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Convenient synthesis of 2-(1-adamantyl)furans.

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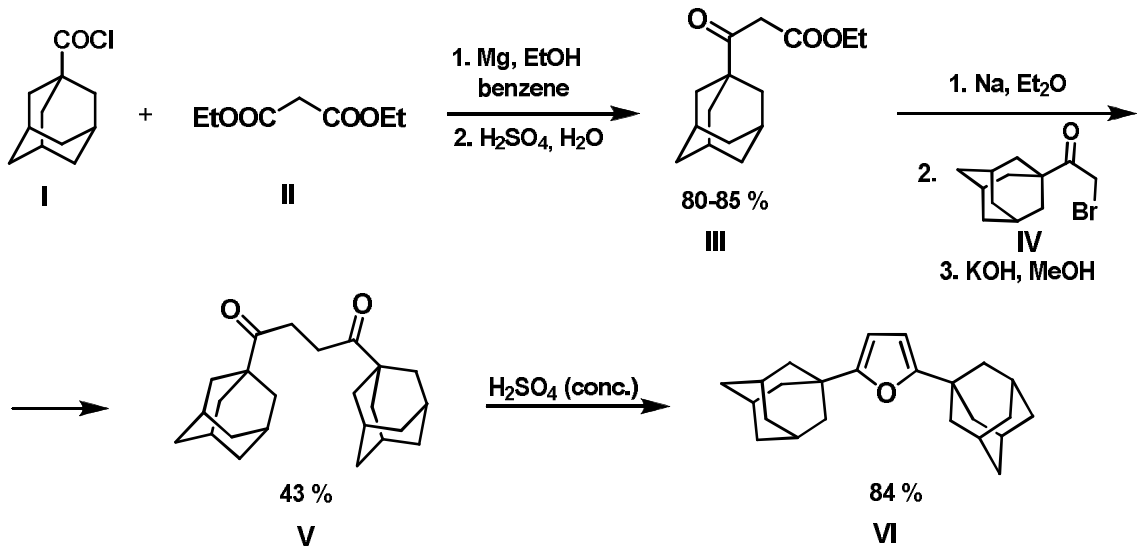
Abstract: A a simple method of obtaining 2-(1-adamantyl)furans using a smaller amount of catalyst, providing a higher yield of the target products, as well as the possibility of varying the substituents in the furan ring was developed. The result is achieved by the adamantylation of furans with 1-adamantanol in a nitromethane medium in the presence of a Lewis acid, for which aluminum or bismuth triflate was used in an amount of 10 mol%.

Keywords: 2-(1-adamantyl)furan; adamantylation; furan; catalysis.

1. Introduction

Among first preparation examples of furans containing the 1-adamantyl moiety is the method where 2,5-di(1-adamantyl)furan was prepared using 1-adamantoyl chloride and malonic ester as the starting compounds [1] (Fig. 1).



I II III IV V VI

Figure 1. Synthesis of 2,5-di(1-adamantyl)furan.

At the first step, diethyl malonate II is acylated with 1-adamantoyl chloride I. Then, the resulting ethyl 3-(1-adamantyl)-3-oxopropionate III is alkylated with 1-(1-adamantyl)-2-bromoethane IV. Subsequent cyclization of 1,4-di(1-adamantyl)butane-1,4-dione V in concentrated sulfuric acid affords the target product VI in yield of 84% (the total yield in all steps was 30%).

The method for preparation of adamantylated furans which includes the radical adamantylation of methyl 5-nitrofuran-2-carboxylic acid VII or 5-nitrofurfural was described. The adamantyl radical in this method was generated by the Ag(I)-catalyzed oxidative decarboxylation of 1-adamantanecarboxylic acid VIII [2] (Fig. 2).

