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Aluminum Triflate—Catalyzed Adamantylation of *N*-Nucleophiles †

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Abstract: An efficient method is proposed for N-adamantylation of primary carboxamides and sulfonamides, ethyl carbamate, and 4-nitroaniline using the stoichiometric amount of 1-adamantanol in the presence of 5 mol.% aluminum triflate in nitromethane. Similarities and differences between adamantylation of some azoles catalyzed by aluminum triflate in nitromethane and the reaction catalyzed by Brønsted acids were revealed.

Keywords: adamantylation; 1-adamantanol; Lewis acid; aluminum triflate

1. Introduction

Adamantylated nitrogen-containing compounds attract attention primarily for their antiviral properties [1]. Along with well-known and comprehensively studied adamantyl-containing amines, amantadine and rimantadine, antiviral activity has been found for adamantylated azoles, amides, sulfamides, urethanes, and some other types of compounds. In addition, adamantylated nitrogen-containing compounds are of interest as intermediates for the synthesis of other compounds with practically valuable properties.The known methods for the preparation of these compounds consist in adamantylation of various *N*-nucleophiles with adamantane, 1-haloadamantanes, or 1-adamantanol in the presence of Lewis or Brønsted acid, i.e., under conditions favoring the formation of 1-adamantyl cation.For example, *N*-adamantylation of amides was proposed to be carried out using manganese catalysts (Figure 1), among which dimanganesedecacarbonyl showed the best results to give target compounds in a yield up to 94% [2].

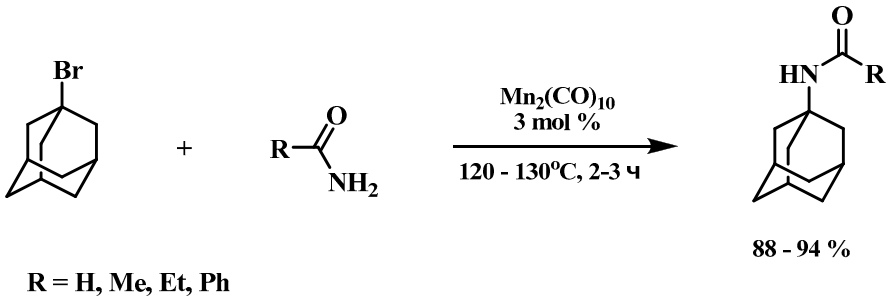

Figure 1. Adamantylation of amides catalyzed by dimanganesedecacarbonyl.

In the trifluoroacetic acid medium (Figure 2), the adamantylation of carboxylic acid amides can be carried out with different efficiency upon long-term reflux [3,4].

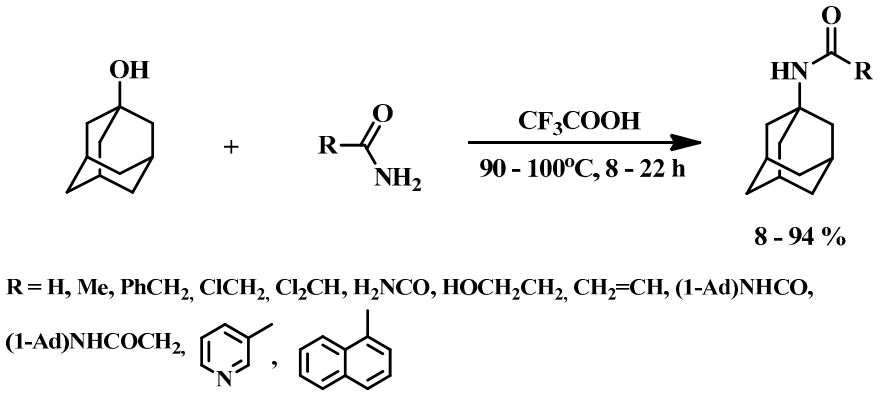

Figure 2. Adamantylation of amides in trifluoroacetic acid.

An interesting approach to adamantylation of several nitrogen-containing nucleophiles was proposed by Chinese chemists in [5] whopromoted the reaction using a carbon tetrabromide—aluminum tribromide super electrophilic system. Some azoles, anilines, and amino heterocycles undergo this reaction. There are numerous examples where nitriles were transformed to adamantylated amines by the Ritter reaction using different reaction conditions and different catalysts or reagents, among which manganese compounds [6], trifluoroacetic acid [7], lead tetraacetate [8], bismuth triflate [9], calcium triflate in the presence of tetrabutylammoniumhexafluorophosphate [10], or nitrosoniumhexafluorophosphate [11] were found to be the most efficient (Figure 3).

