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Arylbutyltellurides as precursors of dilithium arylthienylcyanocuprates in a straightforward approach to phenethylamine derivatives

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Abstract

The ring opening reaction of *N*-tosyl aziridines with dilithium arylthienylcyanocuprates generated from arylbutyltellurides produced phenethylamine derivatives in good to excellent yields.

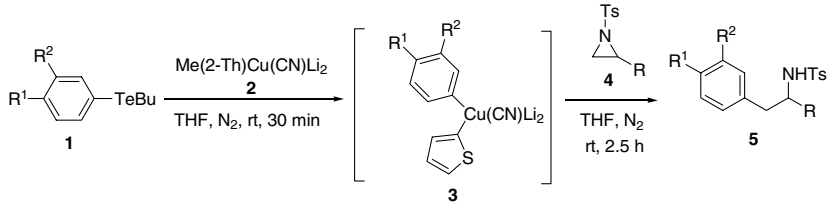
Organotellurium compounds have emerged as important intermediates in organic synthesis because of their potential as electrophiles in cross-coupling reactions[1,2] and extensive use in tellurium–metal exchange reactions.[1,3]

Considering the transformation of organic tellurides into reactive organometallics, we stand out the transmetallation reaction of *Z*-vinylic and arylic tellurides with higher order dilithium cyanocuprates as a versatile method to generate *Z*-vinylic and arylic cyanocuprates,[1,4] which have found application in the construction of unsaturated systems[5] and in the syntheses of natural products.[6]

Having in mind the recent improvement concerning the preparation of activated arylbutyltellurides using a solventless one-pot procedure,[7] and the transmetallation reaction of aromatic tellurides in the presence of copper reagents,[1,4–6] we developed a straightforward route to phenethylamine derivatives (**5**) by treatment of *N*-tosyl aziridines (**4**) with dilithium arylthienylcyanocuprates (**3**), which were generated from arylbutyltellurides (**1**) and dilithium methylthienylcyanocuprate (**2**) (Scheme 1).

Aziridines employed in this communication were prepared from inexpensive aminoalcohols by using a published protocol.[8] In addition, the *N*-tosyl amines produced may be considered important intermediates in the synthesis of biologically active drugs and neurotransmitters.[9]

Employing the conditions depicted in Scheme 1, butylphenyltelluride (**1a**) was added to a solution of dilithium methylthienylcyanocuprate (**2**) in THF at room temperature and the reaction was monitored by TLC. Telluride **1a** was completely consumed after 30 min. Then, a solution



Scheme 1.

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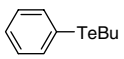
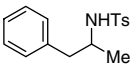
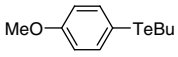
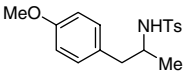
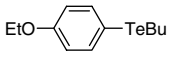
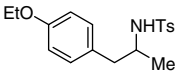
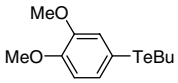
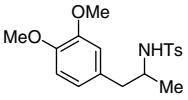
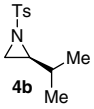
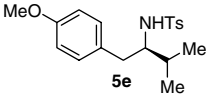
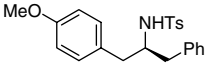
Table 1
Synthesis of phenethylamine derivatives by the ring opening reaction of *N*-tosyl aziridines with dilithium arylthienylcyanocuprates generated from arylbutyltellurides

Entry	Arylbutyltelluride	Aziridine	Product	% Isolated yield
1	 **1a**	 **4a**	 **5a**	73
2	 **1b**	**4a**	 **5b**	88
3	 **1c**	**4a**	 **5c**	71
4	 **1d**	**4a**	 **5d**	65
5	**1b**	 **4b**	 **5e**	70
6	**1b**	 **4c**	 **5f**	70

of aziridine **4a** in THF was added to the reaction mixture and the ring opening reaction took place in 2.5 h according to TLC analysis. We obtained the phenethylamine derivative **5a** in a 73% isolated yield (Table 1, entry 1).[10] Afterwards, treatment of dilithium methylthienylcyanocuprate (**2**) with telluride **1b** for 30 min and subsequent reaction with aziridine **4a** for 2.5 h gave compound **5b** in an excellent 88% yield (entry 2). A 71% isolated yield was obtained for **5c**, when the reaction was carried out using butyl-4-ethoxyphenyltelluride (**1c**) (entry 3). The transmetallation reaction of butyl-3,4-dimethoxyphenyltelluride (**1d**) with cyanocuprate **2** was performed at room temperature in 30 min. *N*-Tosyl aziridine **4a** in THF was added to the mixture and the ring opening reaction led to phenethylamine derivative **5d** in a 65% yield after 2.5 h (entry 4).

To explore the effect of the *N*-tosyl aziridine structure on the sequence of reactions outlined in Scheme 1, we employed the chiral aziridine **4b** bearing an isopropyl group in the synthesis of the asymmetric phenethylamine derivative **5e**, which was obtained in a good yield of 70% (entry 5). The same yield was obtained for **5f**, when the reaction was carried out using the chiral *N*-tosyl aziridine bearing a benzyl group in the 2-position (**4c**) (entry 6). Both reactions (entries 5 and 6) occurred with retention of configuration with respect to the starting (*S*)-aziridines **4b,c**.

