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An unusual solvent effect in the cuprate displacement reaction of indolizidin-5-yl-methyl *p*-toluenesulfonate: stereoselective synthesis of indolizidine alkaloids

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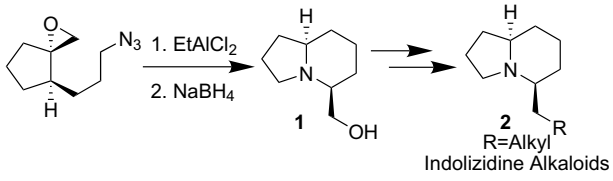
Abstract—An unusual solvent effect in the cuprate displacement reaction of indolizidin-5-yl-methyl *p*-toluenesulfonate with dialkyl cuprates, derived from an alkyllithium and Grignard reagents, during the synthesis of indolizidine alkaloids 167B and 209D is described.

Apart from being the reaction medium, solvents play a vital role in several organic reactions.[1] Especially in organometallic reactions, the solvent is a most critical aspect in terms of the rate of the reaction and stereochemical outcome of the reaction, as it controls the aggregation of the organometallic reagent by chelation.[2] Ethers such as Et_2O, THF, and DME are widely used as solvents in organocuprate reactions.[3] In several instances, unexpected reaction products are obtained by simply changing the reaction medium.[4] Herein, we report an unusual solvent effect in the cuprate displacement reaction of indolizidin-5-yl-methyl *p*-toluenesulfonate with dialkyl cuprates.

Recently, we reported a novel method for the stereoselective construction of an azabicyclic ring skeleton based on the epoxide-initiated cationic cyclization of azides (Scheme 1).[5] The 5-hydroxymethyl indolizidine **1**, readily obtained by our new methodology, was identified as a potential precursor in the synthesis of indolizidine alkaloids 167B and 209D by a cuprate displacement reaction of the corresponding tosylate **3** (Scheme 2). Our initial efforts on cuprate displacement reactions of tosylate **3** with different dialkyl cuprates, derived from alkyllithium or Grignard reagents, in THF were unsuccessful and resulted in the isolation of unexpected products.



Scheme 1. Epoxide-initiated cationic cyclization of azides.

Treatment of tosylate **3** with ethylmagnesium bromide in the presence of CuCN in THF furnished the corresponding bromo derivative **4**[6] in 69% yield (Scheme 2), as the only isolable product, presumably via nucleophilic displacement of the tosylate by a bromide ion present in the medium.

Hence, it was envisaged that a halide-free dialkyl cuprate reagent would be an ideal choice to overcome this problem. Thus, the tosylate displacement reaction was carried out with $Bu_2Cu(CN)Li_2$, generated in situ from the readily available *n*-BuLi and CuCN. To our surprise, this reaction also resulted in the exclusive isolation of an unexpected product **5**, in which the nucleophilic substitution had taken place on the aromatic ring (Scheme 2). The formation of compound **5** was confirmed by ^1H, ^{13}C NMR, and mass spectral data.[7] The ^1H NMR spectrum of compound **5** showed three different sets of protons, two doublets at δ 7.84 and 7.11 and one singlet

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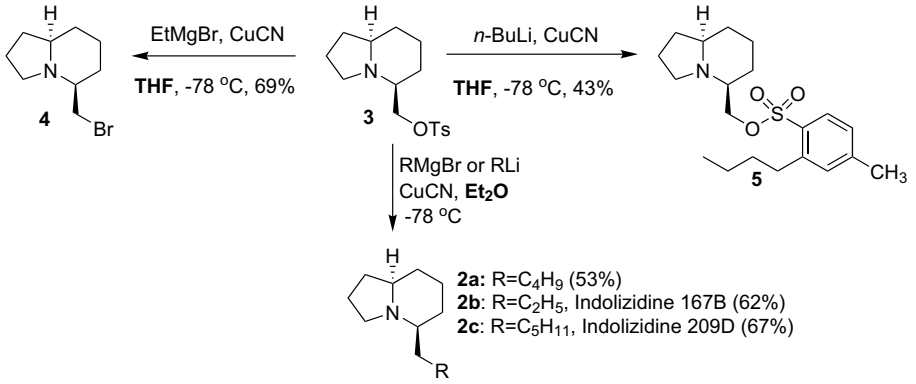


Scheme 2. An unusual solvent effect in the cuprate displacement reaction of indolizidin-5-yl-methyl *p*-toluenesulfonate with cuprates.

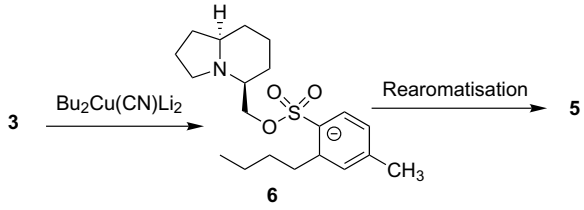
at δ 7.19 corresponding to one proton each, in the aromatic region. In the ^{13}C NMR spectrum, there were six different aromatic carbons of which three were quaternary carbons. The above data clearly indicate that nucleophilic substitution had taken place on the aromatic ring. The remaining signals corresponding to the azabicyclic ring skeleton were found to be unchanged. A mass spectrum of compound **5** showed a molecular ion peak at *m*/*z* 365 corresponding to the molecular weight of the proposed structure.