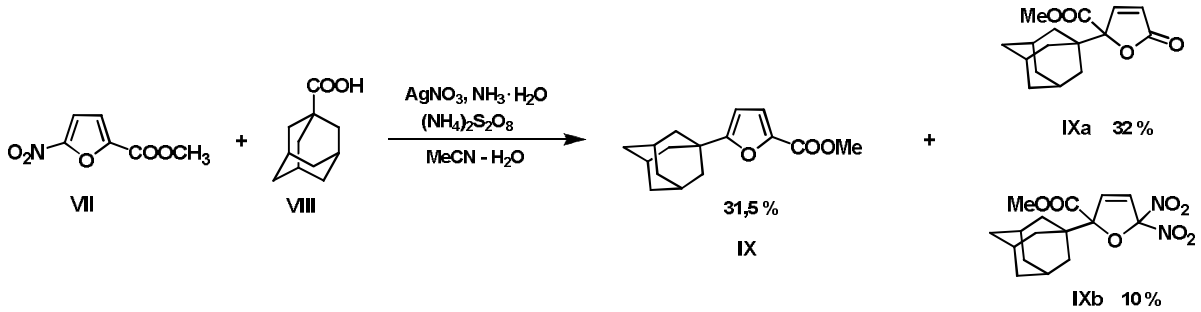


Figure 2. Radical adamantylation of methyl 5-nitrofuran-2-carboxylic acid.

The three-step method for preparation of 1-adamantylfuran was proposed, where the starting compound was 1-adamantanecarbaldehyde X (Fig. 3).

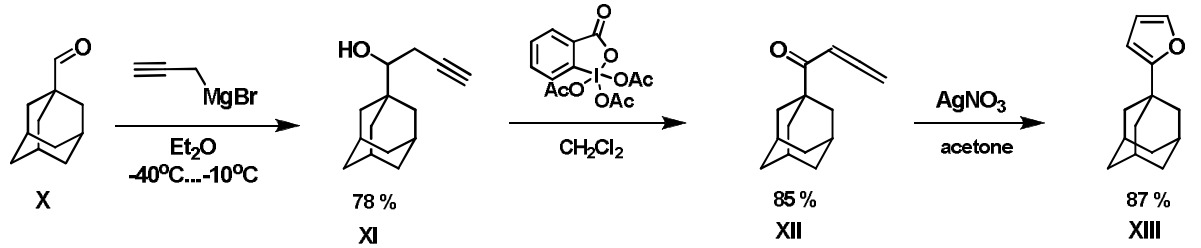


Figure 3. Preparation of 1-adamantylfuran

Initially, the reaction of 1-adamantanecarbaldehyde and propargyl magnesium bromide affords the corresponding homopropargyl alcohol XI which is oxidized by the Dess–Martin periodinane into allenyl ketone XII. Its subsequent heterocyclization on exposure to silver nitrate results in the target 1-adamantylfuran XIII in the total yield of 58% (based on three steps) [3].

The method for 1-adamantylation of furans ring-substituted with electron-withdrawing groups (2-acetylfuran XIV, furan-3-carboxaldehyde XVII) using 1-iodoadamantane XV in the presence of 10 mol.% tetrakis(triphenylphosphine)palladium(0), 14 mol.% 1,3-bis(diphenylphosphino)propane (dppp), and 200 mol.% cesium carbonate in trifluorotoluene is known [4] (Fig. 4).

