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Substituent stereochemistry effects on diastereoselective methylation reaction of 4-chloroadamantan-2-ones

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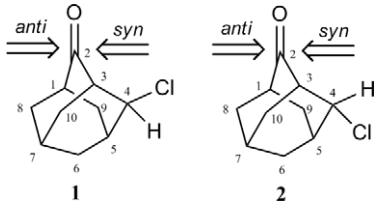
ABSTRACT

π-Facial diastereoselectivity effects of the substituent in 4-position on the nucleophilic addition of substituted adamantan-2-ones were observed for the methylation reaction of 4-chloroadamantan-2-ones. NMR study revealed that when chlorine atom is in axial stereochemical position, exclusively *anti*-addition occurs, whereas selective preference for *syn*-addition was observed with stereochemical equatorial position for chloro substituent. The success of this strategy can be attributed to the important role that $CeCl_3$ plays in increasing the nucleophilicity and decreasing the basicity of the methylorganometallic reagent.

Adamantanes continue to be a significant endeavor and has stimulated great interest in many chemists in these last years. They possess a variety of useful applications as building blocks for complex molecules with pharmaceutical activity,[1] as model compounds for studying reaction mechanisms, for problems in stereochemistry, and for spectroscopic investigations.[2] The adamantane molecule, with rare exceptions,[3] is not used as the starting material for the preparation of adamantyl derivatives. Instead haloadamantanones are often employed in these procedures,[4] whilst the nucleophilic addition to carbonyl group in adamantan-2-ones has been much less utilized. In the latter case, when asymmetrically substituted substrates are placed to react with alkylorganometallic reagents, different (*Z*/*E*) diastereoisomeric adamantan-2-ols are produced with different efficiency.[5] Despite such a π-facial stereochemical effect has been masterfully studied by Adcock et al.[2b,6] the nature of electronic factors induced by the substituent and the dynamics of the reaction remain subjects of continuous debate. A pertinent example is found in works of Duddeck[7] and Nelsen[8] on the fact that bulky organometallic reagents may induce significant deviations from the usual symmetrical adamantane geometry. With these reactants, a six-membered ring to which the alkyl group is fixed in an axial position was observed. Instead, with the smaller methylmetallic reagent, the substituent effect is the dominating one factor in the stereoselectivity.

The diastereoselectivities (*Z*/*E*) for the $NaBH_4$ reduction and methylation of a series of 5-substituted adamantan-2-ones are well studied; however, to the best of our knowledge, reports on the methylation of 4-substituted adamantan-2-ones are scarse.[2a,2b] Le Noble et al.[9] previously explored the diastereoselective reduction of 4-equatorial substituted adamantan-2-ones, and it is also known that 4-axially substituted adamantan-2-ones undergo nucleophilic addition to carbonyl group with lower yield than the corresponding 4-equatorial compounds.[10] For all these reasons, and given that the facial selectivity of the methylation reaction is expected larger than that of hydride reduction,[11] we have chosen the synthesis of 4-substituted 2-methyladamantan-2-ols. Herein we report the results of our study on the methylation of axial-(**1**) and equatorial-4-chloroadamantan-2-one (**2**).[12]



1 **2**

Figure 1.

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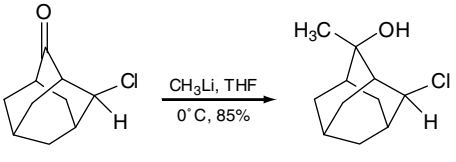
As shown in Figure 1, the attack of the organometallic reagent to the carbonyl group can be *syn*- or *anti*-periplanar respect to the C-4 substituent.[13] The results exhibit that the stereodifferentiation of the chemical environments induced by chloro substituent position produces remarkable equatorial/axial diastereoselectivity in the methyl nucleophilic attack.