The structures of compounds **5a–f** were assigned according to their LRMS, IR, ^{1}H, and ^{13}C NMR spectra. All new compounds (**5c,f**) provided elemental analyses that agree with the proposed structures.

In summary, we developed a straightforward approach to phenethylamine derivatives through a ring opening reaction of *N*-tosyl aziridine with dilithium arylthienylcyanocuprates generated from arylbutyltellurides and dilithium methylthienylcyanocuprate. The synthetic method described in this communication provides an alternative preparation for phenethylamine derivatives and may find use in the construction of molecules with interesting biological properties.

Acknowledgments

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10. *Experimental procedure for the synthesis of phenethylamine derivatives* (**5**): *Metalation of thiophene*: Butyllithium (3.33 mL of a 1.50 mol L^{-1} solution in hexane, 5.0 mmol) was added dropwise to a solution of thiophene (420 mg, 5.0 mmol) in THF (20 mL) under nitrogen atmosphere at −20 °C and the reaction mixture was stirred for 30 min. After this time thienyllithium became ready for use. *Ring opening reaction of N-tosyl aziridines*: The thienyllithium solution previously prepared (5.0 mmol) was added via cannula to a suspension of dry CuCN (445 mg, 5.0 mmol) in THF (25 mL) under nitrogen atmosphere at −70 °C and the mixture was stirred for 15 min. Afterwards, the reaction was warmed to 0 °C and kept under stirring for 15 min. After this time, the mixture was cooled again to −70 °C and methyllithium (4.17 mL of a 1.20 mol L^{-1} solution in hexane, 5.0 mmol) was added dropwise. The resulting solution was stirred at −70 °C for 20 min. Then, the reaction was warmed to room temperature and the appropriate arylbutyltelluride **1** (5.0 mmol) was added. The mixture was stirred for 30 min. After this time, the appropriate *N*-tosyl aziridine **4** (2.5 mmol) in THF (2 mL) was added to the reaction mixture, which was kept under stirring in nitrogen atmosphere at room temperature for 2.5 h. Finally, the reaction was diluted with ethyl acetate (100 mL) and washed with a NH_4OH/NH_4Cl (3:1) solution (3 × 100 mL) and with brine (100 mL). The organic phase was dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using hexane with gradual increase of the polarity of eluent to hexane/ethyl acetate (4:1), affording the desired products **5a**–**f**.

1-(4-Ethoxyphenyl)-N-tosylpropan-2-amine (**5c**): yield 591 mg (71%); white solid; mp 90–91 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.62–7.60 (m, 2H), 7.23–7.21 (m, 2H), 6.91–6.88 (m, 2H), 6.74–6.71 (m, 2H), 4.32 (d, $J = 7.0$ Hz, 1H), 4.00 (q, $J = 7.0$ Hz, 2H), 3.47 (sept, $J = 6.0$ Hz, 1H), 2.61 (dd, $J = 15.5$ Hz, $J = 6.5$ Hz, 1H), 2.58 (dd, $J = 16.0$ Hz, $J = 6.5$ Hz, 1H), 2.41 (s, 3H), 1.41 (t, $J = 7.0$ Hz, 3H), 1.09 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 157.8, 143.0, 137.7, 130.2, 129.5, 128.8, 127.0, 114.5, 63.4, 51.0, 42.5, 21.5, 21.3, 14.9; IR (KBr, cm^{-1}) 3282, 3031, 2978, 2928, 2873, 1512, 1321, 1246, 1160, 1094, 665; LRMS (*m*/*z*, %): 198 (33), 155 (49), 136 (24), 107 (96), 91 (100), 77 (36), 65 (44); Anal. Calcd for $C_{18}H_{23}NO_3S$: C, 64.84; H, 6.95; N, 4.20. Found: C, 64.70; H, 6.68; N,4.36.

(*S*)-*1-(4-Methoxyphenyl)-3-phenyl-N-tosylpropan-2-amine* (**5f**): yield 690 mg (70%); light yellow liquid; $[\alpha]_D^{25}$ +8.8 (*c* 4.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.41–7.38 (m, 2H), 7.22–7.17 (m, 3H), 7.09–7.07 (m, 2H), 7.04–7.02 (m, 2H), 6.93–6.91 (m, 2H), 6.73–6.70 (m, 2H), 4.38 (d, $J = 7.0$ Hz, 1H), 3.78 (s, 3H), 3.55 (sext, $J = 7.0$ Hz, 1H), 2.79 (dd, $J = 14.0$ Hz, $J = 6.5$ Hz, 1H), 2.76 (dd, $J = 13.5$ Hz, $J = 6.5$ Hz, 1H), 2.72 (dd, $J = 13.5$ Hz, $J = 6.5$ Hz, 1H), 2.62 (dd, $J = 14.0$ Hz, $J = 7.0$ Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 158.4, 142.8, 137.2, 137.0, 130.3, 129.4, 129.3, 129.0, 128.5, 126.8, 126.5, 113.9, 56.4, 55.2, 40.9, 39.8, 21.4; IR (film, cm^{-1}) 3289, 3029, 2928, 2837, 1512, 1326, 1247, 1156, 813, 665; LRMS (*m*/*z*, %): 274 (36), 155 (29), 121 (28), 91 (100), 77 (11), 65 (22); Anal. Calcd for $C_{23}H_{25}NO_3S$: C, 69.84; H, 6.37; N, 3.54. Found: C, 69.63; H, 6.34; N, 3.31.