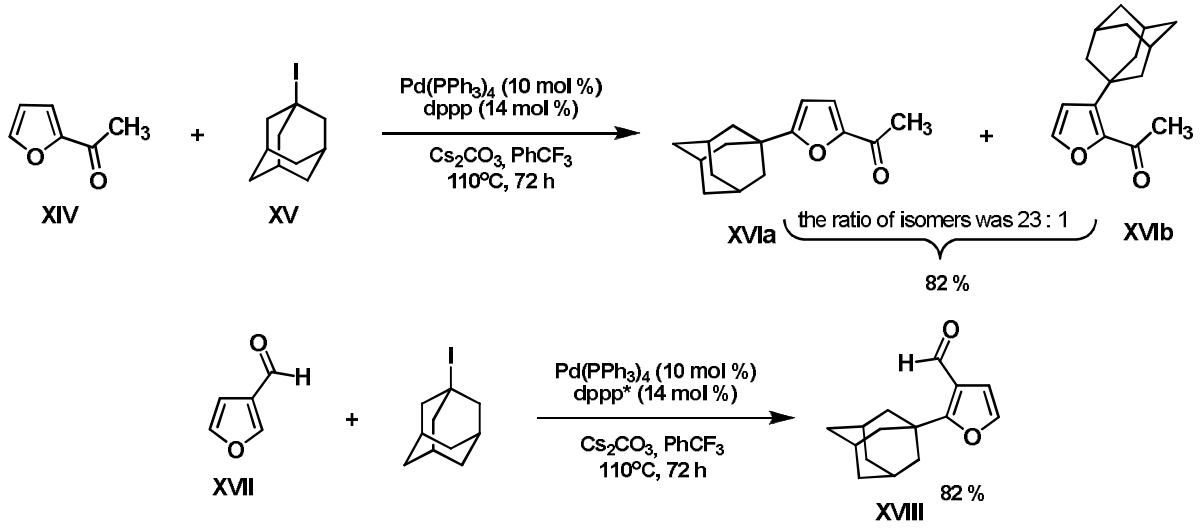


Figure 4. Adamantylation of furans with 1-iodoadamantane.

Adamantylation using 1-bromoadamantane in the presence of Lewis acid was used in the patent application: methyl furan-2-carboxylate XIX was treated with 1-bromoadamantane XX in ortho-dichlorobenzene in the presence of 200 mol.% aluminum chloride. The yield of the target product XXI was 49% [5] (Fig. 5).

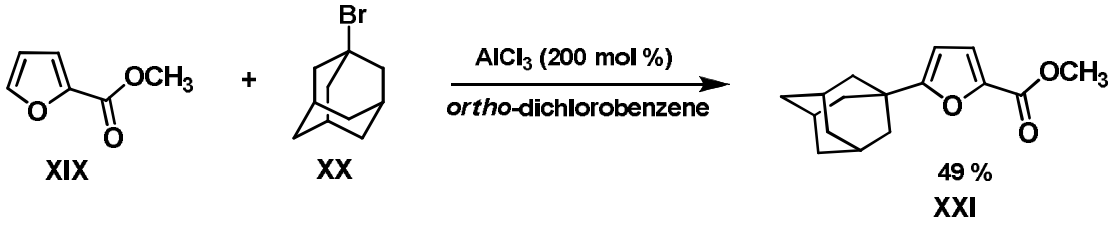


Figure 5. Adamantylation of furans with 1-bromoadamantane.

Adamantylation of 2-furancarboxylic acid XXII in dichloromethane in the presence of 200 mol. % aluminum chloride proceeds similarly. The yield of the target product XIV was 65% [6] (Fig. 6).

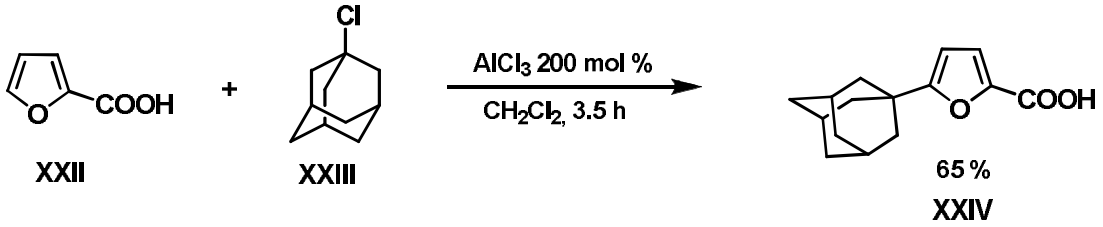


Figure 6. Adamantylation of furans with 1-chloroadamantane.

The above-mentioned methods for the synthesis of 1-adamantylated furans have drawbacks: many steps in the synthesis scheme, the need for expensive palladium catalysts and specific reaction media, or the formation of mixed reaction products. In addition, no one of the above-given methods was realized for a wide spectrum of furan substrates, which would allow one to talk about its versatility.

