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An Efficient Method To Convert Lactams and Amides into 2,2-Dialkylated Amines†

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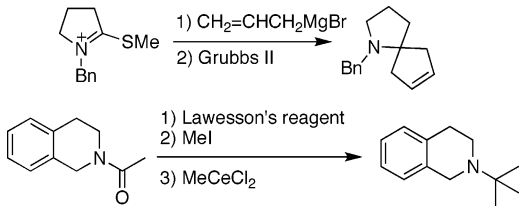
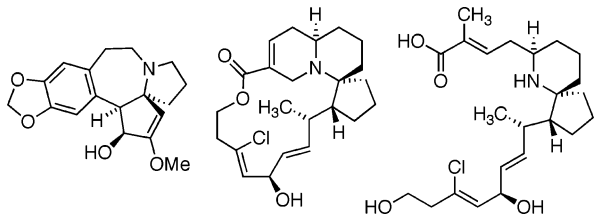
ABSTRACT



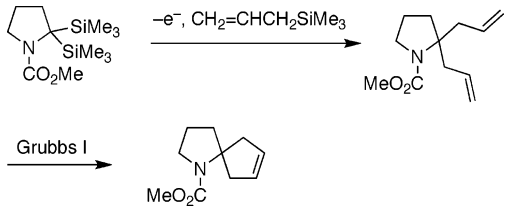
A practical method for the synthesis of *gem*-2,2-disubstituted tertiary amines from the corresponding lactams (or amides) is reported. It is based on the reaction of thioiminium ions, easily prepared from lactams and amides with organometallic reagents such allylmagnesium, benzylmagnesium, and primary alkylcerium reagents.

Geminal 2,2-bisalkylated cyclic amines are interesting building blocks for natural product synthesis as well as important pharmacophores. For instance, 2,2-bisallylated pyrrolidines and piperidines have been used as starting material for the synthesis of azaspirononanes and azaspirodecanes that are present in a variety of natural products such as cephalotaxine, pinnaic acid, and halichlorine.[1]



Yoshida reported an interesting method to prepare azaspirononanes starting from pyrrolidines protected as carbamates via 2,2-bissilylation, electrochemical bisallylation, and ring-closing metathesis (Scheme 1).[2] However, the interest of this procedure is limited by the use of very strong bases such as *sec*-butyllithium to prepare the bis-silylated derivative and by the use of different *N*-protecting groups for the silylation and for the allylation steps.

Scheme 1. Yoshida's Procedure for the Preparation of Azaspirononanes



Luke and Cerny reported an efficient procedure to convert piperidinone into 2,2-diallylpiperidine.[3] This procedure was applied later by Semmelhack to prepare 2,2-diallylpyrrolidine.[4] The azaspirocyclic system was prepared via an acyloin condensation and converted into cephalotaxine. Bubnov[5] and

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(1) For a recent review on the synthesis of 1-azaspirocycles, see: Dake, G. *Tetrahedron* **2006**, *62*, 3467−3492.

(2) Suga, S.; Watanabe, M.; Yoshida, J. *J. Am. Chem. Soc.* **2002**, *124*, 14824−14825.

(3) Lukes, R.; Cerny, M. *Collect. Czech. Chem. Commun.* **1961**, *26*, 2886.

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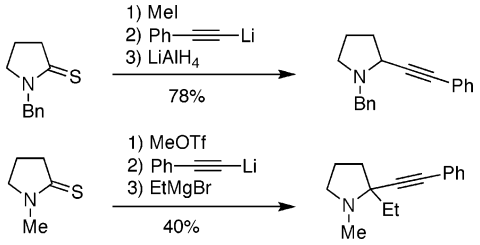
Zhang[6] developed the direct conversion of lactams into the *gem*-diallylderivatives via reaction with triallylborane and allylsamarium bromide, respectively. However, none of the reported approaches (Semmelhack, Bubnov, and Zhang) is compatible with the presence of an alkyl substituent at the nitrogen atom. Therefore, an extra *N*-alkylation step is required for most application in natural product synthesis. The conversion of amides into tertiary 2,2-dimethylamines has been reported by Denton and Wood by direct treatment of amides with methylmagnesium bromide in the presence of zirconium or titanium tetrachloride.[7] So far, this reaction is limited to the introduction of a methyl group. Takahata[8] and more recently Murai[9] have investigated the reactivity of thioiminium salts derived from thioamides and thiolactams with nucleophiles leading to 2-monosubstituted and 2,2-disubstituted amines (Scheme 2). The reaction is promising

