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# Synthesis of amino acid derivatives of 4-(1-adamantyl)benzoic acid obtained by transition metal ion catalyzed oxidation of 4-(1-adamantyl)toluene

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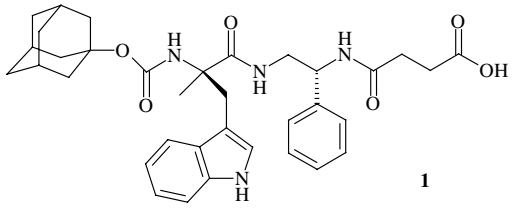
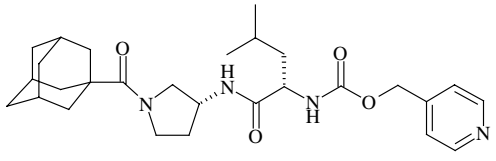
**Abstract**—An efficient synthesis of 4-(1-adamantyl)benzoic acid based on transition metal ion catalyzed oxidation of 4-(1-adamantyl)toluene has been developed. As a catalytic system, cobalt–manganese bromide with addition of manganese acetate was used. A series of amino acid derivatives of 4-(1-adamantyl)benzoic acid was then synthesized and characterized. These derivatives are novel intermediates potentially useful in the design of therapeutically active peptidomimetics with improved pharmacokinetic and pharmacodynamic parameters.


## 1. Introduction

Numerous derivatives of adamantane have been reported as biologically active agents useful in the therapeutic treatment of various human pathological conditions. Among them are well-known drugs, such as Rimantadine, Memantine, Adapalene, and Adatanserin. The growing interest in adamantanes is highlighted by the development of compounds that contain in their structures the adamantane moiety and a natural or modified amino acid residue. Such peptidomimetic compounds were reported as promising anxiyolytics (e.g., PD-134308 **1**[1] now entering phase II clinical trials), agents for treatment of osteoporosis (e.g., compound **2**[2]), and analgesics (e.g., compound **3**[3]). The introduction of a bulky lipophilic adamantane moiety leads to an improvement in the pharmacodynamic and pharmacokinetic properties of potential therapeutic agents.[3,4]



**1**



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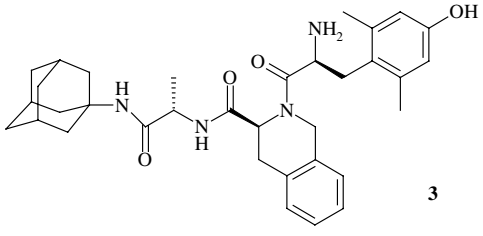

**3**

4-(1-Adamantyl)benzoic acid is a useful intermediate for introduction of the adamantane moiety into synthetic molecules. Synthesis of phenylcarboxylic acid adamantane compounds have been reported using cobalt ion catalyzed oxidation of phenylalkyladamantanes.[5] However, to the best of our knowledge, no biologically active derivatives of 4-(1-adamantyl)benzoic acid have been reported to date. In this work, we have developed an efficient synthetic strategy for the synthesis of 4-(1-adamantyl)benzoic acid and its amino acid derivatives.

*Keywords*: Transition metal; Catalytic oxidation; Cobalt–manganese bromide catalyst; Adamantane derivatives.
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## 2. Results and discussion

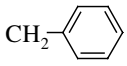
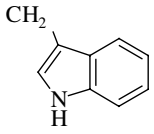
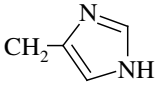
One of the most effective methods for the synthesis of the aromatic oxygen-containing compounds, particularly monocarboxylic acids, is a liquid-phase oxidation of alkylbenzenes with molecular oxygen in the presence of transition metal (TM) ions and promoting additives. These reaction conditions are generally more efficient in comparison to other self-oxidation catalysts, with respect to being able to control the selectivity, and allowing easy separation of the reaction products from the catalyst. In addition, this method is also superior to the so-called 'stoichiometric' methods, which use permanganates and dichromates.[6] This method provides higher yields of the desired products, reduced quantities of the reagents are required, and the absence of additional inorganic side products makes purification easier. Oxidation using nitrous acid, while providing the products in good yields, can lead to undesired nitration side products.[7]

