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A NOVEL APPROACH TO AZASPIROCYCLES VIA NUCLEOPHILIC ADDITIONS

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Abstract. An efficient and simple method has been developed for the synthesis of spirocycles using easily prepared organodicerium reagents. This method can replace the conventional ring closing method performed by very expensive Grubb's and Hoveyda catalysts.

Keywords: Spirocycles, Organodicerium reagents, Lactams, and Cyclization.

1. INTRODUCTION

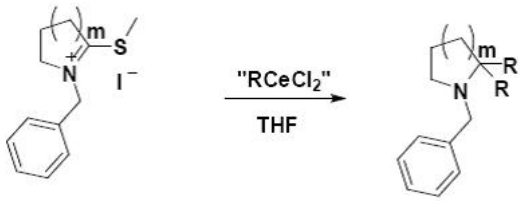
Geminal 2,2-bisalkylated cyclic amines are interesting building blocks for natural product synthesis as well as important pharmacophores [1]. For instance, 2,2-bisallylated pyrrolidines and piperidines have been used as starting materials for the synthesis of azaspirononanes and azaspirodecanes that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

The development of new synthetic methods and strategies for the construction of these motifs is a continuing focus of interest for synthetic organic chemists [1]. In assessing the strengths or weaknesses of a synthetic approach and criteria that can be used to evaluate each method include conciseness, efficiency, functional group compatibility, cost, elegance and other factors.

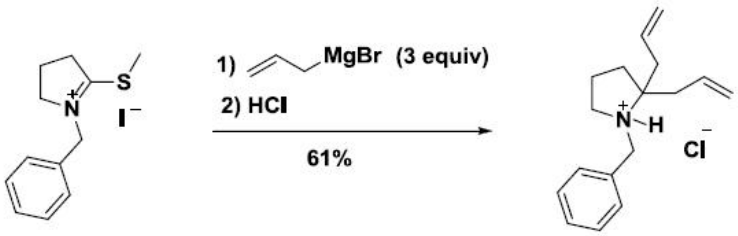
The compounds 1-azaspiro[4,4] nonanones have been used as templates for constructing synthetic receptors and as intermediates in the synthesis of enzyme inhibitors [2]. These cyclic

systems incorporate two rings connected by a spiro ring fusion containing a nitrogen atom adjacent to the ring junction.

Bis addition of organocerium reagents to the thioiminium ions have been extensively studied and reported [3]. We are successful to add alkylcerium reagents to the thioiminium salts which are prepared from the lactams (Scheme 1) [4]. Other reagents like alkylmagesium bromide and alkyllithium reagents are presumably too basic and deprotonate the thioiminium salts rather than undergoing the desired addition. Instead, the bisallylated amine (Scheme 2) was obtained with the thioiminium salt and allylmagnesium bromide, arising from aqueous workup [5]. The introduction of geminal dialkyl group proved not be feasible by using either alkylmagnesium halides or alkyllithium derivatives, despite the isolated example reported by Klaver et al. [6].

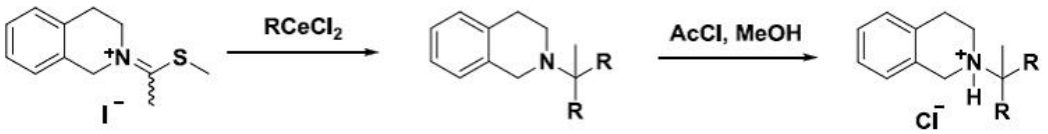


Scheme 1

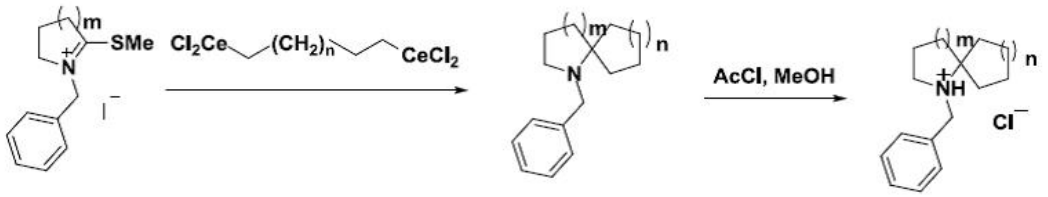


Scheme 2

Scheme 3



Scheme 4



Scheme 5

Organocerium derivatives are often used to avoid undesired deprotonation during addition of organolithium and organomagnesium reagents to ketones [7]. We have observed that the reaction in the presence of 1 equiv of n-butylcerium with the thioiminium salt affords **3** as single isolated product in 20% yield [8]. Accordingly to the results of the organomagnesium allylation, no product resulting from the monoaddition was detected [9].

With alkyl organocerium 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 cerium(III), leading to the iminium ion **II** (Scheme 3). The iminium ion **II** is more electrophilic than the thioiminium ion and therefore, the second nucleophilic addition takes place more rapidly than the reaction with thioiminium ion.