The 4(*ax*)-chloroadamantan-2-one (**1**) and 4(*eq*)-chloroadamantan-2-one (**2**) were prepared from commercially available adamantan-2-one, and the pure stereoisomers (4(*ax*)- and 4(*eq*)-chloroadamantan-2-ones) were isolated by separation of the reaction mixture on silica gel column.[14,15]

Treatment of **1** with methyllithium produced diastereoisomer **3** as the exclusive *anti*-adduct in good yield by carefully monitoring the reaction conditions (Scheme 1).[16] So far only organometallic reagents bulky enough (*tert*-butyl and isopropyl) were able to provide adamantan-2-ol derivatives in moderate yields.[8]

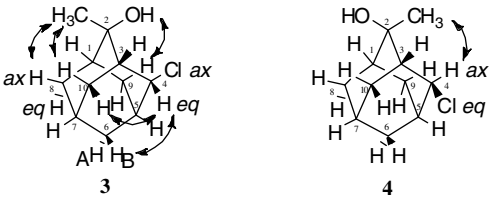
The structure of the 4(*ax*)-chloro-2-methyladamantan-2-ol **3** was established by spectral means.[17] In particular, ^{1}H NMR spectrum showed a double doublet at δ 4.51 ppm with coupling constants of J = 4.27 Hz and J = 1.71 Hz, respectively. To unambiguously assess the structure of **3,** we proceeded preliminarily to the full assignment of the NMR signals[18] that could be done on the basis of gCOSY, TOCSY-1D, gHSQC, gHMBC, and NOESY-1D spectra. The following stereochemical study of **3** was directed to confirm the stereochemistry at C-4 and, mainly, to assign the relative position of the methyl and the hydroxyl group at C-2 (Fig. 2). The ^{1}H NMR spectra of 2,2-disubstituted adamantanes are characterized by the large chemical shift separation between the γ-CH_2 geminal protons due to the γ-*syn* interactions between the substituents and the γ-protons.

The axial protons have a larger chemical shift than the equatorial ones, and the γ-effect is amplified by the presence of a lone pair on the *syn*-substituent, so H-9*ax*/*eq* and H-4*ax*/*eq* show a larger chemical shift separation than H-8*ax*/*eq* and H-10*ax*/*eq*.[19] On the basis of similar considerations, taking also into account an additional γ-effect due to the chlorine at C-4, we attributed the geminal signals at δ 1.60 ppm and δ 2.50 ppm to H-9*eq* and H-9*ax*, respectively. This assignation was confirmed by the HMBC correlation of H-9 with C-5, C-1, C-4, and C-2. Having H-9 the larger chemical shift separation, we concluded that the synthesized alcoholic epimer is the 2(*ax*)-OH (**3** in Scheme 2). The stereochemistry was confirmed by NOESY-1D experiments, which revealed key correlations between H-4 and H-10*eq*, H-4, and H-6B, Me and H-8*ax*, Me and H-10*ax*, OH, and H-9*ax*, as shown in Figure 2. This indicates that the methyl group approaches the carbonyl group of the 4-axially substituted adamantan-2-one **1** exclusively from the back-side (*anti* attack) producing diastereoisomer alcohol **3**.



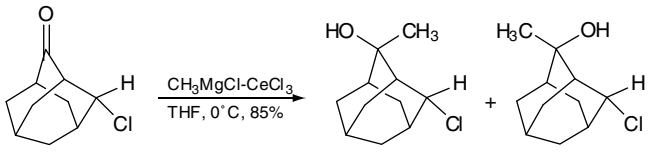
1 **3**

Scheme 1.



3 **4**

Figure 2.



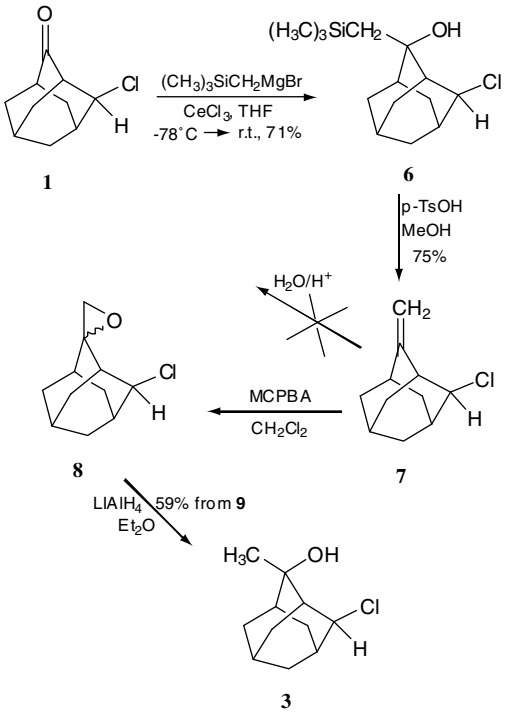
2 **4** **5**

Scheme 2.