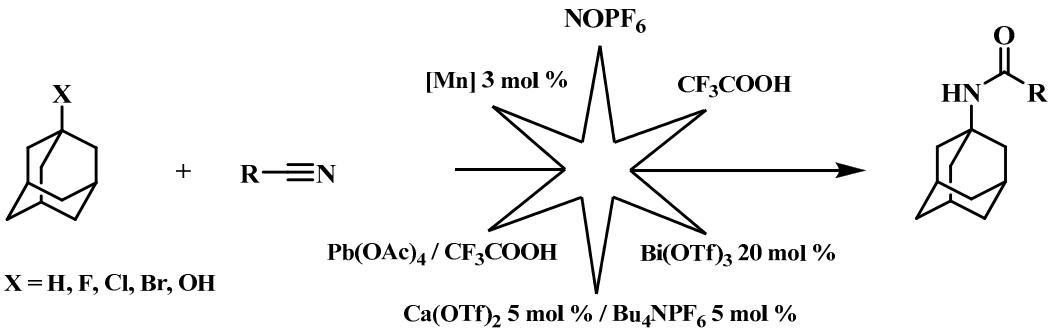

Figure 3. Synthesis of adamantylated amides by the Ritter reaction.

Despite a variety of current approaches to adamantylation, most of them have some significant drawbacks: the use of reagents in non-stoichiometric amounts (two- or three-fold excess of one reagent is often used), or corrosiveness or high toxicity of some catalysts or reagents used, which makes such methods unsuitable for "green" chemistry.

The aim of the present work was to establish whether low-basic nitrogen-containing nucleophiles, such as carboxamides, sulfonamides, and azoles, could be adamantylated with 1-adamantanol under the Lewis acid catalysis.

2. Materials and Methods

1H and 13C nuclear magnetic resonance (NMR) spectra were recorded on an ECA 400 (JEOL) instrument in $CDCl_3$ or $(CD_3)_2SO$ (Cambridge Isotop Laboratories Inc.,Tewksbury, MA, USA) using residual solvent signals as the internal standard. Infrared (IR) spectra were recorded on an IR Prestige instrument (Shimadzu,Kyoto, Japan) 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.

General procedure for adamantylation of amides. A reaction vial was loaded with nitromethane (5 mL) and 1-adamantanol (0.250 g, 1.64 mmol) which was dissolved with stirring and heating. To the resulting solution, amide (1.64 mmol) and aluminum triflate (0.039 g, 0.082 mmol) were added. The reaction mixture was refluxed with stirring for 6–8 h with the course of the reaction being monitored by GC/MS. After the reaction was completed, the mixture was transferred to a separatory funnel containing 2 M HCl (20 mL) and chloroform (5 mL). The organic phase was separated and the aqueous phase was extracted three times with chloroform. The combined extracts were dried with sodium sulfate and the solvent was removed on a rotary evaporator. The residue was purified by flash chromatography on silica gel.

N-(1-adamantyl)formamide (**3a**). Yield 68%. M.p. 139–141 °C.IR (KBr), ν/cm^{-1}: 3186, 3089 (N-H), 2914, 2899, 2850 (Csp^3-H), 1693 (C=O), 1604, 1514 (C=C), 1541 (NH). Mass (EI, 70 eV), *m*/*z* (I_{rel} (%)): 179 (33, M+), 122 (100), 92 (21), 79 (12), 67 (8).

N-(1-adamantyl)acetamide(**3b**). Yield 72%. M.p. 146,7-147,5 °C (EtOH–H_2O 5:3). IR (KBr), ν/cm^{-1}: 3315, 3061 (N-H), 2974, 2941, 2899, 2848 (Csp^3-H), 1674, 1649 (C=O), 1627 (C-N), 1541 (NH). ^{1}HNMR (399.78 MHz, $CDCl_3$, δ, ppm): 1.61–1.68 (m, 6H, CH2), 1,91 (s, 3H, CH3), 1.98–2.01 (m., 6H, CH2), 2.04–2.09 (m., 3H, CH), 5,26 (br.s, 1H, NH).^{13}CNMR (CDCl3), δ, ppm: 24.7 (CH3), 29.4 (CH), 36.4 (CH2), 41.6 (CH2), 51.8 (C), 169.3 (C=O). Mass (EI, 70 eV), *m*/*z* (I_{rel} (%)): 193 (45, M+), 136 (100), 94 (43).

