Coupling of 1-Alkyl-2-(bromomethyl)aziridines with Lithium Dialkylcuprates towards 1,2-Dialkylaziridines

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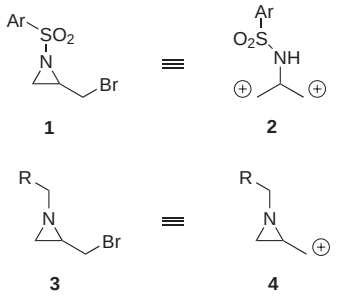
Abstract: The reactivity of 1-alkyl-2-(bromomethyl)aziridines with respect to lithium dialkylcuprates (Gilman reagents) has been evaluated for the first time, pointing to the conclusion that these substrates can be applied successfully as synthetic equivalents for the aziridinylmethyl cation synthon towards, e.g. 2-ethyl-, 2-pentyl- and 2-(phenylmethyl)aziridines in good yields.

Key words: 2-(bromomethyl)aziridines, organometallics, nucleophilic substitution, 1,2-dialkylaziridines

In the past decade, aziridines acquired a prominent place in organic chemistry due to their broad synthetic utility.[1] In analogy with epoxides, N-activated aziridines are prone to ring-opening, which allows the synthesis of a large variety of functionalized amines upon reaction with nucleophiles. In a former communication, it has been demonstrated that 1-arenesulfonyl-2-(bromomethyl)aziridines **1** can be applied successfully as synthetic equivalents for the 2-aminopropane dication synthon **2** towards 1-tosyl-2-alkylaziridines on the one hand and α-branched symmetrical and unsymmetrical *N*-tosylamides on the other hand, depending on the amount of reagent used.[2] A similar ring-opening was observed for the closely related *N*,*O*-bis(diphenylphosphinyl)hydroxymethylaziridine in ring-opening reactions with copper(I)-modified Grignard reagents.[3] In this report, the chemistry of 1-alkyl-2-(bromomethyl)aziridines **3**, a hitherto scarcely investigated class of β-halo amines, is evaluated in terms of their reactivity with regard to carbon-centered nucleophiles. Contrary to the above-mentioned N-activated aziridines, the focus here will be on the absence of ring-opening in order to develop a method for aziridine synthesis. Up to now, no information is available in the literature concerning the behavior of 1-alkyl-2-(bromomethyl)aziridines upon reaction with organocuprate reagents such as lithium dialkylcuprates. Although closely related to *N*-(arenesulfonyl)aziridines, *N*-alkylaziridines **3** appeared to be suitable equivalents for the aziridinylmethyl cation **4**, allowing the selective synthesis of different 1,2-dialkylaziridines in good yields (Figure 1).



1 **2** **3** **4**

Figure 1

1,2-Dialkylaziridines are versatile substrates in organic synthesis, hence the interest in a straightforward strategy for their preparation. Generally, 1,2-dialkylaziridines can be synthesized from the corresponding amino alcohol,[4] by reaction of organoboranes with organic azides,[5] by aminopalladation of alkenes followed by oxidation by bromine[6] and by reduction of α-halogenated imines or α,α-dihalogenated imines.[7] 1,2-Dialkylaziridines have been used as substrates for the synthesis of a whole range of cyclic and acyclic compounds with various applications. An interesting conversion of 1,2-dialkylaziridines comprises the synthesis of biologically and medically important 1,2-diamines.[8] Also a variety of ring expansions towards β-lactams[9] and five-membered heterocycles have been established, furnishing different synthetically and biologically relevant compounds.[10] Therefore, a new and synthetically useful approach towards 1,2-dialkylaziridines is reported here.

1-Alkyl-2-(bromomethyl)aziridines **3** are very easily accessible substrates for further syntheses, prepared in a three-step procedure starting from the appropriate aldehydes.[11] Condensation of benzaldehydes **5a**,**b** with 1 equivalent of allylamine in dichloromethane in the presence of magnesium sulfate afforded the corresponding *N*-allylimines, which were subsequently brominated by bromine in dichloromethane to give *N*-(arylidene)-2,3-dibromopropylamines in a quantitative yield. The latter dibromoimines were used as such because of their instability and hence treated with sodium borohydride in methanol under reflux, furnishing 1-arylmethyl-2-(bromomethyl)aziridines **3a**,**b** in high yields (Scheme 1).[11] Other approaches towards 1-benzylaziridines have been described in the literature.[12]