This discovery prompted us to investigate this diastereoselective methylation by treatment with methyllithium of the 4-substituted adamantan-2-one when chlorine atom is in equatorial stereochemistry (**2**). We tested the effectiveness of methyllithium with poor results.[20]

To overcome these drawbacks, we planned a different methylation reaction for the equatorial substrate **2**. In the course of the program of some us aimed to explore the important role that cerium(III) chloride plays in exerting a strong activation of carbonyl compounds toward addition of Grignard reagents,[21] we sought to extend methylation reaction on the addition of organocerium species. The organometallic compound prepared from dry $CeCl_3$ and methylmagnesium compound[22] stereoselectively adds to 4(*eq*)-chloroadamantan-2-one for producing an alcohol unseparable mixture of diastereoisomers (**4** with *eq*-OH and **5** with *ax*-OH) (Scheme 2). The ^{1}H NMR spectrum showed two distinctive multiplets at δ 4.40 ppm and 4.93 ppm, typical of H-4 of diastereoisomers **4** and **5**, respectively. In the latter, H-4 proton is more deshielded than in the former. This most significant difference can be explained on the basis of the γ-*syn* effect mentioned above. In fact, when the axial H-4 is *syn* respect to the hydroxyl group at C-2, the downfield shift is increased by the lone pair, as in the case of the minor component of the diastereoisomeric mixture. Thus, the main component was identified as 4(*eq*)-chloro-2(*eq*)-hydroxy-2(*ax*)-methyladamantane (**4**). Furthermore, the ^{13}C NMR signals of the product mixture **4** and **5** were identified by comparison with the spectral data reported by Adcock.[2a]

The above NMR results show that 4-Cl atom in adamantan-2-one induces an opposite π-facial selectivity in the reaction with methylmetallic reagents, depending on its spatial orientation. When 4-Cl is axially oriented (**1**) exclusively *anti*-addition was observed, whereas a selective preference for *syn*-addition results with the chloro substituent in the 4-equatorial position (**2**). In order to explore the possibility of having the diastereoisomer 4(*ax*)-chloro-2(*eq*)-hydroxy-2(*ax*)-methyladamantane, we have thought at the hydration of 4(*ax*)-chloromethylideneadamantane (**7**). Unfortunately, any attempt to affect the methylenation of **1** by treatment with methylenetriphenylphosphorane (DMSO, 60 °C)[23] resulted in complex mixture of no characterizable products. In choosing an alternative method for the introduction of the exocyclic methylene, we reasoned that a reagent which would irreversibly add at the hindered carbonyl would be required. Since we observed that organocerium reagents show remarkable nucleophilic properties in addition to adamantanone **1**, we established that the use of trimethylsilylmethylmagnesium chloride in THF and in the presence of dry $CeCl_3$ produced a single tertiary carbinol **6** (Scheme 3). The stereochemistry was assigned by analogy of product **3**. This 2-hydroxy silane was converted to the corresponding methylene compound **7** (Peterson methylenation procedure)[24] by treatment with a catalytic amount of *p*-toluenesulfonic acid in MeOH.[25] Contrary to what had been reported in the literature,[2a,2b]



Scheme 3.

even after several efforts we were unable to carry out the hydration of (**7**). Then, transformation of **7** to the target 4(*ax*)-chloro-2-methyladamantan-2-ols was accomplished by the following sequence: (i) epoxidation (2.1 equiv of *m*-chloroperoxybenzoic acid, 2.5 equiv of $NaHCO_3$ in CH_2Cl_2 at 0 °C for 30 min), and the diastereoisomeric mixture product **8** was used directly without any purification; and (ii) oxirane reduction (with 4.5 equiv of $LiAlH_4$ in ether, at room temperature, 59% yield from **7**).[26] Synthetic column chromatographic purified product was compared with authentic 4(*ax*)-chloro-2-methyladamantan-2-ols by ^1H and ^{13}C NMR, IR and mass spectroscopies, and was found to be identical to the structure of 4(*ax*)-chloro-2(*ax*)-hydroxy-2(*eq*)-methyladamantane (**3**).

Finally, in view of the continuing debate concerning the effect on facial selectivity of the substituent to the 4-position on the nucleophilic addition of substituted adamantan-2-ones, it is important to emphasize that the results of this study clearly indicate that the stereochemistry of the substituent directs the nucleophilic attack.[2a,2b] In particular, the objective of this work was to gain insight into the reaction of methylation of 4-chloroadamantanones, and to make use of the results for the synthesis of 2,4-disubstituted adamantyl derivatives. Further work is in progress in our laboratories to attempt the preparation of units which might function as important synthetic targets in organic chemistry.