N-(1-adamantyl)acrylamide(**3c**). Yield 73%. M.p. 143–146 °C.IR (KBr), ν/cm^{-1}: 3251, 3068 (N-H), 3028 (Csp^2-H), 2962, 2904, 2893, 2854(Csp^3-H), 1655 (C=O + C=C), 1616 (C-N), 1558 (NH). ^{1}HNMR (399.78 MHz, $CDCl_3$, δ, ppm):1.64–1.69 (m, 6H, CH_2), 2.00–2.09 (m, 9H, CH_2 + CH), 5.30 (br.s, 1H, NH), 5.52 (d, 1.6 Hz, 0.5H), 5,54 (d, 1.6 Hz, 0.5H), 5.97–6.04 (m, 1H), 6,17 (1.6 Hz, 0.5H), 6.21 (1.6 Hz, 0.5H). ^{13}CNMR ($CDCl_3$), δ, ppm: 29.4 (CH), 36.3 (CH_2), 41.5 (CH_2), 52.0 (C), 125.5 (CH_2), 132.1 (CH), 164.5 (C=O). Mass (EI, 70 eV), *m*/*z* (I_{rel} (%)): 205 (26, M^+), 148 (100), 94 (32).

N-(1-adamantyl)benzamide(**3d**). Yield 88%. M.p. 148–150 °C.IR (KBr), ν/ cm^{-1}: 3327 (N-H), 3078, 3057, 3026 (Csp^2-H), 2916, 2904, 2848, (Csp^3-H), 1635 (C=O), 1598, 1577 (C=C), 1531 (NH), 1253 (C-N). ^{1}HNMR (399.78 MHz, $CDCl_3$, δ, ppm): 1.55–1.64 (br.m, 6H, CH_2), 1.96–2.05 (br.m, 3H, CH + 6H, CH_2), 5.83 (br.s, 1H, NH) 7.23–7.35 (m, 3H), 7.55–7.61 (m, 2H). ^{13}CNMR ($CDCl_3$), δ, ppm: 29.4 (CH), 36.3 (CH_2), 41.6 (CH_2), 52.2 (C), 126.6 (CH), 128.3 (CH), 130.9 (CH), 135.9 (C), 166.5 (C=O). Mass (EI, 70 eV), *m*/*z* (I_{rel} (%)): 225 (39, M+), 198 (100), 105 (94), 77 (50).

N-(1-adamantyl)-4-nitrobenzamide(**3e**). Yield 48%. M.p. 190–192 °C (EtOH–H_2O4:5). IR (KBr), ν/cm^{-1}: 3340 (N-H), 3104, 3075, 3049 (Csp^2-H), 2950, 2911, 2850, (Csp^3-H), 1635(C=O), 1598, 1577 (C=C), 1531 (NH), 1253 (C-N). ^{1}HNMR (399,78MHz, $CDCl_3$, δ, ppm):1.74 (br.m, 6H, CH_2), 2.14 (br.m, 3H, CH + 6H, CH_2), 5.88 (br.s, 1H, NH) 7.85–7.89 (m, 2H), 7.24–7.27 (m, 2H). ^{13}CNMR ($CDCl_3$), δ, ppm: 29.5 (CH), 36.3 (CH_2), 41.5 (CH_2), 53.0 (C), 123.7 (CH), 127.9 (CH), 141.7 (C), 149.3 (C), 164.6 (C=O). Mass (EI, 70 eV), *m*/*z* (I_{rel} (%)): 300 (31, M+), 243 (100), 207 (8), 150 (38),120 (14), 92 (24).