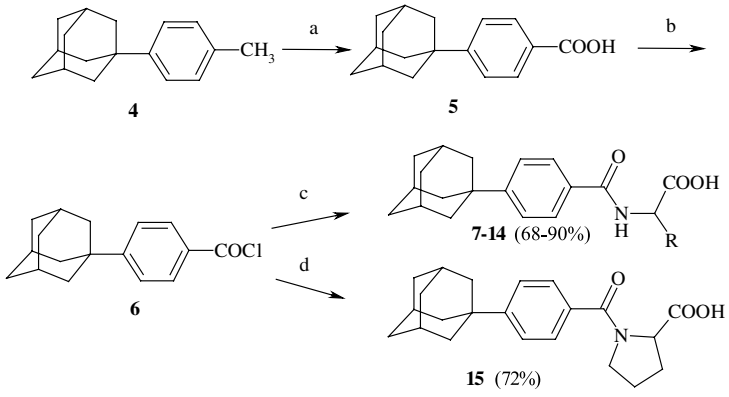
Recently, we have developed an efficient method for the oxidation of alkylbenzenes with molecular oxygen in the presence of a cobalt–manganese bromide catalyst with the addition of manganese acetate.[8] In this work, we obtained 4-(1-adamantyl)benzoic acid **5**[9] from 4-(1-adamantyl)toluene **4** in 90–95% yield (Scheme 1). In comparison to the previously reported synthesis of 4-(1-adamantyl)benzoic acid, where a cobalt-bromide catalyst was used,[5] our method provides better yields, higher efficiency (significantly reduced consumption of catalyst), and synthetic convenience. The acid **5** was quantitatively converted into the chloride **6** by the treatment with thionyl chloride.[10] The target amino acid derivatives **7**–**15**[11] were then obtained using the Schotten–Baumann reaction[12] as pure (*R*)- and (*S*)- or mixed (*R,S*)-stereoisomers with good yields (Scheme 1, Table 1). The enantiomeric purities of the resulting compounds were confirmed by $^1$H NMR spectroscopy recorded in the presence of a chiral shift reagent by the method described in the literature.[13]

Depending on the reaction conditions, oxidation in the presence of TM ions can proceed predominantly in one of two possible directions: chain elongation through the generation of peroxide radicals,[14] or by chain cleavage by the metal ions.[15] It is known that liquid-phase oxidation in protic solvents, such as acetic acid, favors the second mechanism because of the high catalyst concentration that can be obtained.[15] In this instance, the substrate to be oxidized interacts preferentially with the highest valence form of the TM ions with the generation of a free radical. On the other hand, it is well established that the usual reactivity of α-C–H bonds in reactions that proceed via free radicals, tertiary > secondary > primary, proceeds in an inverse manner to the liquid-phase oxidation of alkylbenzenes in acetic acid with addition of $Co(OAc)_2 \cdot 4H_2O$ as the catalyst, and acetaldehyde or NaBr as a promoter.[16] Possible reasons for the inversion of reactivity of C–H bonds may be the multistage character and kinetic control of this reaction.[17] The radicals generated undergo further oxidative conversions.

The oxidation kinetics of *para*-substituted toluenes under the described conditions were studied in our

**Table 1.** Amino acid derivatives of 4-(1-adamantyl)benzoic acid

| Compound | R | Yield (%) |
|---|---|---|
| **7** | $CH_3$ | 85 |
| **8** | $CH(CH_3)_2$ | 90 |
| **9** |  | 75 |
| **10** |  | 77 |
| **11** | $CH_2CH(CH_3)_2$ | 90 |
| **12** | $(CH_2)_2SCH_3$ | 68 |
| **13** |  | 82 |
| **14** |  | 70 |




**Scheme 1.** Reagents and conditions: (a) $O_2$, NaBr, $Mn(OAc)_2$, $Co(OAc)_2$, $CH_3COOH$/1,4-dioxane, 90 °C, 95%; (b) $SOCl_2$, $C_6H_6$, quantitative yield; (c,d) amino acid, 2 N NaOH, $H_2O$/1,4-dioxane, 68–90%.

recent work.[8] Specifically, it was shown that in the first stages of oxidation, an ionic interaction occurs between the catalyst and the initial toluene derivative. The proposed mechanism of oxidation with TM ions in acetic acid is in full agreement with our experimental data. Thus upon oxidation of 4-(1-adamantyl)toluene **4** in the presence of a cobalt–manganese bromide catalyst with the addition of manganese acetate, 4-(1-adamantyl)benzoic acid **5** was obtained via formation of a radical at the methyl group, in high yield. In the proposed mechanism, the C–H bonds of the adamantane moiety do not participate in the radical pathway although they can be easily oxidized by many other oxidizing agents.

