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N-Functionalized Organolithium Compounds *via* Tellurium/Lithium Exchange Reaction

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Um conjunto de amino teluretos foram preparados e testados em reações de troca telúrio/lítio. Os compostos de organolítio contendo nitrogênio foram facilmente preparados utilizando *N*-Bz teluroaminas e uma combinação de *n*-butillítio/naftaleto de lítio nas reações de troca. Os correspondentes intermediários dilitiados foram capturados com vários eletrófilos, levando à formação dos respectivos produtos em bons rendimentos. A reação foi empregada na síntese de fenetilaminas.

A set of tellurium amines have been evaluated in the tellurium/lithium exchange reaction. The nitrogen-containing organolithium compounds were efficiently prepared by using *N*-Bz tellurium amines and a mixture of *n*-butyllithium and lithium naphthalenide (LiNp) for performing the exchange reaction. The corresponding dianion intermediates were trapped with a wide range of electrophiles, furnishing the corresponding products in good to excellent yields. The reaction was also employed in the synthesis of phenethylamines.

Keywords: tellurium/lithium exchange reaction, functionalized organolithium, dianion intermediate, phenethylamines

Introduction

Organolithium compounds are versatile and useful organometallics due to their excellent nucleophilic reactivity and importance in synthetic organic chemistry.[1] Among them, functionalized organolithium compounds represent an important class of intermediates with the ability of transfering the functionality to an electrophilic reagent. In this way, the preparation of functionalized organolithium compounds *via* halogen/lithium[2] and tin/lithium[3] exchange reactions represent an interesting protocol of carbon-carbon bond formation for the synthesis of polyfunctionalized molecules, as well as a wide range of natural products. For years, several groups have been interested in the study and preparation of different α-, β-, γ-, δ-oxygen or nitrogen-functionalized organolithium intermediates and their reaction with electrophiles.[4,5] However, among these intermediates, the corresponding β-functionalized compounds, showed to be very unstable species, decomposing *via* β-elimination to give olefins.[6]

On the other hand, organotellurium chemistry is a very broad and exciting field with many opportunities for research and development of applications in organic synthesis.[7] Many different classes of organotellurium compounds have been prepared to date and successfully employed in different synthetic applications,[8] as well as in the total synthesis of natural products.[9] Among the several applications of organotellurium compounds, the formation of organolithium compounds *via* tellurium/lithium exchange reaction represents an interesting protocol with a number of advantages over alternative methods.[10,11]

Our research group has been working in the preparation and application of hydroxy alkyl tellurides in the tellurium/lithium exchange reaction.[12] These compounds have been efficiently used as alternative organometallic sources of 1,4-dianion intermediates in the synthesis of diols,[13] spiroketals,[14] bioactive butenolides,[15] and in the synthesis of natural products, such as (+/−)-frontalin[16] and (+)-*endo*-brevicomin.[17] In this way, based on the interesting results obtained with the application of oxygen-containing organotellurium compounds[12-16] and following our current interest concerning the development of functionalized alkyl tellurides in organic synthesis, we decided to explore herein

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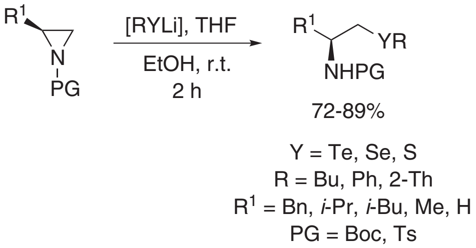
the application of nitrogen-containing organotellurium compounds in tellurium/lithium exchange reactions.

Results and Discussion

The preparation of the corresponding nitrogen-containing organotellurium compounds was described in our previous communication,[18] *via* the ring-opening reaction of aziridines by tellurium nucleophiles generated *in situ*, as depicted in Scheme 1. All the β-organotellurium amines, bearing different steric and electronic characteristics, were obtained in up to 89% yield and under very mild conditions.



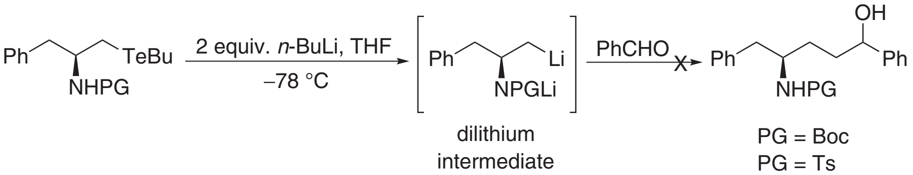
Scheme 1. Ring-opening reaction of aziridines by chalcogen nucleophiles.

