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Reaction of aziridinium ions with organometallic reagents: optimization of the key step of ecopipam synthesis

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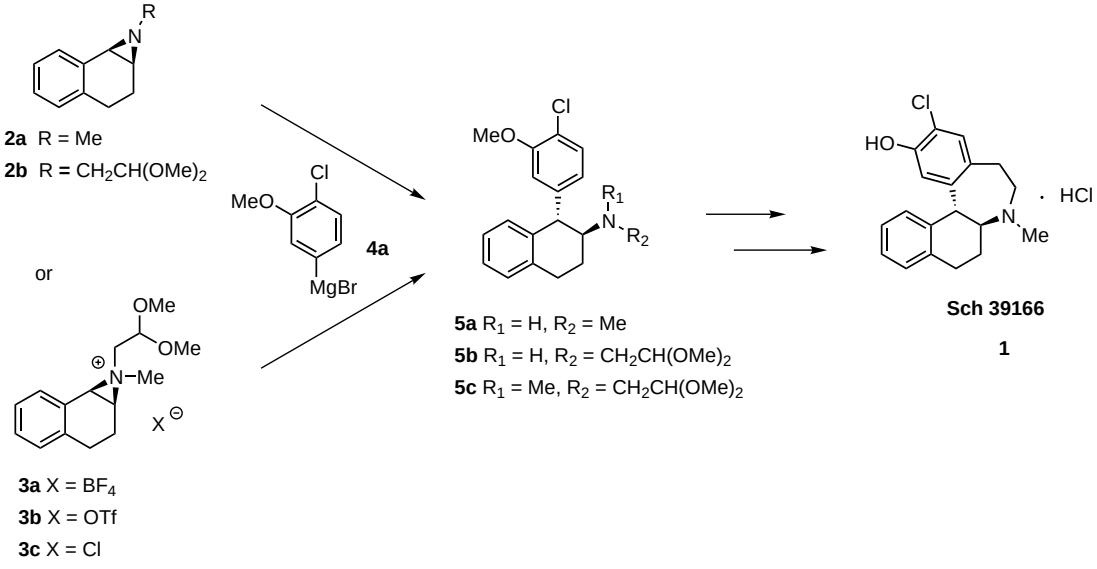
Abstract—Formation, stability and reactivity of aziridinium ions **3** towards organometallic reagents was explored and optimized for the efficient preparation of key drug intermediate **5c**.

Aziridinium ions are versatile synthetic intermediates with a rapidly expanding scope of applications. Efficient methods for their in situ generation and capture by a variety of heteroatomic nucleophiles such as amines, alcohols, halides, thiols and phosphines have recently been reported.[1] In contrast, the synthetically useful reaction of aziridinium ions with carbon nucleophiles such as organometallic reagents remains largely unexplored.[2] While the direct addition of organometallics to *N*-alkyl aziridines is difficult,[1a,b] more reactive *N*,*N*-dialkylated aziridinium ions could offer an attractive alternative as versatile precursors to the various functionalized amine derivatives.

As a part of our ongoing program on the synthesis of novel dopamine D_1 antagonists, we required the preparation of large quantities of drug candidate ecopipam **1** (Scheme 1). A number of different synthetic approaches to prepare **1** were proposed and evaluated in our laboratories. In the most direct and efficient route, the



Scheme 1.

Keywords: aziridinium ions; aziridines; Grignard reagents; electron affinity; SET mechanism.