In summary, cobalt–manganese bromide with addition of manganese acetate in acetic acid is a mild and efficient system for the selective catalytic oxidation of substituted toluenes.[18] Using this approach, we developed an efficient synthetic route to 4-(1-adamantyl)benzoic acid **5**. A series of 4-(1-adamantyl)benzoylated amino acids were then prepared with 60–80% overall yields starting from 4-(1-adamantyl)toluene **4**. Biological evaluation of compounds **7**–**15** is currently in progress and will be reported elsewhere.

## 3. Experimental protocol for the oxidation of 4-(1-adamantyl)toluene

A mixture of cobalt acetate (0.525 g, 2.11 mmol), manganese acetate (0.059 g, 0.24 mmol), sodium bromide (0.24 g, 2.33 mmol), and 4-(1-adamantyl)toluene (10.71 g, 47.4 mmol) in 95% aqueous acetic acid (200 mL) and 1,4-dioxane (20 mL) were stirred in a three-necked round-bottomed flask equipped with an oxygen bubbler, a backflow condenser, a magnetic stirrer, and a thermometer. Oxygen was introduced and the mixture was allowed to react for 2 h at a temperature of 90 °C. Then the reaction mixture was concentrated by evaporating 150 mL of solvent. Cooled water (100 mL) was added to the cooled reaction mixture, and the precipitated crystals were filtered and dried to give 11.53 g (95%) of pure 4-(1-adamantyl)benzoic acid.