N-(1-adamantyl)-4-methylbenzenesulfonamide(**3f**). Yield 70%. M.p. 166–167 °C. R (KBr), ν/cm^{-1}: 3292 (N-H), 3068, 3057, 3030 (Csp^2-H), 2910, 2887, 2848, (Csp^3-H), 1597, 1492 (C=C), 1531 (NH), 1363,1153 (S=O), 1255 (C-N). ^{1}HNMR (399.78 MHz, ($(CD_3)_2SO$), δ, ppm): 1.40–1.53 (br.m, 6H, CH_2), 1.65–1.67 (br.m, 6H, CH_2), 1.86–1.91 (br.m, 3H, CH), 2.35 (s., 3H, CH_3), 7.32–7.34 (m, 2H), 7.42 (br.s, 1H, NH), 7.69–7.71 (m, 2H). ^{13}CNMR ($(CD_3)_2SO$), δ, ppm: 20.9 (CH_3), 28.8 (CH_2), 35.5 (CH), 42.4 (CH2), 53.6 (C), 126.1 (CH), 129.3 (CH), 141.8 (C), 142.2 (C). Mass (EI, 70 eV), *m*/*z* (I_{rel} (%)): 305 (36, M+), 248 (48), 155 (31), 94 (33), 93 (100), 91 (80), 41 (31).

Ethyl 1-adamantylcarbamate(**3g**). Yield 74%. M.p. 90.2–90.8 °C. IR (KBr), ν/cm^{-1}: 3336, 3305 (N-H), 2981, 2904, 2848, (Csp^3-H), 1635 (C=O), 1598, 1577 (C=C), 1531 (NH), 1253 (C-N). ^{1}HNMR (399.78 MHz, $CDCl_3$, δ, ppm): 1.20 (t, 7 Hz, 3H, CH_3), 1.63–1.65 (m, 6H, CH_2), 1.89–1.92 (m, 6H, CH_2), 2.03–2.05 (m, 3H, CH), 4.05 (q, 13.6 Hz, 2H, CH_2), 4.49 (br.s, 1H, NH). ^{13}CNMR ($CDCl_3$), δ, ppm: 14.6 (CH_3), 29.4 (CH), 36.3 (CH_2), 41.8 (CH_2), 50.5 (CH_2), 59.9 (C), 154.5 (C=O). Mass (EI, 70 eV), *m*/*z* (I_{rel} (%)): 223 (80, M+), 166 (100), 138 (75), 135 (22),120 (47), 94 (16).

Adamantylation of 4-nitroaniline. 1-adamantanol (0.122 g, 0.0008 mol) was dissolved with stirring and heating in nitromethane (5 mL). 4-nitroaniline (0.11 g, 0.0008 mol) dissolved in nitromethane (2 mL) and aluminum triflate (0.039 g, 0.00008 mol) were added to the reaction solution. The mixture was stirred with heating (110°C) for 6 h and, on completion of the reaction, transferred to a separatory funnel containing 2 M HCl (20 mL) and chloroform (5 mL). The organic layer was separated and the solvent was removed on a rotary evaporator. The residue was purified by flash chromatography using hexane–ethyl acetate (10:2, *v*/*v*) as the eluent followed by crystallization from aqueous ethanol (5:3, *v*/*v*). Yield 70%, m.p. 180°C. IR (KBr), ν/cm^{-1}: 3369 (N-H), 2960, 2900, 2848 (Csp^3-H), 1595, 1502 (Csp^2-Csp^2), 1533, 1320 (NO_2). ^{1}HNMR (399.78 MHz, $CDCl_3$, δ, ppm): 1.68–1.76 (m, 6H, CH_2), 2.00 (br. s, 3H, CH), 2.13–2.21 (m., 6H, CH_2), 2.04–2.09 (m., 3H, CH), 3.5–5.0 (br.s, 1H, NH), 6.68 (br.s, 2H, CH), 8.02 (d, 9.6 Hz, 2H, CH). ^{13}CNMR ($CDCl_3$), δ, ppm: 29.5 (CH), 36.2 (CH_2), 40.9 (C), 42.1 (CH_2), 113.9 (CH), 126.0 (CH), 131.8 (C), 151,7 (C). Mass (EI, 70 eV), *m*/*z* (I_{rel} (%)): 273 (45, $[M+H]^+$), 176 (23), 135 (40).