In the case of the synthesis of aziridine **3c**, isobutanal **5c** was condensed with 1 equivalent of 2,3-dibromo-1-propylammonium bromide in dichloromethane in the presence of 1 equivalent of triethylamine and magnesium

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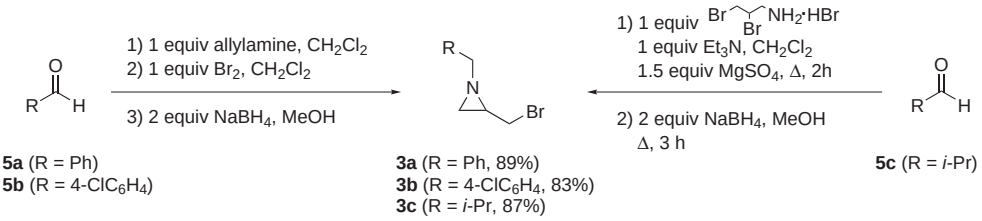
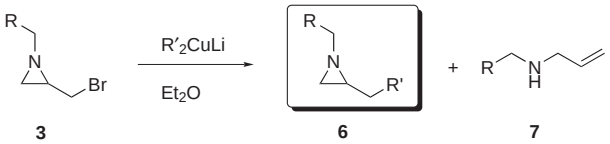


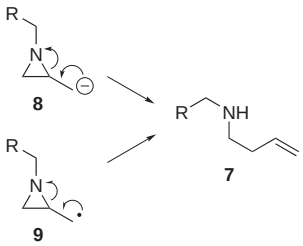
Scheme 1

sulfate as drying agent. Reduction of the dibromoimine, thus obtained, with sodium borohydride in methanol afforded aziridine **3c** in 87% yield after reflux for 3 hours.[13]

Treatment of aziridines **3** with 1.5–5 equivalents of lithium dimethylcuprate, lithium dibutylcuprate and lithium diphenylcuprate in diethyl ether for 3–20 hours afforded the corresponding 2-alkylaziridines **6** in high yields of the crude product (85–95%), which were subsequently purified by means of column chromatography to obtain analytically pure samples (Table 1).[14] When lithium dimethylcyanocuprate (1.05 equiv) was used in diethyl ether at –78 °C instead of lithium dimethylcuprate, a similar result was obtained after 15 hours at room temperature, affording 2-ethyl-1-[4-(chlorophenyl)methyl]aziridine **6c** in 77% yield. In the reaction mixtures, obtained after treatment of aziridines **3** with lithium dibutylcuprate or lithium diphenylcuprate, the formation of the corresponding allylamine **7** was observed as a by-product in small quantities (5–10%, Table 1), except for entry 8 (25%, Table 1), possibly due to the presence of some remaining phenyllithium, used for the in situ preparation of lithium diphenylcuprate. Allylamines **7** (Scheme 2) are probably formed due to the lower nucleophilicity of these Gilman reagents as compared to lithium dimethylcuprate. Apparently, a small amount of the organocuprate reagent provokes metal–halogen exchange or induces electron-transfer, and the resulting aziridinylmethyl carbanion **8** or radical intermediate **9** suffers ring-opening to form the allylamines **7** (Scheme 3).



Scheme 2



Scheme 3

The synthesis of 1,2-di(phenylmethyl)aziridine **6e** required a higher amount of lithium diphenylcuprate, since only with 3 equivalents of Ph_2CuLi the reaction could be driven to completion, whereas the addition of 2 equivalents of Ph_2CuLi resulted in the recovery of most of the starting material (Table 1, entries 6 and 7).

Attempts to functionalize aziridines **3** with lithium bis(isopropenyl)cuprate and lithium bis(allyl)cuprate in diethyl ether were unsuccessful, and only the corresponding allylamines were isolated (Table 1, entries 9–11). Complete conversion of aziridine **3** into allylamine **7** was observed after 6 hours at room temperature upon treatment with bis(isopropenyl)cuprate in diethyl ether at –78 °C, whereas after reaction with bis(allyl)cuprate in diethyl ether also some starting material (ca. 50%) was present in the reaction mixture, even upon a prolonged reaction time of 17 hours (Table 1, entry 10). Furthermore, also lithium bis(phenylethynyl)cuprate was used as a possible carbon-centered nucleophile. However, no reaction was observed after 20 hours at room temperature upon treatment of aziridine **3b** with 1.5 equivalents of this organocuprate in diethyl ether at –78 °C, and the starting material was entirely recovered (Table 1, entry 12). The use of lithium phenylacetylide appeared to be no suitable alternative for lithium bis(phenylethynyl)cuprate, and again the starting aziridine **3b** was recovered after reaction with 1.1 or 1.2 equivalents of lithium phenylacetylide in THF after 1 or 3 hours at room temperature, even when HMPA was added as a co-solvent (THF–HMPA, 4:1).