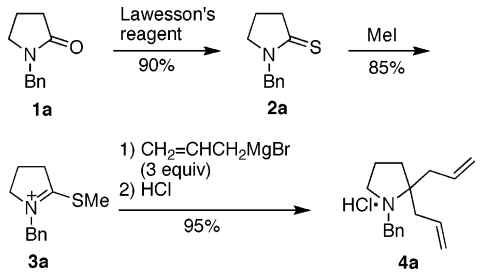
Scheme 2. Takahata and Murai Alkynylation of Thioiminium Ions



when alkynyllithium reagents are used first as the nucleophile. The reaction of a thioiminium salt derived from a [3.2.1] bicyclic amide with a substituted alkyl Grignard reagent has been investigated by Klaver, Speckamp, and Hiemstra.[10] In THF, the reaction afforded the *gem*-dialkylated product in low yield. However, when the reaction was run in dichloromethane, a good yield of the monoalkylated product was obtained. In this paper, we report that thioiminium salts, easily prepared from lactams and amides, can be converted into 2,2-disubstitued amines by reaction with simple nucleophiles such as organomagnesium and organocerium reagents.

***gem*-Diallylation and *gem*-Dibenzylation.** The thioiminium iodide **3a** is prepared from *N*-benzylpyrrolidinone **1a** (Scheme 3). Treatment of **1a** with the Lawesson's reagent affords the thiolactam **2a** that is converted into the thioiminium salt **3a** by treatment with methyl iodide in THF at room temperature. Treatment of the thioiminium salt **3a** with allylmagnesium bromide affords the desired *gem*-diallylated pyrrolidine **4a**. Best results are obtained with 3 equiv of allylmagnesium bromide in THF at room temperature.

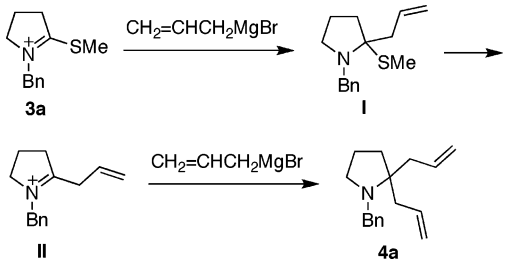
Scheme 3. Optimized Conditions for the Preparation of 2,2-Diallyl-*N*-benzylpyrrolidine from *N*-Benzylpyrrolidinone



In contrast to Klaver et al.,[10] neither the solvent nor the temperature influences the product distribution. For instance, when the reaction of **3a** was performed with only one equivalent of allylmagnesium bromide in dichloromethane at −78 °C, no monoallylation was observed. Instead, the bisallylated amine **4a** was obtained in 40% yield together with lactam **1a** arising from the aqueous workup.

With allylic organomagnesium reagents, the mechanism presumably involves an initial addition to the thioiminium salt leading to the *N*,*S*-acetal **I** followed by a fast fragmentation, favored by the Lewis acidity of magnesium(II), leading to the iminium ion **II** (Scheme 4). The iminium ion **II** is

Scheme 4. Mechanism of the Double-Allylation Reaction



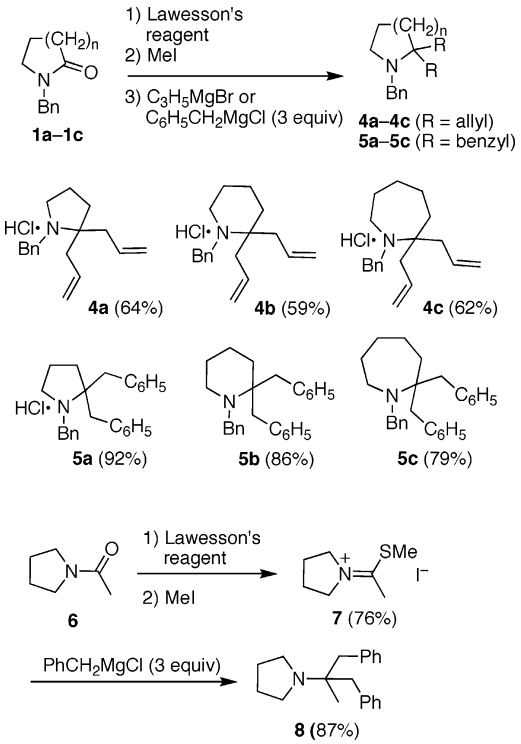
more electrophilic than the thioiminium ion **3a**, and therefore, the second nucleophilic addition takes place more rapidly than the reaction with the thioiminium ion.