Adamantylation of 1,2,3-benzotriazole. A 25-mL round-bottom flask was loaded with aluminum triflate (0.039 g, 0.00008 mol) and nitromethane (7 mL). 1-adamantanol (0.250 g, 0.00164 mol) was dissolved in this mixture with stirring and heating and 1,2,3-benzotriazole (0.195 g, 0.00164 mol) was then added. The reaction mixture was stirred for 6 h at the solvent boiling point. On completion of the reaction, the mixture was transferred to a separatory funnel containing 2 M HCl (20 mL) and chloroform (5 mL). The organic layer was separated and evaporated on a rotary evaporator. The isomers were separated by flash chromatography (gradient elution starting from hexane to hexane–ethyl acetate, 10:5).

1-(1-Adamantyl)-1H-1,2,3-benzotriazole(**3i**). Yield 46%.M.p. 150°C.^{1}H NMR (399.78 MHz, CDCl3, δ, ppm): 1.86–1.90 (m, 6H, CH_2), 2.33 (br.s, 3H, CH), 2.47–2.55 (m., 6H, CH_2), 7.29–7.36 (m, 1H), 7.37–7.44 (m, 1H), 7.81 (d, 8 Hz, 1H), 8.07 (d, 8 Hz, 1H). ^{13}C NMR ($CDCl_3$), δ, ppm: 29.6 (CH), 36.2 (CH_2), 41.1 (CH_2), 61.6 (C), 112.4 (CH), 120.3 (CH), 123.3 (CH), 126.2 (CH), 131.6 (C), 146.9 (C). Mass (EI, 70 eV), *m*/*z* (I_{rel}(%)): 253 (100, (M+), 224 (46), 168 (25), 135 (58).

2-(1-Adamantyl)-2H-1,2,3-benzotriazole(**3j**). Yield 39%.M.p. 94°C.^{1}H NMR (399,78 MHz, $CDCl_3$, δ, ppm): 1.75–1.89 (m, 6H, CH_2), 2.31 (br.s, 3H, CH), 2.39–2.52 (m., 6H, CH_2), 7.29–7.44 (m, 2H), 7.80–7.97 (m, 2H). ^{13}C NMR ($CDCl_3$), δ, ppm: 29.7 (CH), 36.1 (CH_2), 42.8 (CH_2), 64.8 (C), 118.1 (CH), 125.8 (CH), 143.6 (C). Mass (EI, 70 eV), *m*/*z* (I_{rel} (%)): 253 (100, (M+), 224 (39), 168 (16), 135 (75).

3. Results and Discussion

Earlier, our research team hadshown Lewis acids from a series of metal triflates to be efficient catalysts for adamantylation of C-nucleophiles, such as 1,3-dicarbonylcompounds [12,13]. In this work, we decided to use a catalyst from the same series, namely aluminum triflate which has been used earlier to alkylate different N-nucleophiles with propargyl alcohols [14].

The reaction was performed in nitromethane in the presence of 5 mol.% aluminum triflate using the equimolar amount of 1-adamantanol (Figure 4). The GC/MS control of the model acetamide adamantylation showed that the reaction does not proceed at room temperature and requires heating. The highest conversion of reagents was achieved upon heating to the solvent boiling point for 6 h.

The reaction completion time was determined in each case by GC/MS. Primary aliphatic amides **2a**,**b**, unsaturated amide **2c**, and aromatic carboxamides **2d**,**e** underwent this reaction. The preparative yields of target adamantylated compounds **3a–g** were 48–88%.4-nitroaniline reacted similarly to form the adamantylation product, *N*-(4-nitrophenyl)adamantane-1-amine (**3h**), which was isolated in yield of 70% (Figure 5).

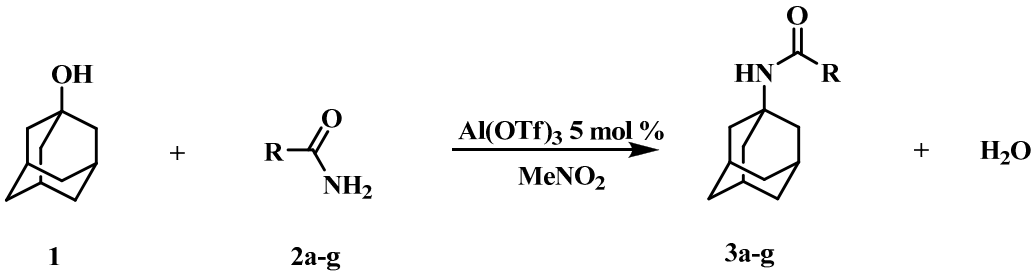

Figure 4. Adamantylation of primary amides and ethyl carbamate.