Acknowledgments

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References and notes

1. (a) Bobek, M. M.; Brinker, U. H. *Synth. Commun.* **1999**, *29*, 3221–3225; (b) Chen, C. S. H.; Shen, D. -M.; Wentzek, S. E. PCT Int. Appl. WO09428.885, 1994.
2. (a) Adcock, W.; Trout, N. A. *J. Phys. Org. Chem.* **2008**, *21*, 68–78; (b) Adcock, W.; Trout, N. A. *J. Phys. Org. Chem.* **2007**, *20*, 791–798; (c) Filippi, A.; Trout, N. A.; Brunelle, P.; Adcock, W.; Speranza, M. *J. Org. Chem.* **2004**, *69*, 5537–5546; (d) Filippi, A.; Trout, N. A.; Brunelle, P.; Adcock, W.; Sorensen, T. S.; Speranza, M. *J. Am. Chem. Soc.* **2001**, *123*, 6394–6403; (e) Sasaki, T.; Eguchi, S.; Suzuki, T. *J.Org. Chem.* **1980**, *45*, 3824–3827.
3. Geluk, H. W.; Schlatmann, J. L. M. A. *Recl. Trav. Chim. Pay-Bas* **1971**, *90*, 516–519.
4. Janku, J.; Burkhard, J.; Vodička, L. *Collect. Czech. Chem. Commun.* **1987**, *52*, 752–755.
5. (a) Wilmot, N.; Marsella, M. J. *Org. Lett.* **2006**, *7*, 3109–3112; (b) González-Nuñez, M. E.; Royo, J.; Mello, R.; Bágnena, M.; Ferrer, J. M.; deArellano, C. R.; Asensio, G.; Prakash, G. K. S. *J. Org. Chem.* **2005**, *70*, 7919–7924; (c) González-Nuñez, M. E.; Royo, J.; Castellano, G.; Andreu, C.; Boix, C.; Mello, R.; Asensio, G. *Org. Lett.* **2000**, *2*, 831–834; (d) le Noble, W. J.; Gung, B. W. *Chem. Rev.* **1999**, *99*, 1069–1480.
6. (a) Adcock, W.; Trout, N. A. *Chem. Rev.* **1999**, *99*, 1415–1436; (b) Adcock, W.; Cotton, J.; Trout, N. *J. Org. Chem.* **1994**, *59*, 1867–1876; (c) Adcock, W.; Coope, J.; Shiner, V. J. Jr.; Trout, N. A. *J. Org. Chem.* **1990**, *55*, 1411–1412.
7. (a) Duddeck, H.; Rosenbaum, D. *J. Org. Chem.* **1991**, *56*, 1700–1707; (b) Duddeck, H.; Rosenbaum, D. *J. Org. Chem.* **1991**, *56*, 1707–1713.
8. Nelsen, S. F.; Kapp, D. L.; Akaba, R.; Evans, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 6863–6871.
9. Kaselj, M.; Le Noble, W. J. *J. Org. Chem.* **1996**, *61*, 4157–4160.
10. Duddeck, H.; Brosch, D.; Koppetsch, G. *Tetrahedron* **1985**, *41*, 3753–3762.
11. (a) Xie, M.; Le Noble, W. J. *J. Org. Chem.* **1989**, *54*, 3863; (b) Lin, M.-H.; Silver, J. E.; le Noble, W. J. *J. Org. Chem.* **1988**, *53*, 5155–5158.
12. It is known that the high reactivity of 4-chloroadamantan-2-ones with organometallic reagents for giving halogen-metal exchange.[7a]
13. The numbering of the adamantane carbons not necessarily conforms to IUPAC nomenclature. For better comparison, however, we employed a numbering which is consistent throughout irregardless of the substituents. The term *axial* (*ax*) and *equatorial* (*eq*) denote the stereochemical position of the substituent with respect to the six-membered ring bearing the highest number of substituents.
14. (a) Sasaki, T.; Eguchi, S.; Torn, T. *J. Org. Chem.* **1970**, *35*, 4100–4114; (b) Murofushi, Y.; Kimura, M.; Iijima, Y.; Yamazaki, M.; Kaneko, M. *Chem. Pharm. Bull.* **1987**, *35*, 4442–4453.
15. Spectroscopical data of compounds **1** and **2** are identical to those previously reported by: (a) Janku, J.; Burkhard, J.; Vodička, L. *Collect. Czech. Chem. Commun.* **1987**, *52*, 2028–2035; (b) Triska, J.; Vodička, L.; Butkus, E. P.; Hájek, M. *Collect. Czech. Chem. Commun.* **1984**, *49*, 752–755.
