

PREPARATION OF TRICYCLIC NITROGEN HETEROCYCLE VIA INTRAMOLECULAR DIELS-ALDER REACTION

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Abstract: Preparation of rigid tricyclic nitrogen heterocycles under radicalic condition has been studied. Cyclisation is performed by Diels-Alder ring closure after radicalic hydrogenation. We did not observe any radicalic Cycloaddition / Fragmentation product 12. Tri-*n*-butyltin hydride (TBTH) and azobisisobutyronitrile were used in toluene or benzene to generate radicalic condition. Intramolecular Diels-Alder (IMDA) reaction on substituted furan species gave tricyclic heterocycle.

Keywords: Tri-*n*-butyltin hydride (TBTH), azobisisobutyronitrile (AIBN), Intramolecular Diels-Alder reaction (IMDA), cycloaddition.

Introduction

The use of radical reactions, particularly radical cyclisation has been very popular in organic chemistry for the last fifteen years.¹ We have recently been investigating novel routes directed to the construction of highly substituted cyclopentenes for the synthesis of natural products including the prostaglandin.² We discovered that alkenyl radicals add to furans and that a fragmentation follows to give cabocyclic rings as depicted in figure 1. Our approach envisaged the intramolecular addition of an alkenyl radical to furan leading to the formation of a cyclopentene. Treatment of the bromoalkene 1 with tri-*n*-butyltin hydride in the presence of AIBN was expected to result in spirocyclisation leading to radical 3. Under high dilution conditions the intermediate radical 3 should fragment to the more stable cyclopenten radical 4 which would then be quenched.

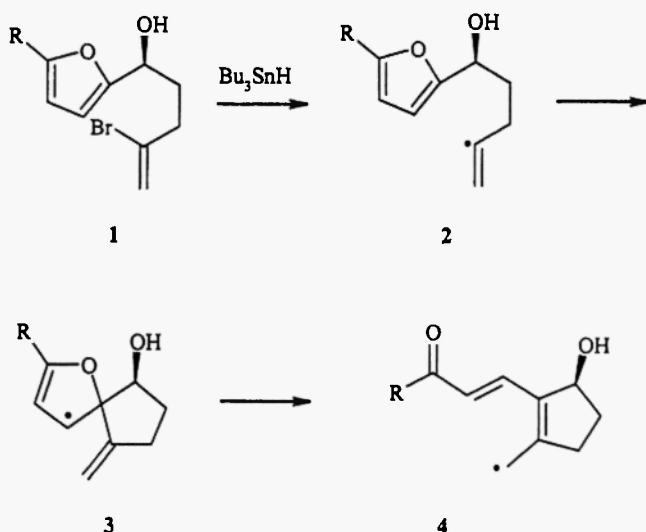


Figure 1: Cycloaddition / fragmentation process of furans.

Experimental

Reactions were conducted in flame-dried glassware, under a nitrogen atmosphere except when noted otherwise. Solvents and reagents were freshly distilled as follows: tetrahydrofuran (THF) and diethylether (E) were distilled from sodium/benzophenone; dichloromethane (DCM) and toluene were distilled from calcium hydride. Reactions were monitored by thin layer chromatography (t.l.c) using pre-coated silica plates (Macharey Nagel Sil G UV₂₅₄). Compounds were visualised using ultra-violet fluorescence, alkaline potassium permanganate solution or acidic cerium (IV) sulfate solution. Column chromatography was carried out on Macheray Nagel Kieselgel 60 (230-240 mesh).

¹H-NMR and ¹³C-NMR spectra were recorded with 300 MHz Bruker DPX 300 spectrometer. Chemical shifts are quoted as δ values downfield of tetramethylsilane (TMS) or relative to the residual solvent resonance in ppm. Resonance multiplets are abbreviated as follows d-doublet, t-triplet, s-singlet, br-broad, q-quaternary, m-multiplet. Infra-red (IR) spectra were recorded using a FT instrument (Perkin-Elmer 1720). Samples were analysed as thin film on KBr plates. High-resolution mass spectra (HRMS) and electron ionisation mass spectra (EI) were obtained on a fisons Instrument VG Autospec.