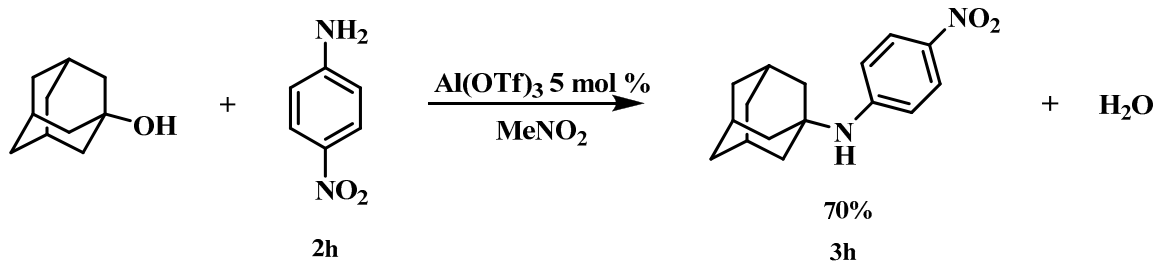

Figure 5. Adamantylationof 4-nitroaniline.

Earlier, several researchers have studied adamantylation of azoles in the presence of Brønsted acids or upon oxidative generation of adamantly cation from haloadamantanes [15], as well as using adamantane in superelectrophilic media, such as polyhalomethane–aluminum halide [5].

We showed that 1,2,3-benzotriazole in the reaction with 1-adamantanol in nitromethane in the presence of 10 mol.% aluminum triflate easily produces an equimolar mixture of *N*-adamantylated isomers (Figure 6), which could be separated by flash chromatography with gradient elution on going from pure hexane to a hexane–ethyl acetate (10:5). Isomers **3i** and **3j** have quite distinct retention times upon GC separation, which is convenient for the reaction and purification controls.

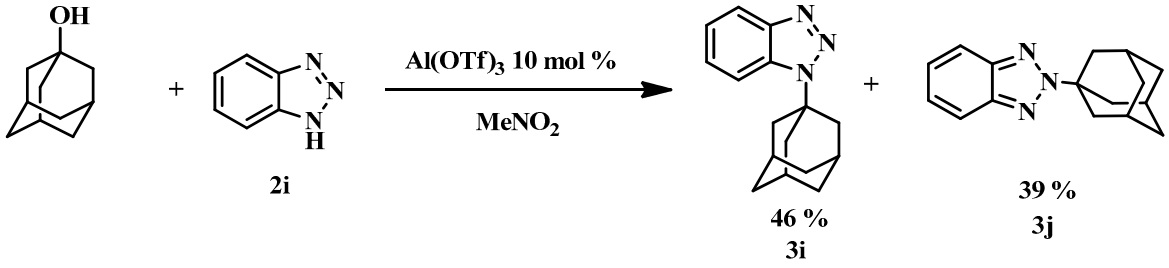

Figure 6. Adamantylationof 1,2,3-benzotriazole.

The total preparative-scale yield of N-adamantylation products of 1,2,3-benzotriazole was 85%, while according to the literature data the yield of isomeric mixture upon adamantylation with 1-iodoadamantane in the presence of iodic anhydride was only 67% (the ratio of isomers was 26:74) [15].

Unfortunately, such representatives of amino azoles as 2-aminotriazole, 3-amino-1,2,4-triazole, and 2-aminobenzothiazole underwent no reaction under these conditions: according to the GC/MS data no consumption of the reagents was observed.

4. Conclusions

In this study 1-adamantanol in the presence of 5 mol.% aluminum triflate in nitromethane was shown to react with such *N*-nucleophiles as primary carboxamides or sulfonamides, ethylcarbamate, low-basic aromatic amines, and 1,2,3-benzotriazole to afford target *N*-adamantylated products in good yields. The proposed adamantylation method hassome advantages over that described earlier

and can be used in the preparation of practically valuable intermediates for the synthesis of bioactive adamantyl-containing compounds.

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