Product **5** is formed presumably as a result of nucleophilic addition of the cuprate on the aromatic ring of tosylate **3**, leading to intermediate **6**, followed by rearomatization (Scheme 3).

Although intramolecular aromatic nucleophilic substitution of aryl sulfones/aryl sulfonamides with alkyllithiums is well documented in the literature,[8] the corresponding intermolecular aromatic nucleophilic displacement with dialkyllithium cuprate is reported for the first time.

After surveying several solvents and additives, a smooth cuprate displacement of the tosylate was realized with $Bu_2Cu(CN)Li_2$ when the reaction was carried out in Et_2O. Thus, treatment of tosylate **3** with $Bu_2Cu(CN)Li_2$ in Et_2O at -78 °C afforded 5-pentyl indolizidine **2a** in 53% yield, which is an analogue of the natural indolizidine alkaloids 167B and 209D (Scheme 2).

Intriguingly, the reaction of tosylate **3** with $Et_2Cu(CN)$-MgBr, in Et_2O at -78 °C, afforded indolizidine 167B **2b** in 62% yield. Under similar reaction conditions, indolizidine 209D **2c** was prepared in 67% yield upon treatment of **3** with $(C_5H_{11})_2Cu(CN)MgBr$ (Scheme 2). The spectroscopic data of these two synthetic products were in complete agreement with the reported data.[5,9]



Scheme 3. Aromatic nucleophilic substitution of tosylate **3** with cuprate.

In conclusion, the present study has illustrated that the reaction medium is critical in organocuprate reactions. An unusual solvent effect in the cuprate displacement reaction of indolizidin-5-yl-methyl *p*-toluenesulfonate with dialkyl cuprates was observed. The total syntheses of the indolizidine alkaloids 167B and 209D was achieved readily by the corresponding cuprate displacement reaction in Et_2O.

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Supplementary data

Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2005.05.008.

References and notes

1. (a) Hallnemo, G.; Ullenius, C. *Tetrahedron* **1983**, *39*, 1621–1625; (b) Mori, S.; Nakamura, E.; Morokuma, K. *J. Am. Chem. Soc.* **2000**, *122*, 7294–7307.
2. (a) Lipshutz, B. H.; Kozlowski, J. A.; Breneman, C. M. *J. Am. Chem. Soc.* **1985**, *107*, 3197–3204; (b) Bertz, S. H.; Chopra, A.; Eriksson, M.; Ogle, C. A.; Seagle, P. *Chem. Eur. J.* **1999**, *5*, 2680–2691; (c) Zhao, S.-K.; Helquist, P. *Tetrahedron Lett.* **1991**, *32*, 447–448; (d) Berlan, J.; Besace, Y.; Pourcelot, G.; Cresson, P. *Tetrahedron* **1986**, *42*, 4757–4765.
3. (a) Lipshutz, B. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 1, pp 107–138; (b) Lipshutz, B. H. *Synthesis* **1987**, 325–341; (c) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron* **1984**, *40*, 5005–5038; (d) Posner, G. H. *An Introduction to Synthesis using Organocopper Reagents*; Wiley: New York, 1980.

