methyl-1-butene:
1-Butene, 4-bromo-2-methyl- (8,9); (20038-12-4)

3-Methyl-3-buten-1-ol:
3-Buten-1-ol, 3-methyl- (8,9); (763-32-6)

Methanesulfonyl chloride (8,9); (124-63-0)

Lithium bromide (8,9); (7550-35-8)

tert-Butyl N-(3-methyl-3-butenyl)-N-(2-furyl)carbamate:
Carbamic acid, 2-furanyl(3-methyl-3-butenyl)-, 1,1-dimethylethyl ester (14); (212560-95-7)

Toluene (8);
Benzene, methyl- (9); (108-88-3)

Tetrabutylammonium hydrogen sulfate:
Ammonium, tetrabutyl-, sulfate (1:1) (8);
1-Butanaminium, N,N,N-tributyl-, sulfate (1:1) (9); (32503-27-8)