2. Materials and Methods.

^{1}H and ^{13}C NMR spectra were recorded on an ECA 400 (JEOL) instrument in $CDCl_3$ or $(CD_3)_2SO$ (Cambridge Isotop Laboratories Inc.) using residual solvent signals as the internal standard. IR spectra were recorded on an IR Prestige instrument (Shimadzu) in KBr pellets. The course of the reactions was monitored by gas chromatography–mass spectrometry (GC/MS) using a GC-2010 instrument (Shimadzu) with QP-2010 Plus mass selective detector (Shimadzu): the column was Supelko SLB-5ms, 30 m; programmed heating from 60 to 265°C at a rate of 30°C/min. Melting points were measured in open-end capillaries on a Stuart SMP30 instrument. The reagents used were commercially available from Aldrich, Acros, or ABCR.

Example of preparation of 2-(1-adamantyl)-5-(*tert*-butyl)furan (2a).

1-Adamantanol (250 mg, 1.64 mmol) and aluminum triflate (78.9 mg, 0.164 mmol) were added to nitromethane (7 mL). 2-(*tert*-Butyl)furan (200 mg, 1.64 mmol) was added and the resulting solution was stirred for 4 h at room temperature. The reaction mixture was transferred to a separatory funnel containing 2 M hydrochloric acid (20 mL) and chloroform (5 mL). The organic layer was separated, the aqueous layer was extracted with chloroform (3 × 5 mL), and the combined chloroform extracts were evaporated on a rotary evaporator. The residue was purified by flash chromatography using hexane–ethylacetate (20 : 1) as the eluent to give product 2a in yield of 83% as colorless crystals, m.p. 60-61°C. IR (KBr), ν/cm^{-1}: 3103 (Csp^2–H), 2964, 2927, 2906, 2848 (Csp^3–H),

1604, 1556 (Csp^2–Csp^2), 1452. MS (EI, 70 eV), m/z (I_{rel} (%)): 258 (15, M^+), 243 (100). ^1H NMR (399.78 MHz, $CDCl_3$), δ: 1.25 (s, 9H, CH_3), 1.72–1.78 (m, 6H, CH_2), 1.88–1.91 (m, 6H, CH_2), 2.01–2.06 (m, 3H, CH), 5.76 (d, 1H, CH, $^3J_{HH}$ = 3.2 Hz), 5.81 (d, 1H, CH, $^3J_{HH}$ = 3.2 Hz). ^{13}C NMR ($CDCl_3$), δ: 28.2 (CH), 29.0 (CH_3), 32.6 (C), 34.5 (C), 36.9 (CH_2), 41.2 (CH_2), 101.0 (CH), 101.4 (CH), 161.7 (C), 162.6 (C).

2-(1-Adamantyl)-5-methylfuran (2b). Yield 79 %. IR (KBr), ν/cm^{-1}: 3103 (Csp^2-H), 2964, 2927, 2906, 2848 (Csp^3-H), 1604, 1556 (Csp^2-Csp^2), 1452. MS (EI, 70 eV), m/z (I_{rel} (%)): 216 (75, M^+), 159 (100), 131 (15), 122 (34). ^1H NMR (399.78 MHz, $CDCl_3$), δ: 1.71–1.77 (m, 6H, CH_2), 1.87–1.90 (m, 6H, CH_2), 1.99–2.06 (m, 3H, CH), 2.25 (s, 9H, CH_3), 5.76 (d, 1H, CH, $^3J_{HH}$ = 2.7 Hz), 5.82 (d, 1H, CH, $^3J_{HH}$ = 2.7 Hz). ^{13}C NMR ($CDCl_3$), δ: 13.5 (CH_3), 28.3 (CH), 34.3 (C), 36.8 (CH_2), 41.3 (CH_2), 101.7 (CH), 105.4 (CH), 149.6 (C), 163.1 (C).

2-(1-Adamantyl)furan (2c) Yield 79 %. Colorless oil. MS (EI, 70 eV), m/z (I_{rel} (%)): 202 (71, M^+), 159 (10), 145 (100), 117 (28), 108 (33). NMR spectrum corresponds to the published at [3].