4. (a) Sato, F.; Kobayshi, Y.; Takahashi, O.; Chiba, T.; Takeda, Y.; Kusakabe, M. *J. Chem. Soc., Chem. Commun.* **1985**, 1636–1641; (b) Mead, K.; MacDonald, T. L. *J. Org. Chem.* **1985**, *50*, 422–424; (c) Mead, K. *Tetrahedron Lett.* **1987**, *28*, 869–872; (d) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowshki, J. A.; Parker, D. *J. Org. Chem.* **1984**, *49*, 3928–3937.
5. (a) Reddy, P. G.; Baskaran, S. *J. Org. Chem.* **2004**, *69*, 3093–3101; (b) Reddy, P. G.; Varghese, B.; Baskaran, S. *Org. Lett.* **2003**, *5*, 583–585.
6. Cuprate displacement reaction of tosylate **3** with $Et_2Cu(CN)MgBr$ in THF: CuCN (15 mg, 0.162 mmol) was placed in a dry round-bottomed flask and azeotropically dried with toluene (2×2 mL) at room temperature under high vacuum. The flask was flushed with argon gas and THF (5 mL) was introduced. The slurry was cooled to −78 °C and a solution of ethyl magnesium bromide (0.45 mmol, prepared from 44 mg of ethyl bromide and 10 mg of Mg turnings) in dry THF was added. The resultant mixture was warmed to 0 °C, to give a homogeneous solution, stirred for an additional 2 min and re-cooled to −78 °C. A solution of tosylate **3** (50 mg, 0.162 mmol) in dry THF (1 mL) was added to the reaction mixture and the resultant mixture was stirred for 30 min, warmed to 0 °C and allowed to stir for another 2 h. The reaction mixture was allowed to stir at room temperature until the reaction went to completion (6 h) to give a product less polar than the starting material (TLC). Column chromatography of the crude compound (gradient elution with 0–30% EtOAc in hexane) afforded a pure compound as a colorless liquid, which was found to be 5-bromomethyl indolizidine **4** (24 mg, 69% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.56 (dd, J = 2.9, 10.3 Hz, 1H), 3.36 (dd, J = 6.8, 10.3 Hz, 1H), 3.25 (dt, J = 2.4, 8.8 Hz, 1H), 2.18–2.23 (m, 1H), 2.05 (app. q, J = 8.8, 9.3 Hz, 1H), 1.62–1.98 (m, 7H), 1.16–1.49 (m, 4H). Anal. Calcd for $C_9H_{16}BrN$: C, 49.55; H, 7.39; N, 6.42. Found: C, 49.76; H, 7.44; N, 6.61.
7. Cuprate displacement reaction of tosylate **3** with $Bu_2Cu(CN)Li_2$ in THF: CuCN (152 mg, 1.7 mmol) was placed in a dry round-bottomed flask and azeotropically dried with toluene (2×2 mL) at room temperature under high vacuum. The flask was flushed with argon gas and 2 mL of dry THF was introduced. The slurry was cooled to −78 °C and *n*-BuLi (2.8 mL of a 1.2 M solution in hexane, 3.4 mmol) was added dropwise. The heterogeneous mixture was allowed to warm to 0 °C, to give a homogeneous solution, and re-cooled to −78 °C. A solution of tosylate **3** (105 mg, 0.34 mmol) in dry THF (1 mL) was added dropwise and the resultant mixture was stirred at −78 °C for an additional 4 h. No reaction was observed by TLC. Hence, the reaction mixture was allowed to warm to −10 °C and stirred for an additional 4 h. The reaction mixture was quenched with 25% aqueous ammonia solution (10 mL) at −10 °C and stirred for another 10 min. The reaction mixture was extracted with ethyl acetate (2×15 mL), the combined organic extracts were washed with water (2×15 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a crude compound, which was purified by column chromatography (gradient elution with 0–5% EtOAc in hexane) over deactivated silica gel (Et_3N), to afford pure compound **5** (53 mg, 43% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.3 Hz, 1H), 7.19 (s, 1H), 7.11 (d, J = 7.8 Hz, 1H), 4.08 (dd, J = 5.1, 10.0 Hz, 1H), 3.84 (dd, J = 5.6, 10.0 Hz, 1H), 3.07 (dt, J = 1.96, 8.3 Hz, 1H), 2.93–2.97 (m, 2H), 2.39 (s, 3H), 2.25–2.35 (m, 1H), 2.04 (app. q, J = 8.8, 9.3 Hz, 1H), 1.60–1.88 (m, 9H), 1.11–1.49 (m, 6H), 0.95 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 143.2, 132.1, 130.8, 130.3, 126.6, 72.6, 64.8, 61.8, 51.7, 33.3, 32.6, 30.4, 29.9, 28.6, 23.9, 22.9, 21.4, 20.6, 13.9; MS (EI) *m/z* (relative intensity, %) 365 (M^+, 0.5), 209 (3), 138 (4), 124 (100), 96 (16), 84 (84), 70 (5), 55 (8); HRMS (ESI) calcd for $C_{20}H_{32}NO_3S$ $(M+1)^+$: 366.2025. Found: 366.2056.

8. (a) Clayden, J.; Kenworthy, M. N. *Synthesis* **2004**, 1721–1736; (b) Krief, A.; Kenda, B.; Barbeaux, P.; Guittet, E. *Tetrahedron* **1994**, *50*, 7177–7192; (c) Breternitz, H.-J.; Schaumann, E.; Adiwidjaja, G. *Tetrahedron Lett.* **1991**, *32*, 1299–1302; (d) Aggarwal, V. K.; Ferrara, M. *Org. Lett.* **2000**, *2*, 4107–4110; (e) Aggarwal, V. K.; Alonso, E.; Ferrara, M.; Spey, S. E. *J. Org. Chem.* **2002**, *67*, 2335–2344.
9. (a) Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1990**, *55*, 4688–4693; (b) Chenevert, R.; Ziarani, G. M.; Dasser, M. *Heterocycles* **1999**, *51*, 593–598; (c) Chalard, P.; Remuson, R.; Gelas-Mialhe, Y.; Gramain, J.-C.; Canet, I. *Tetrahedron Lett.* **1999**, *40*, 1661–1664; (d) Angel, S. R.; Henry, R. M. *J. Org. Chem.* **1997**, *62*, 8549–8552; (e) Kim, G.; Jung, S.-D.; Kim, W.-J. *Org. Lett.* **2001**, *3*, 2985–2987; (f) Back, T. G.; Nakajima, K. *J. Org. Chem.* **2000**, *65*, 4543–4552; (g) Chenevert, R.; Ziarani, G. M.; Morin, M. P.; Dasser, M. *Tetrahedron: Asymmetry* **1999**, *10*, 3117–3122; (h) Nukui, S.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 398–404; (i) Ahman, J.; Somfai, P. *Tetrahedron* **1995**, *51*, 9747–9756.