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# Direct aminoalkylation of cycloalkanes through dimethylzinc-initiated radical process

Ken-ichi Yamada, Yasutomo Yamamoto, Masaru Maekawa, Jingbo Chen and Kiyoshi Tomioka*

*Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan*

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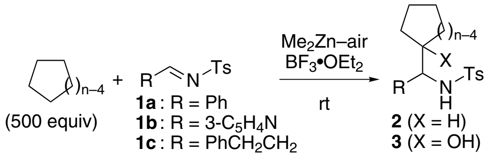
**Abstract**—Cycloalkyl radicals were directly generated from cycloalkanes via C–H bond cleavage by the action of dimethylzinc–air and underwent an addition reaction with *N*-tosylimines, giving aminoalkylation products in fair to high yields.

We describe herein a direct aminoalkylation of cycloalkanes with imines using dimethylzinc–air as a radical initiator. We have recently reported the radical addition of ethers to imines by the action of dimethylzinc–air.[1] The process is supposed to proceed through consecutive four chemical steps: (1) generation of methyl radicals from dimethylzinc and molecular oxygen,[2] (2) subsequent abstraction of an α-hydrogen of ethers to generate α-alkoxyalkyl radicals,[3] (3) addition to imines, and finally (4) zinc amide formation from the resulting aminyl radicals. This reaction can be regarded as a direct substitution of an α-hydrogen of ethers for aminoalkyl groups. The comparison of the bond dissociation energy (BDE)[4] of methyl-H (440 kJ/mol), tetrahydrofuran-2-yl-H (385 kJ/mol), and cyclohexyl-H (400 kJ/mol) led us to the expectation that a methyl radical could abstract a hydrogen atom from cycloalkanes to generate cycloalkyl radicals. Consequently, direct aminoalkylation of cycloalkanes[5] would be possible using dimethylzinc–air as a radical initiator (Scheme 1).



**Scheme 1.** Aminoalkylation of cycloalkanes with **1** using dimethylzinc.

A suspension of benzaldehyde *N*-tosylimine **1** (1.0 mmol) and dimethylzinc (12 mL, 1 M hexane solution, 12 mmol) in cyclohexane (54 mL, 0.50 mol) was stirred at rt for 48 h with continuous air supply through a bubbler (0.5 mL/h) (Table 1, entry 3). Aminoalkylated cyclohexane **2a** ($n = 6$) was obtained in 68% yield along with oxidized product **3a** ($n = 6$) in 10% yield. The formation of **3a** was not decreased even when the reaction was conducted under ordinary atmosphere without air bubbling, to give **2a** in 61% yield together with **3a** in 13% yield. The formation of **3a** was remarkably suppressed by the addition of boron trifluoride etherate (2.0 mmol) to a reaction mixture, giving **2a** in 80% yield without production of **3a** (entry 4).

Cycloalkanes of other ring size ($n = 5$, 7, and 8) also underwent the aminoalkylation reaction under the same conditions. Cyclopentane, cycloheptane, and cyclooctane were aminoalkylated to give the products in 68%, 61%, and 54% yield, respectively (entries 2, 6, and 8). In all the reactions, the addition of boron trifluoride suppressed the production of oxidized products **3** to improve the yields of **2** (entries 1 vs 2, 3 vs 4, 5 vs 6, and 7 vs 8).

Imine **1b** derived from 3-pyridinecarbaldehyde was a source of aminoalkylation agent, giving cyclohexane adduct **2b** ($n = 6$) in 38% yield (entry 9). Imine **1c** derived from 3-phenylpropanal underwent an addition reaction with cyclohexane, giving **2c** ($n = 6$) in 34% yield (entry

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*Keywords*: Radicals; Dimethylzinc; Imines; Cycloalkanes.

* Corresponding author. Tel.: +81-757534553; fax: +81-757534604; e-mail: tomioka@pharm.kyoto-u.ac.jp

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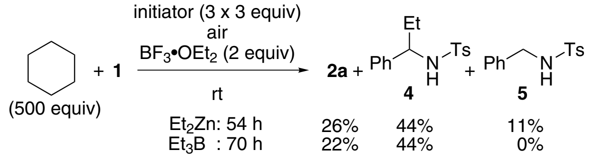
**Table 1.** Aminoalkylation of cycloalkanes with imines **1** by dimethylzinc–air[a] in the presence or absence of boron trifluoride diethyl etherate

| Entry | Cycloalkane (*n*) | **1** | $Me_2Zn$ (equiv) | $BF_3 \cdot OEt_2$ (equiv) | Time (h) | **2** (%) | **3** (%) |
|---|---|---|---|---|---|---|---|
| 1 | 5 | **a** | 12[b] | 0 | 61 | 59 | 12 |
| 2 | 5 | **a** | 9[b] | 2 | 70 | 68 | 0 |
| 3 | 6 | **a** | 12 | 0 | 48 | 68 | 10 |
| 4 | 6 | **a** | 9[b] | 2 | 56 | 80 | 0 |
| 5 | 7 | **a** | 12 | 0 | 108 | 48 | 3 |
| 6 | 7 | **a** | 9[b] | 2 | 72 | 61 | 2 |
| 7 | 8 | **a** | 9[b] | 0 | 64 | 34 | 5 |
| 8 | 8 | **a** | 9[b] | 2 | 72 | 54 | 1 |
| 9 | 6 | **b** | 9[b] | 0 | 72 | 38 | 0 |
| 10 | 6 | **c** | 9[b] | 0 | 72 | 34 | 0 |

[a] The reaction was conducted under ordinary atmosphere (entries 2, 4, 6, and 8) in a round bottom flask equipped with a drying tube, or air was introduced into a reaction mixture through a bubbler at the rate of 0.1 (entries 1 and 5) or 0.5 L/(h·mol) (entries 3 and 7).

[b] Dimethylzinc (3 equiv each) was portionwise added.



**Scheme 2.** Aminoalkylation of cyclohexane with imine **1a** using diethylzinc or triethylborane as an initiator.

10). Boron trifluoride negatively influenced these two reactions, giving messy mixtures of products.

Efficiency of other radical initiators was tested in the reaction of cyclohexane with **1a** (Scheme 2). When the reaction was performed using diethylzinc[6] as an initiator, instead of dimethylzinc, **2a** was obtained in 26% yield after 54 h, and ethyl adduct **4** was a main product in 44% yield along with reduction product **5** in 11% yield. By the initiation with triethylborane–air, the yield of **2a** was 22%, and ethyl adduct **4** was mainly produced in 44% yield after 70 h. Because an ethyl radical is more stable (BDE of ethyl-H = 411 kJ/mol)[4] than a methyl radical, the hydrogen abstraction from cyclohexane by an ethyl radical would be slower than that by a methyl radical, and the addition of an ethyl radical and/or the reduction of imine **1** could be competitive.[1d] Accordingly, dimethylzinc–air was the most efficient initiator for this aminoalkylation reaction among those examined.

In conclusion, direct aminoalkylation of cycloalkanes was achieved in fair to high yields at rt through a radical process by the action of dimethylzinc–air. Since hydroxyalkylation[7] and aminoalkylation[5] reactions of alkanes are quite few, the present aminoalkylation provides a new methodology for the direct functionalization of simple alkanes under mild conditions.

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