In conclusion, 1-alkyl-2-(bromomethyl)aziridines are suitable synthetic equivalents for the aziridinylmethyl cation, providing an easy access to 1,2-dialkylaziridines as substrates for further elaboration. In this way, 2-ethyl-, 2-pentyl- and 2-(phenylmethyl)aziridines have been prepared in a preparative way via a new route starting from 1-alkyl-2-(bromomethyl)aziridines upon treatment with the appropriate lithium dialkylcuprate reagent. Furthermore, it was demonstrated that 1-alkyl-2-(bromomethyl)aziridines are considerably less reactive than the structurally related 1-arenesulfonyl-2-(bromomethyl)aziridines, which creates the possibility to develop new synthetic strategies with different applications. In contrast with 2-alkyl-1-(arenesulfonyl)aziridines, the aziridine ring of 1,2-dialkylaziridines is not susceptible to ring-opening upon treatment with an excess of lithium cuprate reagent.

Table 1 Reactions of 2-(Bromomethyl)aziridines **3** with Lithium Dialkylcuprates

Entry	R	R′	Conditions[a]	Yield of **6** (%)[b]	Yield of **7** (%)[c]
1	Ph	Me	1.5 equiv R'_2CuLi, 0 °C to r.t., 3.5 h	**6a** (76)	**7a** (–)
2	Ph	Me	3 equiv R'_2CuLi, –78 °C to r.t., 16 h	**6a** (65)	**7a** (–)
3	Ph	Bu	3 equiv R'_2CuLi, –78 °C to r.t., 19 h	**6b** (54)	**7b** (10)
4	4-ClC_6H_4	Me	3 equiv R'_2CuLi, –78 °C to r.t., 6 h	**6c** (67)	**7c** (–)
5	4-ClC_6H_4	Bu	3 equiv R'_2CuLi, –78 °C to r.t., 20 h	**6d** (47)	**7d** (<5)
6	Ph	Ph	2 equiv R'_2CuLi, –78 °C to r.t., 5 h	**6e** (<5)[c]	**7e** (–)
7	Ph	Ph	3 equiv R'_2CuLi, –78 °C to r.t., 19 h	**6e** (76)	**7e** (<5)
8	4-ClC_6H_4	Ph	5 equiv R'_2CuLi, –78 °C to r.t., 20 h	**6f** (45)	**7f** (25)
9	Ph	Allyl	1.5 equiv R'_2CuLi, –78 °C to r.t., 6 h	**6g** (–)	**7g** (40)
10	Ph	Allyl	1.5 equiv R'_2CuLi, –78 °C to r.t., 17 h	**6g** (–)	**7g** (40)
11	4-ClC_6H_4	CH_2=C(Me)	1.5 equiv R'_2CuLi, –78 °C to r.t., 6 h	**6h** (–)	**7h** (78)
12	4-ClC_6H_4	PhC≡C	1.5 equiv R'_2CuLi, –78 °C to r.t., 20 h	**6i** (–)	**7i** (–)
13	*i*-Pr	Me	1.5 equiv R'_2CuLi, 0 °C to r.t., 3 h	**6j** (83)	**7j** (–)
14	*i*-Pr	Bu	1.5 equiv R'_2CuLi, 0 °C to r.t., 4 h	**6k** (63)	**7k** (–)
15	*i*-Pr	Ph	1.5 equiv R'_2CuLi, 0 °C to r.t., 4 h	**6l** (–)	**7l** (–)

[a] All reactions were performed in dry Et_2O.
[b] Yield after column chromatography.
[c] Derived from ^1H NMR and/or GC.