5-(2'-(*N*-*tert*-Butoxycarbonyl)-ethylamide)-2-methylfuran ³ 7

N,N-Dimethylaminopyridine (56mg 0.46mmol) was added to a solution of 5-methyl-2-(2'-aminoethyl) furan **6** (570mg, 4.6mmol) and di-*tert*-butoxy dicarbonate, $(\text{BOC})_2\text{O}$ (1000mg, 4.6mmol) in DCM (50mL) at 0°C. The reaction mixture was stirred for 2h at ambient temperature and then concentrated under reduced pressure. The

residue was subjected to flash column chromatography to give the title compound as colourless oil (950mg, 92%).

t.l.c., Petroleum Ether (40-60°C) (PE) : E; (7:3)) R_f : 0.3; ν_{max} (thin film)/cm⁻¹: 3353(br, NH), 2978(s, CH), 1700(s, C=O), 1618(w, C=C), 1172(s, C-C). δ_{H} (CDCl₃): 5.90(d, 1H, J 2.9Hz), 5.83(d, 1H, J 2.9Hz), 4.62(br, 1H, NH), 3.42(t, 2H, J 6.3Hz), 2.76(t, 2H, J 6.3Hz), 2.2(s, 3H), 1.41(s, 9H). δ_{C} (75.5MHz, CDCl₃): 156.2, 151.6, 151.4, 107.0, 106.4, 80.0, 40.0, 29.1, 28.8 (x3C), 14.0. % (GC-MS): 225[M⁺, 13%], 169[M⁺-('Bu+H), 42%] 152[M⁺-O^tBu, 33%], 95[M⁺, -(CH₂NHCOO^tBu), 100%].

5-(2'-(N-2"-Bromoprop-2"-ene)ethylamino)-2-methylfuran: 8

To a stirred solution of 5-methyl-2-(2'-aminoethyl)furan 6 (700mg, 5.6mmol) in THF (15mL) was added 2,3-dibromopropene (560mg, 2.8mmol) and the resulting solution was heated to reflux for 12h. A portion of potassium carbonate (1760mg, 12.8mmol) was then added, and the reaction mixture was heated at reflux for a further 48h. On cooling a precipitate was formed which was washed with diethyl ether (3x15mL). The filtrate was extracted with 10% NaOH (15mL) and the combined organic phases were dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was subjected to flash column chromatography to afford the title compound as a colourless oil (660mg, 48%).

t.l.c., (PE : E; (7:3)), R_f : 0.22; ν_{max} (thin film)/cm⁻¹: 3339(br., NH), 2921(s, C-H), 1739(s, C=C), 783(s, C-Br). δ_{H} (CDCl₃): 5.89(d, 1H, J 3.2Hz), 5.80(d, 1H, J 3.2Hz), 5.65(s, 1H), 5.44(s, 1H), 3.40(s, 2H), 2.84-2.80(m, 4H), 2.20(s, 3H), 1.82(br. s, NH). δ_{C} (75.5MHz, CDCl₃): 155.0, 153.2, 135.8, 120.2, 109.2, 108.5, 60.0, 49.7, 31.2, 16.0. % (GC-MS): 245[M⁺(⁸¹Br), 27%], 243[M⁺(⁷⁹Br), 28%], 150[M⁺(CH₂NHCH₂C⁸¹BrCH₂), 100%], 148 [M⁺, (CH₂NHCH₂C⁷⁹BrCH₂), 100%]. HRMS(C₁₀H₁₄⁷⁹BrNO): Calc.: 243.0258 Found: 243.0270.

5-(2'-(N-2"-Bromoprop-2"-ene)-N-*tert*-butoxycarbonylethylamine)-2-methyl-furan: 9

Procedure 1:

To a solution of 5-(2'-(N-*tert*-butoxycarbonyl)-ethylamide)-2-methylfuran 7 (0.34g, 1.53mmol) in THF (10mL) was added *n*-BuLi (2.4M in hexane) (0.64mL, 1.53mmol) at -78°C. The reaction mixture was stirred for 30min, before a solution of 2,3-dibromo propene (0.31g, 1.53mmol) in THF (5mL) was added dropwise at -78°C. The solution was then warmed to ambient temperature, and stirred for additional 2h. The reaction was then quenched with water (15mL) and extracted with diethyl ether (3x10mL). The combined organic layers were washed with brine (20mL), dried over MgSO₄ and concentrated under reduced pressure. The residue was subjected to flash column chromatography to afford the title compound as a pale yellow oil (180mg, 35%).