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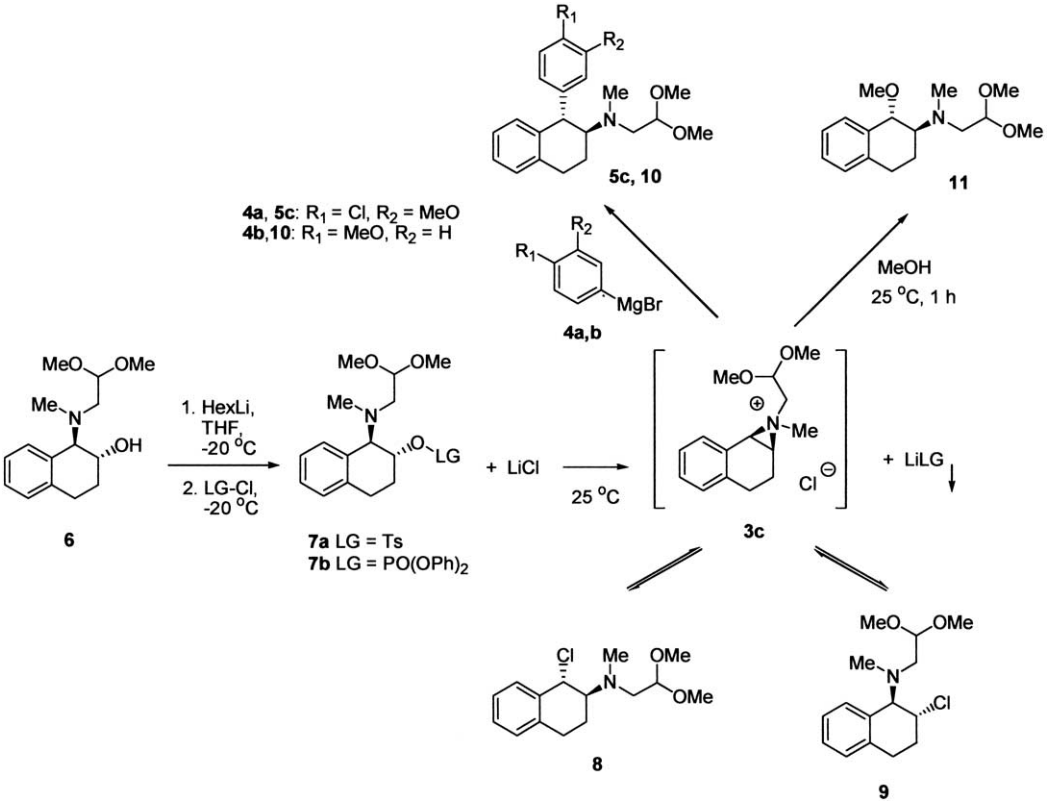
desired *trans*-ring stereochemistry was envisioned to be set at the key step by regio- and diastereoselective opening of either aziridine **2** or aziridinium ion **3** with *p*-chloro-*m*-methoxyphenylmagnesium bromide **4a**.[3] While aziridines **2a** and **2b** proved to be unreactive towards **4a** under a variety of conditions screened, aziridinium ions **3** did react as expected to furnish **5c** as a single isomer, albeit in low yields and poor overall mass balance.[4] Our initial attempts to increase the yield of the desired product by standard variation of reaction parameters (e.g. temperature, solvent, order of addition) were not successful, prompting us to undertake a more detailed study of the formation of aziridinium ions **3**, their stability and reactivity with organometallic reagents.

Aziridinium ions **3a** and **3b** could be prepared in good yields by the direct methylation of aziridine **2b** at −20°C. Moreover, aziridinium tetrafluoroborate **3a** was isolated out of reaction solution by precipitation with diethyl ether and proved quite stable as a solid even upon prolonged storage.[4] To assess the stability of the aziridinium ions **3a** and **3b** in solution under the typical reaction conditions (THF, −20°C), corresponding ion solutions in several deuterated solvents were prepared and monitored by ^{1}H NMR. The results of these experiments indicated that both aziridinium tetrafluoroborate **3a** and aziridinium triflate **3b** decomposed in solution over the course of several hours even at −20°C. Among the aziridinium decomposition products, the major ones were identified as *cis*- and *trans*-piperazinium dimers whose facile generation from *N*,*N*-disubstituted aziridinium ions is well documented in the literature.[5] The rate of aziridinium ion decay in this case did not appear to depend on the reaction solvent and was strongly accelerated at higher temperatures. Such instability of **3a** and **3b** in solution rendered their handling on scale difficult and resulted in unacceptably low yields (40–45%) of product **5c** contaminated with piperazinium impurities.

Interestingly, when aziridinium chloride **3c** was used in the reaction with **4a**, consistently higher yields of **5c** were obtained (55–60%) with no detectable piperazinium impurities. The most common way of preparing aziridinium chlorides from amino alcohols is via treatment of the latter with MsCl or TsCl in the presence of triethylamine.[1] These conditions were not readily applicable in our case due to the presence of byproduct triethylamine hydrochloride which was incompatible with organometallics. Therefore, our initial experimental protocol for the preparation of **5c** through aziridinium chloride **3c** involved deprotonation of β-amino alcohol precursor **6** with HexLi in the presence of 1,10-phenanthroline indicator, treatment of the resulting lithium alkoxide with TsCl at −20°C to give tosylate **7a**, followed by addition of **7a** to the solution of Grignard reagent **4a** kept at 25°C (Scheme 2). NMR spectroscopy studies of the tosylate formation step in THF-d_8 indicated that **7a** was quite stable at −20°C but quickly decomposed upon warming with the