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References

(1) (a) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701. (b) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247. (c) Zwanenburg, B.; ten Holte, P. *Top. Curr. Chem.* **2001**, *216*, 93. (d) McCoull, W.; Davis, F. A. *Synthesis* **2000**, 1347. (e) Lindström, U. M.; Somfai, P. *Synthesis* **1998**, 109. (f) Somfai, P.; Ahman, J. *Targets in Heterocyclic Systems*, Vol. 3; Italian Chemical Society: Rome, Italy, **1999**, 341.
(2) D'hooghe, M.; Kerkaert, I.; Rottiers, M.; De Kimpe, N. *Tetrahedron* **2004**, *60*, 3637.
(3) Sweeney, J. B.; Cantrill, A. A. *Tetrahedron* **2003**, *59*, 3677.
(4) (a) Sekar, G.; Vinod, K. S. *J. Org. Chem.* **1999**, *64*, 2537. (b) Kelly, J. W.; Anderson, N. L.; Evans, S. A. Jr. *J. Org. Chem.* **1986**, *51*, 95.
(5) Brown, H. C.; Midland, M. M.; Levy, A. B.; Suzuki, A.; Sono, S.; Itoh, M. *Tetrahedron* **1987**, *43*, 4079.
(6) (a) Bäckvall, J.-E. *J. Chem. Soc., Chem. Commun.* **1977**, *12*, 413. (b) Barelle, M.; Apparu, M. *Tetrahedron* **1977**, *33*, 1309.
(7) (a) De Kimpe, N.; Verhé, R.; De Buyck, L.; Schamp, N. *Synth. Commun.* **1975**, *5*, 269. (b) Duhamel, L.; Valnot, J. Y. *Tetrahedron Lett.* **1974**, *36*, 3167. (c) De Kimpe, N.; Moens, L. *Tetrahedron* **1990**, *46*, 2965. (d) De Kimpe, N.; Schamp, N.; Verhé, R. *Synth. Commun.* **1975**, *5*, 403. (e) De Kimpe, N.; Verhé, R.; De Buyck, L.; Dejonghe, W.; Schamp, N. *Bull. Soc. Chim. Belg.* **1976**, *85*, 763.
(8) (a) Hancock, M. T.; Pinhas, A. R. *Tetrahedron Lett.* **2003**, *44*, 7125. (b) Hancock, M. T.; Pinhas, A. R. *Organometallics* **2002**, *21*, 5155. (c) Chandrasekhar, M.; Sekar, G.; Singh, V. K. *Tetrahedron Lett.* **2000**, *41*, 10079.
(9) Chamchaang, W.; Pinhas, A. R. *J. Org. Chem.* **1990**, *55*, 2943.
(10) (a) Hancock, M. T.; Pinhas, A. R. *Tetrahedron Lett.* **2003**, *44*, 5457. (b) Nomura, R.; Nakano, T.; Nishio, Y.; Ogawa, S.; Ninagawa, A.; Matsuda, H. *Chem. Ber.* **1989**, *122*, 2407.
(11) (a) De Kimpe, N.; Jolie, R.; De Smaele, D. *J. Chem. Soc., Chem. Commun.* **1994**, 1221. (b) Abbaspour Tehrani, K.; Van Nguyen, T.; Karikomi, M.; Rottiers, M.; De Kimpe, N. *Tetrahedron* **2002**, *58*, 7145. (c) De Kimpe, N.; De Smaele, D.; Szakonyi, Z. *J. Org. Chem.* **1997**, *62*, 2448.
(12) (a) Davoli, P.; Caselli, E.; Bucciarelli, M.; Forni, A.; Torre, G.; Prati, F. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1948. (b) Jahnisch, K. *Liebigs Ann. Recl.* **1997**, 757. (c) Lohray, B. B.; Gao, Y.; Sharpless, K. B. *Tetrahedron Lett.* **1989**, *30*, 2623.
(13) **Synthesis of 2-(Bromomethyl)-1-isobutylaziridine (3c).** To a solution of isobutanal (**5c**, 0.14 g, 2 mmol) in CH_2Cl_2 (10 mL) was added 2,3-dibromo-1-propylammonium bromide (0.60 g, 2 mmol, 1 equiv), $MgSO_4$ (0.5 g) and Et_3N (0.20 g, 2 mmol, 1 equiv) at 0 °C, and the mixture was heated