Procedure 2:

To a stirred solution of 5-(2'-(N-2"-bromo prop-2"-ene) ethylamino)-2-methyl-furan 8 (0.56g, 2.3mmol) and di-*tert*-butoxy dicarbonate (BOC)₂O (0.55g, 2.5mmol) in DCM (10mL) was added *N,N*-dimethylaminopyridine (30mg, 0.25mmol) at 0°C. The reaction mixture was stirred for 2h at ambient temperature and then concentrated

under reduced pressure. The residue was subjected to flash column chromatography to afford the title compound as a pale yellow oil (650mg, 83%).

t.l.c., (PE : E; (7:3)), R_f : 0.42; ν_{max} (thin film)/cm⁻¹: 2976(s, C-H), 1702(s, C=O), 1639(w, C=C). δ_{H} (CDCl₃): 5.83(d, 1H, J 5.42Hz), 5.77(d, 1H, J 5.42Hz), 5.61(s, 1H), 5.54(s, 1H), 3.90(s, 2H), 3.51(m, 2H), 2.86-2.82(m, 2H), 2.25(s, 3H), 1.45(s, 9H). δ_{C} (75.5MHz, CDCl₃): 158.0, 154.3, 152.1, 134, 120.2, 109.5, 108.4, 83.2, 60.0, 48.3, 28.7(x3C), 30.2, 15.9. $^{\text{m}}/\%$ (GC-MS): 345[M⁺(⁸¹Br), 33%], 343[M⁺(⁷⁹Br), 33%], 288[M⁺(⁸¹Br)-(^tBu), 15%], 286[M⁺(⁷⁹Br)-(^tBu), 15%], 150[M⁺(NHC⁸¹BrCH₂), 24%], 57[^tBu⁺, 100%].

HRMS (C₁₅H₂₂⁷⁹BrNO₃): Calc: 343.0783 Found: 343.0796.

4-Methyl-8-aza-8-N-tert-butoxy-1,4-epoxybicyclo[4.4.0]dec-2-ene: 10

To a boiling solution of 5-(2'-[N-2"-bromoprop-2"-ene]-N-*tert*-butoxycarbonyl ethylamine)-2-methyl-furan 9 (680mg, 2.0mmol) and AIBN (20mg, 0.1mmol) in toluene (45mL) was added a solution of tri-*n*-butyltin hydride (1.48mL, 4.9mmol) and AIBN (26mg, 0.15mmol) in toluene (19mL) over a period of 12h via syringe pump. The reaction was heated at reflux for an additional 5h, allowed to cool and then concentrated under reduced pressure. The resultant liquid was diluted with ethyl acetate (46mL) and KF (2.0g) was added followed by water (2mL) and the mixture was stirred for 3h. Potassium carbonate was then added to the mixture and the solids were filtered. The filtrate was concentrated under reduced pressure and the residue was subjected to flash column chromatography to afford the title compound as a pale yellow oil (120mg, 22%).

t.l.c., (PE : E (7:3)) R_f : 0.38; ν_{max} (thin film)/cm⁻¹: 2975(s, C-H), 1699(s, C=O), 1479(w, C-H) δ_{H} (CDCl₃): 5.95(d, 1H, J 6.8Hz), 5.82(d, 1H, J 6.8Hz), 3.54-3.50(m, 2H), 3.46-3.42(m, 2H), 2.85-2.81(m, 2H), 2.18(s, 3H), 1.79-1.75(m, 1H), 1.43(s, 9H), 1.33(d, 2H, J 6.7Hz). δ_{C} (75.5MHz, CDCl₃): 154.2, 151.1, 150.3, 106.4, 105.8, 79.2, 52.7, 50.2, 44.7, 38.3, 28.6 (x3C), 16.2, 13.6. $^{\text{m}}/\%$ (GC-MS): 265[M⁺, 24%], 208[M⁺-^tBu, 85%], 164[M⁺-BOC, 55%], 149[[M⁺-(CH₃+BOC), 28%], 57[^tBu⁺, 100%]. HRMS(C₁₅H₂₃NO₃): Calc: 265.1677 Found: 265.1688.

Discussion and Results

Alkenyl furan species 9 was prepared by the process described in figure 2. Henry reaction with 2-methyl-5-furfural 5 gave nitrofuran, this yellow crystalline compound was then reduced to the amine 6 using lithium aluminium hydride in 56% yield.⁴ The furanyl amine 6 was protected to 7 in 85% yield using di-*tert*-butyl dicarbonate in the presence of *N,N*-dimethylaminopyridine.⁵ The carbamate 7 was reacted with *n*-butyllithium and then 2,3-dibromopropene to provide precursor adduct 9 in 35% yield.