2-(1-Adamantyl)-5-(4-nitrophenyl)furan (2d). Yield 83 %. Желтые кристаллы. m.p. 169 - 170°C. IR (KBr), ν/cm^{-1}: 3012 (Csp^2-H), 2920, 2904, 2893, 2852 (Csp^3-H), 1602, 1508 (Csp^2-Csp^2), 1535 (NO_2 as), 1332 (NO_2 sy). MS (EI, 70 eV), m/z (I_{rel} (%)): 323 (100, M^+), 266 (68), 229 (24), 150 (14). ^1H NMR (399.78 MHz, $CDCl_3$), δ: 1.75 - 1.82 (м, 6H, CH_2), 1.96 – 1.99 (м, 6H, CH_2), 2.06 – 2.10 (м., 3H, CH), 2.07 – 2.12 (м., 6H, CH_2), 6.08 (*д*, 3.2 Гц, 1H, CH), 6.77 (*д*, 3.2 Гц, 1H, CH), 7.72 (м, 2H, CH), 8.20 (м, 2H, CH). ^{13}C NMR ($CDCl_3$), δ: 28.2 (CH), 34.9 (C), 36.7 (CH_2), 41.2 (CH_2), 104.8 (CH), 109.9 (CH), 123.3 (CH), 124.3 (CH), 137.0 (C), 145.8 (C), 149.4 (C), 167.0 (C).

2-((5-(1-Adamantyl)-2-furyl)methyl)-1H-isoindole-1,3(2H)-dione (2e). Yield 77 %. IR (KBr), ν/cm^{-1}: 3115, 3103 (Csp^2-H), 2906, 2848 (Csp^3-H), 1774, 1722 (C=O). MS (EI, 70 eV), m/z (I_{rel} (%)): 361 (96, M^+), 333 (21), 267 (10), 226 (44), 157 (92), 135 (100). ^1H NMR (399.78 MHz, $CDCl_3$), δ: 1.70 - 1.78 (м, 6H, CH_2), 1.85 (уш.с, 6H, CH_2), 2.00 (уш.с, 3H, CH), 4.81 (с, 2H, CH_2), 5.81 (*д*, 3.2 Гц, 1H, CH), 6.21 (*д*, 3.2 Гц, 1H, CH), 7.67 – 7.73 (м, 2H, CH), 7.82-7.88 (м, 2H, CH). ^{13}C NMR ($CDCl_3$), δ: 28.2 (CH), 34.6 (CH_2), 36.7 (CH_2), 41.1 (CH_2), 43.2 (C), 102,3 (CH), 108.9 (CH), 123.4 (CH), 132.2 (C), 134.0 (CH), 147.0 (C), 164.6 (C), 167.7 (C=O).

Ethyl 5-(1-adamantyl)-2-furoate (2f). Yield 72 %. Colorless crystals. m.p. 84°C. IR (KBr), ν/cm^{-1}: 3169, 3128 Csp^2-H), 2981, 2941, 2900, 2850 (Csp^3-H), 1720 (C=O). MS (EI, 70 eV), m/z (I_{rel} (%)): 274 (100, M^+), 229 (19), 217 (63), 180 (23). ^1H NMR (399.78 MHz, $CDCl_3$), δ: 1.36 (t, 7 Hz, CH_3, 3H), 1.73 -1.80 (m, 6H, CH_2), 1.91 (s, 3H,), 1.93 – 1.98 (m., 6H, CH_2), 2.03 – 2.09 (m., 3H, CH), 4.33 (q, 7 Hz, 2H, CH_2), 6.04 (d, 3.4 Hz, 1H, CH), 7.06 (d, 3.5 Hz, 1H, CH). ^{13}C NMR ($CDCl_3$), δ: 14.4 (CH_3), 28.1 (CH), 35.0 (C), 36.5 (CH_2), 41.8 (CH_2), 60.5 (CH_2), 104.2 (CH), 118.7 (CH), 142.7 (C), 159.0 (C), 169.0 (C=O).