under reflux for 2 h. After evaporation of the solvent, dry Et_2O (20 mL) was added, the resulting precipitate was filtered and the solvent evaporated, affording the corresponding dibromoimine in 94% yield. This imine was used as such in the next step due to its lability. To a solution of *N*-(isobutylidene)-2,3-dibromopropylamine (0.54 g, 2 mmol) in MeOH (2 mL) was added $NaBH_4$ (0.15 g, 4 mmol, 2 equiv) in small portions at 0 °C, and the mixture was heated under reflux for 3 h. Extraction with CH_2Cl_2 (2 × 10 mL), drying ($MgSO_4$) and filtration afforded 2-(bromomethyl)-1-isobutylaziridine (**3c**, 0.33 g, 87%), which was purified by distillation (65–69 °C/11–12 mmHg); colorless liquid, bp 65–69 °C/11–12 mmHg. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 and 1.01 [6 H, 2 d, *J* = 6.6 Hz, $(CH_3)_2$], 1.47 [1 H, d, *J* = 6.1 Hz, (H_{cis}CH)N], 1.68–1.76 (1 H, m, C*H*Me_2), 1.75 [1 H, d, *J* = 3.0 Hz, (HCH_{trans})N], 1.80–1.93 (1 H, m, CHN), 2.05 and 2.17 [2 H, 2 dd, *J* = 5.8, 8.1, 11.6 Hz, N(*HCH*)CHMe_2], 3.27 and 3.36 [2 H, 2 dd, *J* = 5.4, 7.3, 10.3 Hz, (HCH)Br]. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.80 and 20.92 [$(CH_3)_2$], 28.99 (*C*HMe_2), 35.77 and 36.00 (N*C*H_2CH and CH_2Br), 40.03 (NCH_2*C*H), 69.18 (N*C*H_2*i*-Pr). IR (NaCl): ν = 3040, 1469, 1383, 1364, 1238, 1220 cm^{-1}. MS (70 eV): *m/z* (%) = 191/193 (1) [M$^+$], 148/150 (20), 119/121 (18), 112 (100), 70 (7), 68 (5), 57 (41), 56 (77), 42 (73), 41 (45). Anal. Calcd for $C_7H_{14}BrN$ (%): C, 43.77; H, 7.35; N, 7.29. Found: C, 43.94; H, 7.55; N, 7.17.

(14) As a representative example, the synthesis of 2-ethyl-1-(phenylmethyl)aziridine (**6a**) is described. To a suspension of CuI (1.52 g, 8 mmol, 2 equiv) in dry Et_2O (40 mL) was added slowly MeLi (10 mL, 4 equiv, 1.6 M in Et_2O) via a syringe at –78 °C under nitrogen atmosphere. After stirring for 30 min at –78 °C, a solution of 1-benzyl-2-(bromomethyl)aziridine (**3a**, 0.90g, 4 mmol) in Et_2O (10 mL) was added at –78 °C, and the resulting suspension was further stirred for 6 h at r.t. The reaction mixture was quenched with a sat. solution of NH_4Cl (20 mL), filtered over Celite® and washed with Et_2O (2 × 20 mL). The filtrate was poured into H_2O (100 mL), extracted with Et_2O (2 × 75 mL), and the combined organic extracts were washed with sat. NH_4Cl (50 mL) and brine (50 mL). Drying ($MgSO_4$), filtration and evaporation of the solvent afforded 2-ethyl-1-(phenylmethyl)aziridine (**6a**), which was purified by means of column chromatography on silica gel (EtOAc–hexane, 1:4). Spectroscopic data of, e.g. 1-(phenylmethyl)-2-pentylaziridine (**6b**): yield 54%, colorless liquid. Flash chromatography on silica gel: EtOAc–hexane, 1:4, R_f = 0.32. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.84 (3 H, t, *J* = 6.2 Hz, CH_3), 1.22–1.47 [10 H, m, (H_{cis}CH)N, CHN and $(CH_2)_4CH_3$], 1.60 [1 H, d, *J* = 2.9 Hz, (HCH_{trans})N], 3.30 and 3.49 [2 H, 2 d, *J* = 13.2 Hz, (*HCH*)C_6H_4], 7.22–7.35 (5 H, m, C_6H_5). ^{13}C NMR (68 MHz, $CDCl_3$): δ = 14.00 (CH_3), 22.62, 27.12, 31.57 and 32.96 [$(CH_2)_4CH_3$], 34.07 (N*C*H_2CH), 39.82 (NCH_2*C*H), 65.00 ($CH_2C_6H_4$), 126.95 (HC_{para}), 128.17 and 128.26 (2 HC_{ortho} and 2 HC_{meta}), 139.40 ($C_{arom,quat}$). IR (NaCl): ν = 1607, 1496, 1454 cm^{-1}. MS (70 eV): *m/z* (%) = 203 (6) [M$^+$], 202 (9), 174 (11), 173 (20), 161 (26), 160 (51), 147 (19), 146 (39), 121 (23), 112 (22), 92 (56), 91 (100), 65 (13). Anal. Calcd for $C_{14}H_{21}N$ (%): C, 82.70; H, 10.41; N, 6.89. Found: C, 82.84; H, 10.55; N, 6.74.
Spectroscopic data of aziridines **6a**,**c**–**f**,**j**,**k** are available upon request.