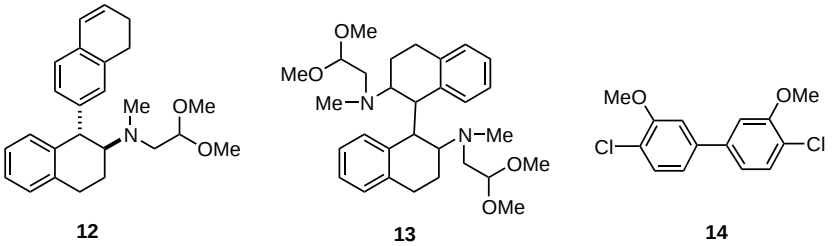
Scheme 2.

elimination of lithium tosylate to give two new species whose spectra were consistent with chloroamines **8** and **9** (characteristic ^{13}C NMR signals for **8**: 68.2, 61.2, 57.6, 53.9 ppm; for **9**: 70.7, 59.3, 58.3, 53.3 ppm). Inspection of ^{1}H and ^{13}C NMR spectra of the reaction mixture taken at different temperatures during the warm up of **7a** and comparison to the spectra of authentic aziridinium tetrafluoroborate **3a** confirmed the absence of detectable quantities of aziridinium chloride intermediate **3c** at any point during the reaction. After ageing the chloroamine mixture at 25°C for several days, ^{1}H and ^{13}C NMR indicated complete rearrangement of chloroamine **8** into more stable chloroamine **9**. The identity of chloroamine **9** was further ascertained by its isolation and complete spectroscopic characterization.[6] These results are consistent with the findings of other workers in structurally similar pseudoephedrine and ephedrine systems where benzylic chloroamine was proposed to be the initially formed kinetic product which then slowly rearranged into the more stable non-benzylic chloroamine via intermediate aziridinium chloride.[7]

Although aziridinium chloride **3c** could not be detected spectroscopically, it clearly was a common reaction intermediate on the path from **7a**, **8** and **9** to the product **5c** (Scheme 2). Neither tosylate **7a** nor chloroamines **8**/**9** coupled with **4a** directly.[8] Instead, chloroamines **8**/**9** served as a stable latent form[1e,f] of aziridinium chloride **3c**, capturing it on formation and releasing it on demand in a low steady-state concentration. The benefit of such 'chloroamine sink' in the reaction with **4a** was apparently in preventing the buildup of aziridinium chloride in solution and its unproductive dimerization. Indeed, in comparison to 'naked' aziridinium ions **3a** and **3b**, reaction of preformed tosylate **7a** with **4a** resulted in about 10% increase in solution yields of **5c** and minimized piperazinium impurity formation.

In order to assess the efficiency of aziridinium chloride formation step, we needed a reliable assay method for the 'total aziridinium' concentration in solution. After screening several derivatizing agents, we found that reaction of a mixture of **7a**, **8** and **9** with methanol at ambient temperature was rapid, quantitative and gave **11** as the sole reaction product. Given the ready availability and stability of analytical standards of **11**, we developed a simple and convenient HPLC assay method whereby the 'total aziridinium' concentration in the reaction mixture was determined from the amount of **11** obtained upon the methanolysis of a small reaction aliquot.[9] Using this assay, we established that formation of aziridinium chloride from **6** in our HexLi/TsCl procedure proceeded in 90–92% solution yields, and that once formed, the 'total aziridinium' concentration in solution remained constant over several weeks at 25°C. Besides TsCl, we also examined a range of other activating reagents containing chloride such as MsCl, $ClPO(OPh)_2$, $ClPO(OEt)_2$, $SOCl_2$, and $(COCl)_2$. The highest solution yields of aziridinium chloride of 95–97% were obtained using $ClPO(OPh)_2$, which therefore was selected as the preferred reagent. Better yields of aziridinium chloride obtained in $ClPO(OPh)_2$ procedure were primarily due to improved reaction conversion and reduced amount of unreacted **6**. With TsCl and MsCl, 3–5% of **6** remained unreacted even when using large excesses of these reagents. Another advantage of $ClPO(OPh)_2$ compared to TsCl and MsCl was that the rate of phosphate adduct **7b** conversion to chloroamines was relatively slow below −10°C, allowing for smooth transfers on scale without the risk of line plugging by precipitating lithium salt.