16. To a well-stirred solution of 0.2 g (1.08 mmol) of the 4(*ax*)-chloroadamantan-2-one (**1**) in dry THF (15 mL) maintained at 0 °C was added an excess of methyllithium (1.44 mL, 2.16 mmol). The reaction mixture was allowed to warm to room temperature over 4 h. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl and extracted with Et_2O. The extracts were washed with brine and dried with Na_2SO_4. After filtration, the organic solvent was distilled and the crude product was purified by chromatography column (petroleum ether–EtOAc, 20:1) for giving 0.18 g (0.92 mmol) of 4(*ax*)-chloro-2(*ax*)-hydroxy-2(*eq*)-methyladamantane (**3**). This value (yield 85%) refers to isolated compound after chromatographic purification taking heed of removal of the solvent. The procedure has required atmospheric pressure distillation because distillation of the solvent on a rotary evaporator caused losses of material due to the volatility of the adamantane derivative product.
17. (a) Duddeck, H. *Tetrahedron* **1978**, *34*, 247–251; (b) Duddeck, H.; Wolff, P. *Org. Magn. Reson.* **1977**, *9*, 528–532.
18. NMR spectra data for diastereoisomer **3**: ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.32 (s, 3H, Me), 1.60 (br d, 1H, J = 13.8 Hz, H-9*eq*), 1.68–1.80 (m, 5H, H-1, H-7, H-6B, H-8*eq*, H-10*eq*), 1.86–1.95 (m, 2H, H-6A, H-8*ax*), 2.08 (m, 1H, H-10*ax*), 2.12 (br s, 1H, H-3), 2.15 (br s, 1H, H-5), 2.50 (br d, 1H, J = 13.8 Hz, H-9*ax*), 3.87 (br s, 1H, 2-OH), 4.51 (dd, 1H, J = 4.27 and J = 1.27 Hz, H-4); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 25.84 (C-7), 27.05 (C-9), 27.21 (Me), 34.85 (C-8), 35.75 (C-5), 36.10 (C-10), 38.47 (C-1), 39.28 (C-6), 44.33 (C-3), 68.76 (C-4), 74.64 (C-2).
19. Kolocouris, A. *Tetrahedron Lett.* **2007**, *48*, 2117–2122.
20. The major products identified by GC–MS were a dehalogenated compound and a tetracyclic compound.
21. (a) Bartoli, G.; Bosco, M.; Marcantoni, E.; Massaccesi, M.; Rinaldi, S.; Sambri, L. *Synthesis* **2004**, 3092–3096; (b) Badioli, M.; Ballini, R.; Bartolacci, M.; Bosica, G.; Torregiani, E.; Marcantoni, E. *J. Org. Chem.* **2002**, *67*, 8938–8942; (c) Bartoli, G.; Marcantoni, E.; Petrini, M.; Sambri, L. *Chem. Eur. J.* **1996**, *2*, 913–917; (d) Bartoli, G.; Marcantoni, E.; Sambri, L.; Tamburini, M. *Angew. Chem., Int. Ed.* **1995**, *34*, 2046–2048; (e) Bartoli, G.; Marcantoni, E.; Petrini, M. *Angew. Chem., Int. Ed.* **1993**, *32*, 1061–1062.
22. It is desirable to use the Grignard reagent as the source of transferable methyl group, which was purchased as solution in THF and titrated just before use: Bergbreit, D. E.; Pendergrass, E. *J. Org. Chem.* **1981**, *46*, 219–220.
23. Corey, E. J.; Greewald, R.; Chaykovsky, M. *J. Org. Chem.* **1963**, *28*, 1128–1129.
24. Johnson, C. R.; Tait, B. D. *J. Org. Chem.* **1987**, *52*, 281–283 and references cited therein.
25. Konosu, T.; Miyaoka, T.; Tajima, Y.; Oida, S. *Chem. Pharm. Bull.* **1991**, *39*, 2241–2246.
26. Corey, E. J.; Liu, K. *J. Am. Chem. Soc.* **1997**, *119*, 9929–9930.