The reaction sequence was applied to *N*-benzylpiperidinone **1b** and *N*-benzylazepanone **1c**. As nucleophiles, both allylmagnesium bromide and benzylmagnesium chloride were successfully tested (Scheme 5). In all cases, the *gem*-dialkylated products **4** and **5** are obtained in excellent yields over the three steps from the parent lactams. The reaction was also tested with the acetamide **6**. Successive treatment with Lawesson's reagent, methyl iodide, and benzylmagnesium chloride affords the tertiary amine **8** in 66% overall yield.

Ring-Closing Metathesis (RCM). The bisallylated cyclic amines **4a**−**c** were then subjected to the RCM reaction. Despite their high functional group tolerance, ruthenium carbenes catalysts do not work well in the presence of basic nitrogen atoms.[11] Running the reaction on the free amine led to low conversion (≤20%) after 5 h in refluxing toluene

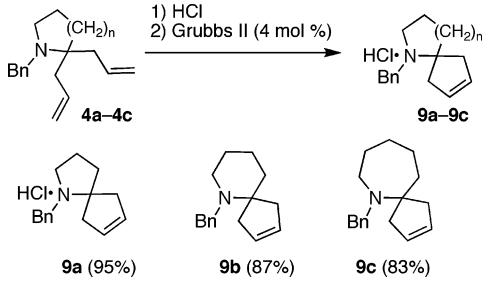
(4) Semmelhack, M. F.; Chong, B. P.; Stauffer, R. D.; Rogerson, T. D.; Chong, A.; Jones, L. D. *J. Am. Chem. Soc.* **1975**, *97*, 2507−2516.
(5) Nieczypor, P.; Mol, J. C.; Bespalova, Y.; Bubnov, N. *Eur. J. Org. Chem.* **2004**, 812−819.
(6) Li, Z.; Zhang, Y. *Tetrahedron* **2002**, *58* (26), 5301−5306.
(7) Denton, M. S.; Wood, A. *Synlett* **1999**, 55−56.
(8) Takahata, H.; Takahashi, K.; Wang, E. C.; Yamazaki, T. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1211−1214.
(9) Murai, T.; Toshio, R.; Mutoh, Y. *Tetrahedron* **2006**, *62*, 6312−6320.
(10) Klaver, W. J.; Hiemstra, H.; Speckamp, W. N. *J. Am. Chem. Soc.* **1989**, *111*, 2588−2595.

Scheme 5. *gem*-Dialkylation of Lactams and Amides with Allylic and Benzylic Organomagnesium Reagents



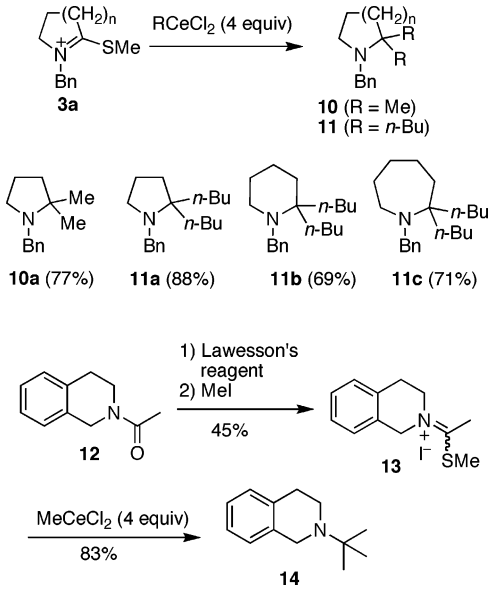
with 10 mol % of Grubbs second-generation catalyst.[12] However, when the corresponding hydrochlorides were used, the RCM reactions took place in refluxing CH_2Cl_2 and afford the 1-azaspirocycles **9a**−**c** in higher yield and shorter reaction time (90 min) in the presence of 5 mol % of Grubbs II catalyst (Scheme 6).[13]