The β-organotellurium compounds derived from L-phenylalanine bearing *t*-butoxycarbonyl and tosyl protecting groups were employed as model substrates in order to evaluate the formation of the nitrogen-functionalized organolithium intermediates by tellurium/lithium exchange reaction (Scheme 2). In this way, the corresponding alkyl tellurides were initially submitted to the conditions successfully employed by our group for hydroxy tellurides, previously used as substrates in the tellurium/lithium exchange reaction.[13]

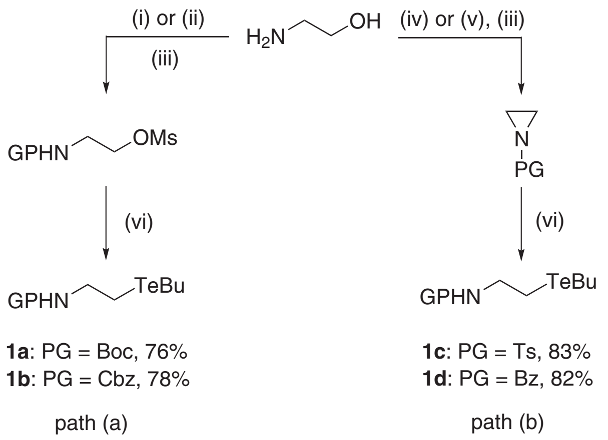
According to the reaction conditions described in Scheme 2, *n*-BuLi (2 equiv.) was used to generate the dianion intermediate. When *N*-Ts β-tellurium amine was used as substrate, the Te/Li exchange reaction could be followed by TLC (disappearance of the starting material). However, after addition of benzaldehyde to the dilithium intermediate, and even after prolonged reaction time at −78 ºC to r.t., the formation of the expected γ-aminoalcohol could not be observed. Flash chromatography of the crude product revealed the presence of *p*-toluenesulphonamide and other side products, probably arising from a β-elimination reaction on the corresponding dilithium intermediate. The same results were observed, by using different solvents (THF, ether), temperatures (−78, −20, 0 ºC, r.t,), additives such HMPA, TMEDA and LiNp (lithium naphtalenide[19]), as well as *t*-BuLi. Based on these unsucessful results obtained with the β-tellurium amines derived from L-phenylalanine in Te/Li exchange reactions, we decided to evaluate the behaviour of a very simple class of β-tellurium amines, containing different protecting groups (PG = Boc, Cbz, Bz and Ts) and only a C2 carbon chain between the tellurium and nitrogen moieties, aiming to minimize the possibility of β-elimination. Thus, the *N*-Boc and *N*-Cbz β-telluro amines **1a** and **1b** were prepared in 76 and 78% yields, respectively, by nucleophilic displacement of the mesylate groups of $BocHNCH_2CH_2OMs$[20] and $CbzHNCH_2CH_2OMs$,[21] using *n*-BuLi and elemental tellurium [BuTeLi] in a mixture of THF and ethanol (Scheme 3, path a). On the other hand, the *N*-Ts and *N*-Bz β-telluro amines **1c** and **1d** were easily obtained *via* the ring-opening reaction of the corresponding aziridines,[17,22] using the same tellurium nucleophilic species (Scheme 3, path b).

The β-tellurium amines **1a-d** were evaluated in the tellurium/lithium exchange reaction. In this way, when the β-tellurium amines containing carbamate moieties (**1a**, PG = Boc and **1b**, PG = Cbz) were used as substrates, we could not observe the tellurium/lithium exchange reaction by TLC, evidencing that the presence of these groups, attached to nitrogen, have a negative effect on the present exchange reaction. On the other hand, under several reaction conditions, the β-tellurium amine **1c** showed a similar behaviour to the *N*-Ts β-tellurium amine presented in Scheme 2. After the reaction work up, we could only observe the presence of *p*-toluenesulphonamide and additional by-products. However, when the *N*-Bz β-tellurium amine **1d** was employed as starting material, the tellurium/lithium exchange reaction ocurred in the presence of a mixture of *n*-butyllithium and lithium naphthalenide (LiNp), developed by Yus *et al.*[23] for chloroamide lithiation. The corresponding β-dilithium intermediate was trapped with benzaldehyde, furnishing the corresponding γ-aminoalcohol **2a** in 79% yield (Scheme 4).

After determining the best experimental conditions to generate the corresponding *N*-Bz β-dilithium intermediate, the tellurium/lithium exchange reaction was further expanded to a broader range of electrophilic species, as

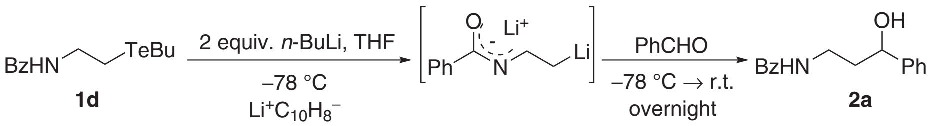


Scheme 2. Tellurium/lithium exchange reaction of β-tellurium amines bearing *t*-butoxycarbonyl and tosyl protecting groups.