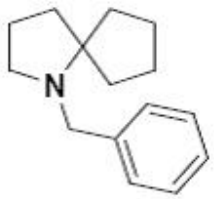
The acetylation-gem-dimethylation process represents a useful method for the conversion of secondary amines into tert-butyl tertiary amines (Scheme 4). Secondary and tertiary alkylcerium reagents do not add to the thioiminium salts and after aqueous work up, the parent lactams are recovered [3]. It is unclear whether this result is due to a lack of reactivity or a competitive deprotonation.

We extended the utility of organocerium reagents towards the spirocyclization (Scheme 5). Treatment of the corresponding thioiminium salts with dicerium reagents afforded the desired spirocylces (**12-14**) [10]. One of them (**12**) was converted into its hydrochloride (**15**) [11] which is stable at room temperature for a long time in closed container. This reaction proves the efficiency of cerium reagent in spirocyclization reactions. The same reaction conditions of scheme 1 were applied to spirocyclization also [8].

Further, addition of cerium reagent to the thioiminium salt provided good yield whereas the addition of salt to the cerium reagent gave poor yield. The open bis addition product was also isolated when the salt was added to the reagent. The yield of spiro compound obtained from dicerium reagent was always lower than that of the bis addition product obtained by monoalkylcerium reagent. Perhaps, the monoalkylcerium reagents are better nucleophiles than the dicerium reagents.

2. Synthetic Procedures

2.1. **Synthesis of 1-benzyl-1-azaspiro[4.4] nonane 12:** The suspension of $CeCl_3$ (1.479 g, 6 mmol) in 25 mL of THF was soniccated for about 30 min under nitrogen and cooled to -78 ^oC. 0.92 M of dilithiobutane (3 mL, 3 mmol) was added to the suspension and stirred for about 30 min at the same temperature. This mixture was transferred to another suspension of 1-benzyl-5-(methylthio)-3,4-dihydro-2H-pyrrolium iodide (0.500 g, 1.5 mmol) in 5 mL of THF through cannula at -78 ^oC and stirred for 6 hours at room temperature. The reaction was treated with NH_4Cl and the aq layer was extracted by EtOAc. The combined extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude was purified by flash column using cyclohexane-TBME (9:1 v/v mixture) as eluent to afford **12** (0.09 g, 28%). Pale yellow oily liquid.



IR (diamond ATR) ν 2950, 2862, 1494, 1451 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz)

δ 7.28-7.11 (m, 5H) 3.47 (s, 2H) 2.53-2.48 (t, 2H) 1.67-1-51 (m, 10H) 1.40-1.34 (m, 2H) ppm

^{13}C NMR ($CDCl_3$, 75.5 MHz)

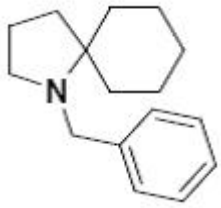
δ 140.95, 128.76, 128.15, 126.68, 72.23, 67.69, 53.56, 51.74, 39.79, 32.10, 25.83, 24.20, 20.90 ppm

MS (EI^+) e/z (% intensity) 216 (23) 215 (68) 214 (15) 200 (15) 188 (24) 187 (62) 186 (82) 184 (9) 175 (17) 174 (66) 172 (80) 170 (22) 160 (14) 158 (37) 146 (6) 145 (22) 144 (18) 132 (7) 131 (15) 130 (42) 117 (12) 110 (10) 105 (16) 104 (73) 103 (13) 98 (5) 96 (38) 91 (100) 89

(16) 86 (7) 82 (25) 77 (17) 69 (7) 67 (29) 65 (66) 63 (10) 55 (27) 53 (14) 44 (7) 41 (61) 39 (39)

HRMS: calcd. for $C_{15}H_{22}N$ 216.1752; found 216.1756

2.2. **Synthesis of 1-benzyl-1-azaspiro [4.5] decane 13:** The above procedure was followed to prepare **13**. 0.54 M of dilithiopentane with $CeCl_3$ was added to 1-benzyl-5-(methylthio)-3,4-dihydro-2H-pyrrolium iodide (0.500 g, 1.5 mmol) in 5 mL of THF through cannula. The crude was purified by flash column using cyclohexane-TBME (1:1 v/v mixture) as eluent to afford **13** (0.074 g, 21%). Pale yellow oily liquid.