## References and notes


1. Moody, T. W.; Jensen, R. T. *J. Pharmacol. Exp. Ther.* **2001**, *299*, 1154–1160.
2. Ru, Y.; Marquis, R. W.; Veber, D. F. U.S. Patent 6,369,077, 2002; *Chem. Abstr.* 130(02)014263C.
3. Salvadori, S.; Guerrini, R.; Balboni, G.; Bianchi, C.; Bryant, S. D.; Cooper, P. S.; Lazarus, L. H. *J. Med. Chem.* **1999**, *42*, 5010–5019.
4. Lazarus, L. H.; Bryant, S. D.; Salvadori, S.; Attila, M.; Jones, L. S. *Trends Neurosci.* **1996**, *19*, 31–35.
5. Feinstein, A. I.; Fields, E. K. U.S. Patent 4,142,036, 1979; *Chem. Abstr.* 090(26)204842U.
6. Hudlicky, M *Oxidations in Organic Chemistry*. In ACS Monograph 186; American Chemical Society: Washington DC, 1990; p 106.
7. Weissermel, K.; Arpe, H.-J. *Industrial Organic Chemistry*, 2nd ed.; Chemie: Weinheim, NY, 1993; Chapter 14.
8. (a) Obuchova, T. A.; Kluev, I. V.; Krasnikov, S. V.; Betnev, A. F. RU Patent 2183620, 2002; *Der. Abstr.* C2002-581461; (b) Betnev, A. F.; Obuchova, T. A.; Kluev, I. V.; Krasnikov, S. V. *Izv. Vuzov. Khim. Techn.* (*Proc. Inst. Higher Edu.: Chem. Technol.*) **2000**, *43*, 73–75.
9. 4-(1-Adamantyl)benzoic acid **5**: white crystals with mp 308–310 °C; $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 1.78 (m, 6H), 1.92 (m, 6H), 2.12 (m, 3H), 7.38 (d, 2H, $J = 7.8$ Hz), 7.88 (d, 2H, $J = 7.8$ Hz), 12.30 (s, 1H); $R_f$ 0.66 (toluene/petroleum ether/acetone/acetic acid, 16:16:10:1). Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.7; H, 7.8; O, 12.5. Found: C, 79.5; H, 7.7; O, 12.6.
10. 4-(1-Adamantyl)benzoic acid chloride **6** was quantitatively obtained from acid **5** by reaction with thionyl chloride in benzene and was used in the next step without purification.
11. Satisfactory analytical data ($^1$H NMR, mass spectra, elementary analysis) were obtained for all new compounds. For example: (2*S*)-[4-(1-adamantyl)phenylcarboxamido]-3-methylbutanoic acid **8**: mp 215–218 °C; $^1$H NMR [DMSO-$d_6$+$CCl_4$ (1:3), 500 MHz]: $\delta = 1.00$ (d, 6H, $J = 6.0$ Hz), 1.78 (m, 6H), 1.92 (m, 6H), 2.12 (m, 3H), 2.22 (m, 1H), 4.40 (dd, 1H, $J = 6.7$, 6.4 Hz), 7.37 (d, 2H, $J = 7.8$ Hz), 7.74 (m, 1H), 7.80 (d, 2H, $J = 7.8$ Hz); EIMS: $m/z$ 355 (9%) $[M]^+$; $R_f$ 0.36 (toluene/petroleum ether/acetone/acetic acid, 16:16:10:1). Anal. Calcd for $C_{22}H_{29}NO_3$: C, 74.3; H, 8.2; N, 3.9; O, 13.6. Found: C, 74.4; H, 8.0; N, 4.1; O, 13.3. (2*S*,*R*)-[4-(1-Adamantyl)phenylcarboxamido]-3-phenylpropanoic acid **9**: mp 108–110 °C; $^1$H NMR [DMSO-$d_6$+$CCl_4$ (1:3), 500 MHz]: $\delta$ 1.78 (m, 6H), 1.93 (m, 6H), 2.12 (m, 3H), 3.10 (dd, 1H, $J = 14.8$, 10.0 Hz), 3.20 (dd, 1H, $J = 14.8$, 4.6 Hz), 4.65 (m, 1H), 7.15 (m, 1H), 7.23 (m, 2H), 7.28 (m, 2H), 7.36 (d, 2H, $J = 7.8$ Hz), 7.73 (d, 2H, $J = 7.8$ Hz), 8.12 (m, 1H); EIMS: $m/z$ 403 (6%) $[M]^+$; $R_f$ 0.39 (toluene/petroleum ether/acetone/acetic acid, 16:16:10:1). Anal. Calcd for $C_{26}H_{29}NO_3$: C, 77.3; H, 7.2; N, 3.5; O, 12.0. Found: C, 77.0; H, 7.2; N, 3.3; O, 12.1.
12. Steiger, R. *J. Org. Chem.* **1944**, *92*, 396.
13. Coxon, J. M.; Cambridge, J. R. A.; Nam, S. G. C. *Org. Lett.* **2001**, *3*, 4225–4227.
14. Emanuel, N. M.; Denisov, E. T.; Maizus, S. K. *Chain Oxidation Reactions of Hydrocarbons in Liquid Phase*; Nauka: Moscow, 1965; p 375.
15. Obuchova, T. A.; Mironov, G. S. *Izv. Vuzov. Khim. Techn.* (*Proc. Inst. Higher Edu.: Chem. Technol.*) **1991**, *34*, 3–13.
16. Obuchova, T. A.; Basaeva, N. N.; Mironov, G. S.; Kuznetsov, M. M.; Bondarenko, A. V. *Petrochemistry* **1978**, *28*, 573–578.
17. (a) Dessau, R. H.; Shih, S.; Heiba, E. I. *J. Am. Chem. Soc.* **1970**, *92*, 412–413; (b) Todres, S. V. *Ion Radicals in Organic Synthesis*; Khimiya: Moscow, 1986; p 275; (c) Obuchova, T. A.; Rusakov, A. I.; Koshel, S. G.; Mironov, G. S. *Zh. Org. Khim.* (*J. Org. Chem.*) **1992**, *28*, 756–759; (d) Simkin, B. Y.; Sheikhet, I. I. *Quantum-Chemical and Statistical Theory of Solutions*; Khimiya: Moscow, 1989; p 252.
18. For other examples of catalytic aerobic oxidation of substituted toluene derivatives, see: (a) Towla, P. H.; Baldwin, R. H. *Hydrocarbon Process.* **1964**, *43*, 149–153; (b) Tmenov, D. N.; Lisukho, T. V.; Shcherbina, F. F. U.S.S.R. Patent 614090, 1978; *Chem. Abstr.* 089(13)108705K; (c) Kharlampovich, G. L.; Borovkova, G. G.; Khaybullin, U. G. *Petrochemistry* **1978**, *18*, 641–646; (d) Vora, B. V. U.S. Patent 4,172,209, 1979; *Chem. Abstr.* 092(11)094071Y; (e) Barton, D. H. R.; Doller, D.;

Geletti, Y. U.; Csuhai, E. *Tetrahedron* **1991**, *47*, 6561–6570; (f) Barton, D. H. R.; Beviere, S. D.; Chavasiri, W.; Csuhai, E.; Doller, D.; Liu, W.-G. *J. Am. Chem. Soc.* **1992**, *114*, 2147–2156.