(i) $(Boc)_2O$, CH_3CN, r.t., 4 h (ii) CbzCl, $NaHCO_3$, dioxane, r.t., 12 h (iii) MsCl, CH_2Cl_2, r.t., overnight
(iv) TsCl, CH_2Cl_2, r.t., 4 h (v) BzCl, THF/H_2O, Et_3N, r.t., 20 h; (vi) [BuTeLi], THF/EtOH, r.t. 2 h.

Scheme 3. Synthesis of β-tellurium amines **1a-d**.



Scheme 4. Tellurium/lithium exchange reaction of **1d**.

well as to γ- and δ-tellurium amines, in order to evaluate its scope and limitations of such protocol (Table 1).

As can be seen, all the desired products were obtained in good to excellent yields. The tellurium/lithium exchange reaction was evaluated in the presence of a wide range of carbonyl compounds and the respective products were isolated in up to 82% yield (Table 1, entry 3). When *para*, *ortho*, and *meta* tolualdehyde were employed as electrophiles, the aminoalcohols **2b-d** were obtained in a similar yield, showing that steric hindrance does not play an important role in the exchange reaction (Table 1, compare entries 2-4). The same protocol, using 2-furylaldehyde as electrophile, afforded product **2e** in 68% yield. When aromatic aldehydes were replaced by octyl aldehyde, butyraldehyde and isobutyraldehyde the corresponding aminoalcohols **2g-i** were obtained in yields ranging from 75 to 79% (Table 1, entries 7-9). Ketones were also successfully employed in the process. However, the tertiary alcohols **2j-l** were isolated in lower yields (Table 1, entries 10-12) as compared to the more reactive aldehydes. Additionally, trimethylsilylchloride and water were also employed as electrophiles, yielding the corresponding products **2m** and **2n** in 67 and 78% yields, respectively (Table 1, entries 13 and 14). The organolithium species derived from tellurides **1e** (n = 2) and **1f** (n = 3) were also efficiently trapped with benzaldehyde, furnishing the corresponding aminoalcohols **2o** and **2p** in good yields (Table 1, entries 15 and 16).

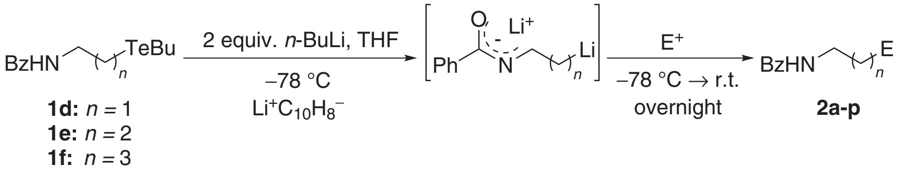
The present tellurium/lithium exchange reaction was also extended to prepare a class of phenethylamines (PEAs),[24] that are interesting substructures for a variety of biologically important compounds, including dopamine, tyrosine, amphetamine, and adrenaline, and are also widely found as components of alkaloid natural products.[25] Moreover, such compounds often serve as key building blocks in the synthesis of numerous nitrogen-containing complex molecules.

The desired products were obtained using the same reaction conditions previously developed for the exchange reaction, but using aryl halides instead of aldehydes or ketones. It should be mentioned that the reaction proceeds with comparable yields when bromine and chlorine are used as leaving groups on the aryl moiety (Table 2, entries 1 and 2). The reaction also works using brominated substrates with different electronic demands at the *ortho*, *meta* and *para* positions, furnishing products **3b-e** in moderate to good yields (Table 2, entries 4-7).

Conclusions

In summary, we have described the synthesis of structurally diverse β-tellurium amines that were transformed into the corresponding nitrogen-containing organolithium compounds *via* Te/Li exchange reaction of *N*-Bz protected derivatives by using a mixture of *n*-butyllithium and lithium naphthalenide (LiNp). The

Table 1. Tellurium/lithium exchange reaction of *N*-Bz β-tellurium amine **1d-f** with different electrophiles