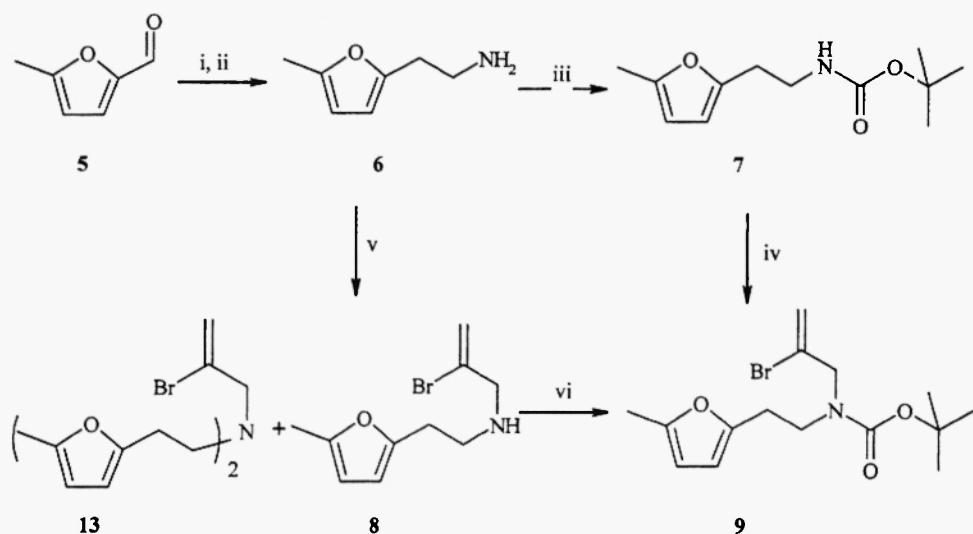


Figure 2: i. CH_3NO_2 , NaOH , MeOH , H_2O , -10°C , 80%; ii. LiAlH_4 , THF , reflux, 12h, 54%; iii. $(\text{BOC})_2\text{O}$, DMAP , DCM , 0°C , 2h, 92%; iv. $n\text{-BuLi}$, THF , 2,3-dibromopropene, -78°C , 35%; v. K_2CO_3 , THF , 2,3-dibromopropene, reflux, 48%; vi. $(\text{BOC})_2\text{O}$, DCM , DMAP , 83%.

Alternatively, the amine **6** was treated with potassium carbonate, and then addition of 2,3-dibromopropene provided the bromoamide **8** (48%) yield with dialkylated side product **13**.⁶ Treatment of the amide **8** with *tert*-butoxy dicarbonate and DMAP afforded precursor compound **9** in 83% yield (Figure 2). The radical reaction was carried out with slow addition of tri-*n*-butyltin hydride in the presence of AIBN to the refluxing solution of bromocarbamate **9** provided Diels-Alder type product **10** in 22% yield, instead of the fragmented product towards **12**. There was also 23% reduced starting material. The majority of the product was dimerised adduct of starting material in 43%. (Figure 3)

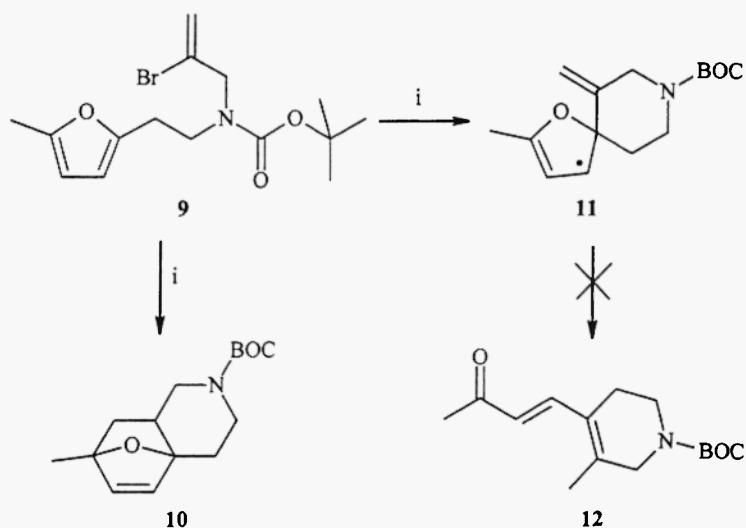


Figure 3: i. Bu_3SnH , AIBN , PhMe , 21h, reflux, 22%.

We did not observe any IMDA adduct from heated **8**, due to the reversibility. Kinetically, six-member cyclisation pathway might be difficult, therefore the reaction might have gone under [4+2] cycloaddition due to the steric buttress of *tert*-butoxy carbonate.⁷ Furans have been used as an electron rich diene partners in the Diels-Alder reactions to prepare rigid oxygenated bicyclic systems enroot to various natural products.⁸

As a conclusion, this is a simple and efficient route to construct rigid tricyclic molecules, also this reaction has not been fully utilised in organic synthesis. Further progress in this area will be reported in due course.

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