IR (diamond ATR) ν 2923, 2852, 1494, 1452 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz)

δ 7.27-7.11 (m, 5H) 3.53 (s, 2H) 2.59-2.55 (t, 2H) 1.67-1.56 (m, 6H) 1.41-1.18 (m, 8H) ppm

^{13}C NMR ($CDCl_3$, 75.5 MHz)

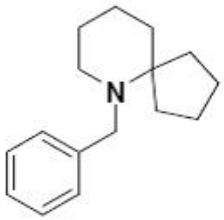
δ 141.49, 128.49, 128.15, 128.05, 126.39, 63.09, 52.54, 50.61, 31.89, 26.38, 25.74, 24.39, 14.15, 14.09 ppm

MS (EI^+) e/z (% intensity) 230 (6) 229 (29) 200 (8) 187 (24) 186 (61) 175 (6) 174 (27) 173 (33) 172 (31) 160 (6) 140 (11) 115 (12) 115 (12) 112 (34) 111 (27) 104 (16) 101 (22) 99 (36) 97 (50) 91 (69) 87 (35) 83 (77) 81 (54) 79 (12) 73 (6) 71 (38) 69 (86) 67 (50) 65 (19) 57 (34) 55 (95) 53 (21) 51 (7) 45 (17) 43 (76) 41 (100) 39 (52)

HRMS: calcd. for $C_{16}H_{24}N$ 230.1908; found 230.1905

2.3. **Synthesis of 6-benzyl-6-azaspiro[4.5]decane 14:** The above procedure was followed to prepare **14**. 0.92 M of dilithiobutane with $CeCl_3$ was added to the suspension of 1-benzyl-6-(methylthio)-2,3,4,5-tetrahydropyridinium iodide (0.500 g, 1.45 mmol) in 5 mL of THF through cannula. Flash column using cyclohexane-TBME (1:1 v/v mixture) as eluent afforded **102**

(0.014 g, 4%) Colourless oily liquid.



IR (diamond ATR) ν 2926, 2860, 1493, 1451 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz)

δ 7.31-7.13 (m, 5H) 3.40 (s, 2H) 2.30-2.27 (t, 2H) 1.75-1.71 (m, 2H) 1.56-1.37 (m, 12H) ppm

^{13}C NMR ($CDCl_3$, 75.5 MHz)

δ 141.56, 128.36, 128.05, 126.35, 66.60, 54.44, 48.98, 39.01, 33.69, 33.66, 29.70, 25.47, 22.32 ppm

MS (EI^+) e/z (% intensity) 230 (13) 229 (65) 228 (10) 217 (20) 214 (8) 203 (20) 202 (67) 200 (75)188 (34) 187 (81) 186 (78) 184 (7) 173 (22) 172 (50) 160 (9) 158 (16) 147 (8) 146 (28) 144 (12) 126 (53) 117 (13) 110 (18) 104 (28) 96 (22) 91 (100) 89 (11) 84 (7) 82 (25) 65 (47) 63 (6) 55 (44) 53 (13) 51 (8) 44 (6) 41(52) 39 (25)

HRMS: calcd. for $C_{16}H_{24}N$ 230.19; found 230.1910

3. Acknowledgement

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[5] Allylmagnesium bromide (15 mL, 15 mmol) was added to a suspension of thioiminium ion (5 mmol) in dry THF (50 mL) at 0°C, the cooling bath was removed and stirring was continued for 5h. The mixture was treated with saturated ammonium chloride solution and the aqueous phase extracted with CH_2Cl_2. The collected organic phases were washed with brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to afford the crude product, which was purified by FC (cyclohexane/EtOAc) affording the pure bisallylated amine.

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[7] H. Liu, K. Shia, X. Shang and B. Zhu, *Organocerium compounds in synthesis*, Tetrahedron, **55**, (1999), 3803-3830.

[8] A suspension of $CeCl_3$ (0.296 g. 1.2 mmol) in dry THF (4 mL) was soniccated at room temperature for about 30 min. The suspension was cooled down to -78°C and the alkyllithium reagent solution (1.2 mmol) was added dropwise. The solution became pale yellow and stirring was continued for about 30 min. The thioiminium salt was added as a solid (1.2 mmol), the cooling bath was removed and the mixture was stirred for about 6 h. The dark brown suspension was treated with saturated NH_4Cl and the aqueous phases were extracted with dichloromethane (3 x). The collected organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by FC (cyclohexane/tert-BuOMe) to afford the gem-dialkylated amine.

[9] H. B. Kagan and J. L. Namy, *Tetrahedron report number 213 : Lanthanides in organic synthesis*, Tetrahedron, **42**, (1986), 6573-6614.

[10] The suspension of $CeCl_3$ (6 mmol) in 25 mL of THF was soniccated for about 30 min under nitrogen and cooled to -78 °C. 0.92 M of dilithioalkane (3 mmol) was added to the suspension and stirred for about 30 min at the same temperature. This mixture was transferred to another suspension of thioiminium iodide (1.5 mmol) in 5 mL of THF through cannula at -78 °C and stirred for 6 hours at room temperature. The reaction was treated with NH_4Cl and the aq layer was extracted by EtOAc. The combined extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude was purified by flash column using cyclohexane-TBME (9:1 v/v mixture) as eluent to afford **12-14.**

[11] The spirocycle **12** was treated with HCl (generated from the addition of acetyl chloride to MeOH at 0 °C) to give its corresponding amine hydrochloride