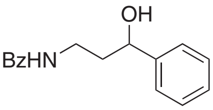
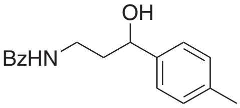
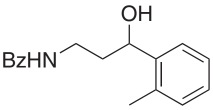
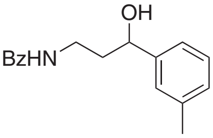
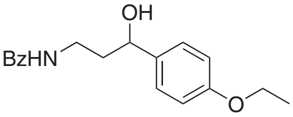
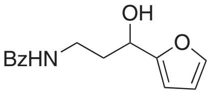
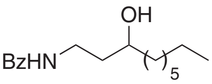
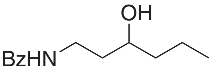
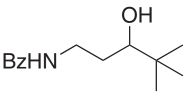
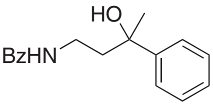
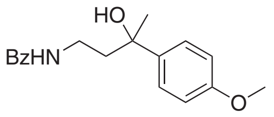
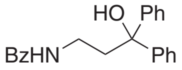
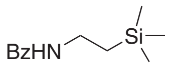
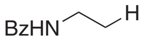
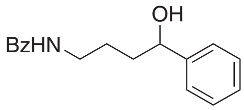
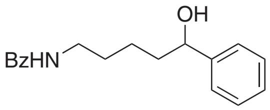
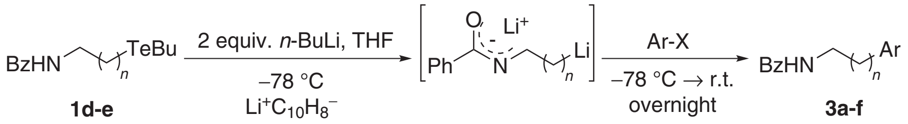
entry	n	Electrophile	Product	Yield (%)[a]
1	1	PhCHO	 **2a**	79
2	1	4-Me-C_6H_4CHO	 **2b**	72
3	1	2-Me-C_6H_4CHO	 **2c**	82
4	1	3-Me-C_6H_4CHO	 **2d**	72
5	1	4-EtO-C_6H_4CHO	 **2e**	70
6	1	2-FurylCHO	 **2f**	68
7	1	$CH_3(CH_2)_6$CHO	 **2g**	79
8	1	$CH_3(CH_2)_2$CHO	 **2h**	75
9	1	$(CH_3)_3$CCHO	 **2i**	76
10	1	PhC(O)Me	 **2j**	69

Table 1. continuation

entry	n	Electrophile	Product	Yield (%)[a]
11	1	4-MeO-$C_6H_4C(O)CH_3$	 **2k**	65
12	1	PhC(O)Ph	 **2l**	61
13	1	TMSCl	 **2m**	67
14	1	H_2O	 **2n**	78
15[b]	2	PhCHO	 **2o**	72
16[b]	3	PhCHO	 **2p**	70

[a]Isolated yield of the corresponding product. [b]The corresponding γ- and δ-tellurium amines **1e** and **1f** were prepared by nucleophilic displacement of $BzHNCH_2CH_2CH_2OMs$ and $BzHNCH_2(CH_2)_2CH_2OMs$ with [BuTeLi] , respectively.

Table 2. Preparation of phenethylamines *via* the tellurium/lithium exchange reaction



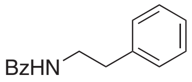
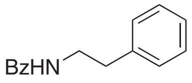
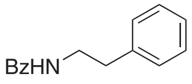
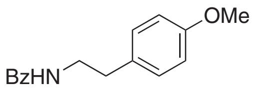
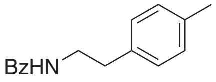
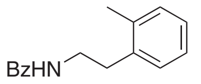
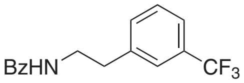
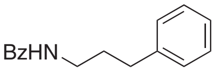
entry	n	Ar-X	Product	Yield (%)[a]
1	1	PhBr	 **3a**	65
2	1	PhI	 **3a**	66
3	1	PhCl	 **3a**	traces
4	1	4-MeO-C_6H_4Br	 **3b**	69
5	1	4-Me-C_6H_4Br	 **3c**	66

Table 2. continuation

entry	n	Ar-X	Product	Yield (%)[a]
6	1	2-Me-C_6H_4Br	 **3d**	42
7	1	3-CF_3-C_6H_4Br	 **3e**	35
8	2	PhBr	 **3f**	57

[a]Isolated yield of the corresponding product.

dilithium intermediate was conveniently trapped with several electrophiles, furnishing the desired products in good to excellent yields. The reaction was also employed in the synthesis of phenethylamines and their derivatives. To the best of our knowledge this is the first time that nitrogen-containing organotellurium compounds have been successfully used as a source of *N*-functionalized organolithium compounds.

Supplementary Information

Experimental details and spectra are available free of charge at http://jbcs.sbq.org.br, as PDF file.

Acknowledgments

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