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C-Alkylation of Dialkylamides by Acetaldehyde Generated from *t*-BuLi and Tetrahydrofuran

T. Tuulamari Helaja[a*], Barbro Löfgren[b] and Tapio Hase[a]

[a]*Department of Chemistry, P.O. Box 55, FIN-00014 University of Helsinki, Finland.*
[b]*Helsinki University of Technology, Polymer Science Centre, P.O. Box 356, FIN-02151 Espoo, Finland.*

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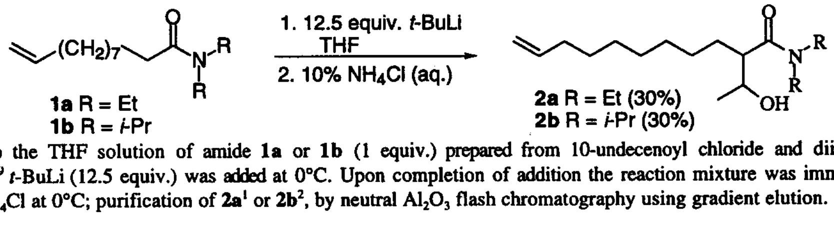
Abstract

A novel reaction involving α-*C*-alkylation of *N,N*-dialkylamides by acetaldehyde generated from *t*-BuLi and THF is reported.

Keywords: amides; *C*-alkylation; acetaldehyde

The cleavage of tetrahydrofuran (THF) by various organometallic reagents is well documented.[1-9] In the presence of *n*-butyllithium, THF is decomposed to the enolate ion of acetaldehyde.[10-12] The cycloreversion of THF has previously been utilized in the synthesis of amines, formamides and arylhydroxytriazoles from substituted arylazides,[13,14] in the synthesis of 3-aryl-5-hydroxyisoxazolines and 3-aryl-5-hydroxyisoxazolidines from benzonitrile oxides[15] or from *N*-phenylnitrones.[16] Similar treatment of nonenolizable aldehydes produced *prim* alcohols the enolate being converted into ketene.[17] Moreover, the *O*-acylation and *O*-silylation of the acetaldehyde enolate generated from THF and *n*-BuLi has been accomplished.[12,18] The authors[12] reported that the attempted *C*-alkylation of the acetaldehyde enolate afforded mainly polymeric material. Herein we report an unexpected *C*-alkylation of *N,N*-dialkylamides (Scheme 1) by acetaldehyde generated from the known cycloreversion of THF.



Scheme 1. To the THF solution of amide **1a** or **1b** (1 equiv.) prepared from 10-undecenoyl chloride and diisopropylamine or diethylamine,[19] *t*-BuLi (12.5 equiv.) was added at 0°C. Upon completion of addition the reaction mixture was immediately quenched with 10 % NH_4Cl at 0°C; purification of **2a**[1] or **2b**[2], by neutral Al_2O_3 flash chromatography using gradient elution.

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[*] Corresponding author. Tel: +358-9-191 40344; fax: +358-9-191 40366; e-mail: tuulamari.helaja@helsinki.fi

[1] Data for compound **2a**: IR (KBr) ν_{max} 3440, 2940, 1620 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.80 (m, 1 H, C=CH), 5.00 (m, 2H, CH_2=C), 4.05 (s, OH), 3.95 (m, 1 H), 3.50 (m, 2 H), 3.30 (m, 2 H), 2.55 (m, 1 H), 2.00 (m, 2H, C=C-CH_2), 1.75 (m, 2 H), 1.65 (m, 2 H), 1.24-1.42 (broad, 3 CH_3 & 4 CH_2); ^{13}C NMR (300 MHz, $CDCl_3$) δ 176.0, 139.2, 114.2, 68.2, 46.2, 42.3, 40.5, 33.8, 30.0, 29.3, 29.1, 28.9, 27.9, 26.0, 20.5, 14.9, 13.0; HRMS calculated for $C_{17}H_{33}O_2N$ 283.2511, found 283.2505.

[2] Data for compound **2b**: IR (KBr) ν_{max} 3440, 2950, 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.80 (m, 1 H, C=CH), 5.00 (m, 2H, CH_2=C), 4.10 (m, 1 H), 3.95 (s, OH), 3.90 (m, 1 H), 3.50 (m, 1 H), 2.55 (m, 1 H), 2.00 (m, 2H, C=C-CH_2), 1.76 (m, 2 H), 1.65-1.10 (broad, 5 CH_3 & 5 CH_2); ^{13}C NMR (300 MHz, $CDCl_3$) δ 175.8, 139.1, 114.1, 68.3, 48.6, 47.2, 46.1, 33.8, 30.0, 29.8, 29.4, 29.1, 28.9, 28.0, 26.1, 21.4, 21.1, 20.7, 20.6; HRMS calculated for $C_{19}H_{37}O_2N$ 311.2824, found 311.2825.

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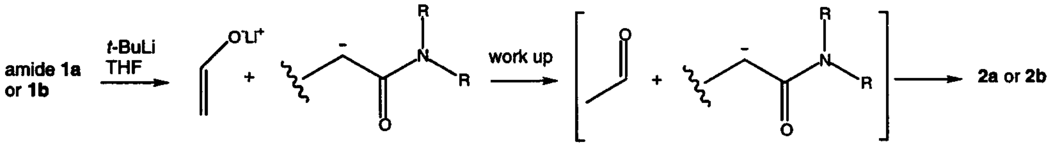
We found that a large excess of *t*-BuLi (12.5 equiv.) is necessary to obtain a 30% yield of **2a** or **2b**; treatment of the amide - THF mixture at 0°C with 3.5 equiv. of *t*-BuLi afforded 13% of **2a** or **2b**. The yield seems not to be affected by the reaction time since 30 % of **2a** or **2b** was obtained whether the reaction mixture was stirred for 2 h 30 min or quenched immediately after *t*-BuLi addition. However, by lowering the reaction temperature to -70°C, only the starting amide **1a** was recovered even after a prolonged reaction time of 7 h. Similarly, there was no reaction when the acetaldehyde enolate was generated[12] from *t*-BuLi and THF at 0°C or from *n*-BuLi and THF at 25°C prior to addition of **1a**. This indicates that the aldol addition reaction is not due to an interchange of protons between the acetaldehyde enolate and neutral amide. It appears that there exist two carbanions in solution of which the amide enolate is more long-lived during the aqueous work-up (Scheme 2).

Scheme 2



Although *C*-alkylation of the acetaldehyde enolate was accomplished via its tributyltin enolate,[12] we are not aware of any previous reports on α-*C* alkylation of an amide by acetaldehyde generated from an organolithium compound and THF. Moreover, the treatment of *N,N*-diethyl or *N,N*-di-*i*-propyl butylamide with *t*-BuLi (12.5 equiv.) at 0°C produced the corresponding α-*C* alkylated products (raw product yield ca. 30% for each) whereas none of the aldol product was formed in case of a *N,N*-dimethyl butyl or *N,N*-dimethyl undecenoyl amide. The latter gave a mixture containing the expected *t*-butyl ketone derivative as a main product.

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