2-(1-Adamantyl)-5-(2-nitrovinyl)furan 2g. Yield 37 %. Lemon yellow crystals. IR (KBr), ν/cm^{-1}: 3147, 3103, 3066 (Csp^2-H), 2908, 2848 (Csp^3-H), 1627, 1492 (Csp^2-Csp^2), 1523 (NO_2 as), 1330 (NO_2 sy). MS (EI, 70 eV), m/z (I_{rel} (%)): 273 (15, M^+), 230 (37), 145 (15), 135 (100). ^1H NMR (399.78 MHz, $CDCl_3$), δ: 1.73 -1.81 (m, 6H, CH_2), 1.91 – 1.93 (m., 6H, CH_2), 2.07 (br.s., 3H, CH), 6.13 (d, 3.7 Hz, 1H, CH), 6.80 (d, 3.7 Hz, 1H, CH), 7.47 (d, 12.8 Hz, 1H, CH), 7.70 (d, 13.2 Hz, 1H, CH). ^{13}C NMR ($CDCl_3$), δ: 28.0 (CH), 35.2 (C), 36.5 (CH_2), 40.8 (CH_2), 106.3 (CH), 121.9 (CH), 125.7 (CH), 133.2 (C), 144.7 (C), 170.4 (C).

3. Results and Discussion.

We propose to perform adamantylation of furans with 1-adamantanol in nitromethane in the presence of Lewis acid, which could be aluminum or bismuth triflate in the amount of 10 mol. %, according to the Figure 7.

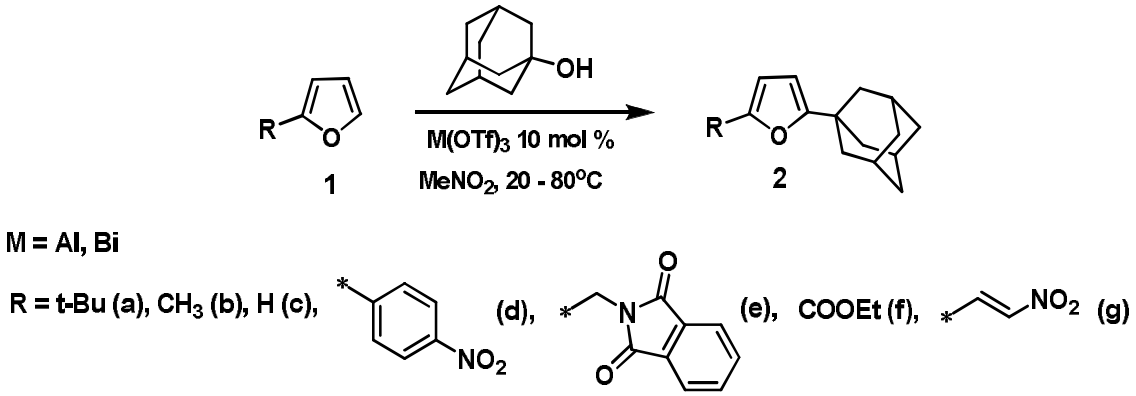


Figure 7. Adamantylation of furans with 1-adamantanol.

Optimum conditions for the preparation of adamantylated furans were selected on the model reaction of 2-*tert*-butylfuran with 1-adamantanol whose course was controlled by chromatography–mass spectrometry.

The degree of conversion of 1-adamantanol into 2-(1-adamantyl)-5-(*tert*-butyl)furan depending on the Lewis acid used is shown in the figure.

As the figure shows, consumption of 1-adamantanol and accumulation of the adamantylation product occur most rapidly in using 10 mol. % of bismuth triflate (97% conversion after 2.5 h at room temperature), while the same amount of aluminum triflate within the same time provides a conversion of 85%. Nevertheless, aluminum triflate gives a conversion of 97% upon mixing the reagents for 4 h. In the case of scandium triflate, the 82% conversion is achieved only after 22 h and, in the case of zinc triflate, the conversion within the same time was only 5%.

Depending on the nature of substituents at the furan ring, adamantylation was carried out at room temperature or upon heating to 50-80°C.

This method can be extended to a number of alkyl- and arylfurans, as well as to furans containing functional groups, such as carbethoxy and β-nitrovinyl which are most promising to be used in the synthesis of bioactive substances.

4. Conclusions.

A a simple method of obtaining 2-(1-adamantyl)furans using a aluminum or bismuth triflate in nitromethane an amount of 10 mol % was developed. This method can be extended to a number of alkyl- and arylfurans, as well as to furans containing functional groups, such as carbethoxy and β-nitrovinyl which are most promising to be used in the synthesis of bioactive substances.

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