Scheme 6. Preparation of Azaspiro Derivatives by RCM



***gem*-Dialkylation.** Extension of the allylation-benzylation process to the introduction of geminal dialkyl group proved not to be feasible by using either alkylmagnesium halides or alkyllithium derivatives, despite the isolated example reported by Klaver et al.[10,14] Indeed, these reagents are presumably too basic and deprotonate the thioiminium salts rather than undergoing the desired addition. Organocerium derivatives are offen used to avoid the undesired deprotonation during the addition of organolithium and organomagnesium reagents to ketones.[15] Therefore, methylcerium dichloride and *n*-butylcerium dichloride, easily prepared from the commercially available organolithium derivatives, were tested. Both reagents react cleanly with the thioiminium iodides **3a**−**c** and afford the *gem*-dimethyl and *gem*-dibutyl derivatives **10a**, **11a**−**c** in good yield (Scheme 7). Interestingly, the reaction in the presence of 1 equiv of *n*-butylcerium with **3a** affords **11a** as single isolated product in 20% yield. Accordingly to the results of the organomagnesium allylation, no product resulting from the monoaddition was detected.[16]

Scheme 7. *gem*-Dialkylation with Organocerium Reagents



The *gem*-dialkylation process can also be applied to amides. For instance, we prepared *N*-*tert*-butyltetrahydroisoquinoline **14** from the acetamide **12** via the thioiminium ion **13**. The acetylation−*gem*-dimethylation process represents a useful method for the conversion of secondary amines into *tert*-butyl tertiary amines. In the literature, the *tert*-butylation of secondary amines is scarcely reported, low yielding, and requires drastic reaction conditions.[7,17,18]

Secondary and tertiary alkylcerium reagents do not add to the thioiminium salts and after aqueous work up the parent lactams are recovered. It is unclear whether this result is due to a lack of reactivity or to a competitive depronation.

(11) Deiters, A.; Martin, S. F *Chem. Rev.* **2004**, *104*, 2199−2238.
(12) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.
(13) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371−388.
(14) All our attempts to apply Klaver's procedure to monocyclic thioiminium salts bearing acidic H-atoms, such as **3a**, failed to give the expected monoalkylated or dialkylated products due to competitive deprotonation of the thioiminium salts.
(15) Liu, H.; Shia, K.; Shang, X.; Zhu, B. *Tetrahedron* **1999**, 3803−3830.
(16) Recently, the monoalkylation of thioiminium ion with alkylcuprates has been reported by Amat et al.: Amat, M.; Llor, N.; Hidalgo, J.; Escolano, C.; Bosch, J. *J. Org. Chem.* **2003**, *68*, 1919−1928.
(17) Direct reaction of secondary amines with *tert*-butyl halides did not afford the *tert*-butyl amines in useful yields: Drake, W. V.; McElvain, S. M. *J. Am. Chem. Soc.* **1933**, *55*, 1155−1158.

In conclusion, we have developed a practical method for the synthesis of *gem*-2,2-disubstituted amines from the corresponding lactams and amides. So far, the reaction allows the introduction of allyl, benzyl and primary alkyl chains. Further investigation of this chemistry as well as applications in alkaloid synthesis are underway.

(18) For examples of multistep *tert*-butylation of a secondary amines, see: Knabe, J.; Grund, G. *Arch. Pharm.* **1963**, *296*, 820−828. Lattes, A.; Perie, J. J. *Tetrahedron Lett.* **1967**, 5165−5168. Suzuki, K.; Okano, K.; Nakai, K.; Terao, Y.; Sekiya, M. *Synthesis* **1983**, 723−725. Guan, H.; Saddoughi, S. A.; Shaw, A. P.; Norton, J. R. *Organometallics* **2005**, *24*, 6358−6364.

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Supporting Information Available: Full experimental procedures, spectral data, and ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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