With a robust and high yielding procedure for the generation of aziridinium chloride **3c** in hand, we next turned our attention to the optimization of the Grignard addition step. Despite the benefits realized on switching from aziridinium triflate and tetrafluoroborate to aziridinium chloride, overall solution yields of **5c** from **6** remained below 60%. In order to establish the causes behind the depressed product yield, we added phosphate **7b** preformed at −20°C to **4a** in THF at 25°C and monitored the progress of the reaction by taking aliquotes of reaction mixture at specified time intervals, quenching them with methanol and assaying for the concentration of **5c** and **11**. As the solution yield of **5c** peaked at 55–60% after approximately 4 h reaction time, concentration of **11** approached zero indicating that there was no more unreacted aziridinium species left in the reaction mixture. Apparently, the remaining 40% of aziridinium species was consumed in some unproductive side reactions. A thorough analysis of reaction mixture revealed the presence of three dimeric impurities **12**, **13** and **14** (Scheme 3).[10] The presence of these dimeric impurities points to the operation of the SET mechanism, which is typical for reactions of Grignard reagents with electrophiles possessing low reduction potential (e.g. benzophenone).[11] Indeed, ab initio calculations[12] predict for cation **3c** adiabatic electron affinity $E_{ad} = 5.25$ eV and vertical electron affinity $E_v = 2.10$ eV in the gas



12 **13** **14**

Scheme 3.

Table 1. Effect of Cu(I) salt additives on the rate and yield of reactions of Grignard reagents **4a** and **4b** with phosphate **7b**[a]

Entry	Grignard reagent	Cu(I) salt added	Reaction time (h)	Product (solution yield, %)
1	**4a**	None	4	**5c** (58)
2	**4b**	None	0.5	**10** (95)
3	**4a**	5 mol% CuCN·2LiCl	0.5	**5c** (82)
4	**4a**	5 mol% CuCl·2LiCl	0.5	**5c** (80)
5	**4b**	5 mol% CuCl·2LiCl	0.5	**10** (94)
				Product ratio **5c**/**10**
6	**4a**+**4b**	None	1	1/5.4
7	**4a**+**4b**	5 mol% CuCl·2LiCl	1	1/1.7
8	**4a**+**4b**	5 mol% CuCN·2LiCl	1	1/1.5

[a] See Ref. 18 for experimental procedure. Experiments on competition kinetics performed using equimolar mixtures of **4a** (2.5 equiv.) and **4b** (2.5 equiv.).

phase, demonstrating that aziridinium ion **3c** is a better electron acceptor than benzophenone ($E_{ad}=0.64$ eV)[13] and even *p*-benzoquinone ($E_{ad}=1.85$ eV).[14] Thus, the electron transfer from Grignard reagent to aziridinium ion is expected to be fast and the subsequent carbon–carbon bond formation to be rate limiting.[15] Lack of intermediate aziridinium radical racemization on formation of **5c** is apparently a consequence of close radical association within a solvent cage.[16]

In contrast to slow reaction with deactivated **4a** (Table 1, entry 1), we found that reaction of **7b** with more nucleophilic *p*-methoxyphenylmagnesium bromide **4b** proceeded almost instantaneously to give **10** quantitatively as a single isomer with very small amounts (<1% combined) of dimeric radical impurities (entry 2).[17] Following this lead, we attempted to increase the nucleophilicity of reagent **4a** by adding catalytic amounts of copper(I) salts. Gratifyingly, addition of just 5 mol% of CuCN·2LiCl or CuCl·2LiCl salt to the solution of organomagnesium reagent **4a** prior to its coupling with **7b** dramatically increased the rate of the reaction and yield of **5c** by at least 20% (entries 3 and 4).[18] The amount of impurities **12**–**14** was also significantly reduced. Apparently, copper(I) catalysts accelerated the rate limiting recombination of intermediate aryl-aziridinium radical pair, thereby shifting the mechanism towards more polar and reducing the chances for radical pair diffusive breakup and dimerization. This postulate was also supported by simple competition kinetics experiments where equimolar mixtures of **4a** and **4b** were reacted with **7b** (entries 6–8). In the presence of catalytic amounts of copper(I) salts, the difference in reaction rates between the two organomagnesium reagents became significantly smaller.

Besides organomagnesium reagents, other organometallic reagents examined in the present reaction failed to provide any of the desired product. Thus, reactions of phenyllithium and *p*-chloro-*m*-methoxyphenyllithium[19] with **7b** at −20°C resulted in exclusive attack at the phosphorus atom of phosphate moiety to give back starting material **6**, while reactions of these aryllithiums with chloroamine mixture **8**/**9** at 0–25°C resulted in deprotonation and formation of various elimination byproducts (mostly naphthalene). Both freshly prepared *p*-chloro-*m*-methoxyphenylzinc bromide and commercially available phenylzinc bromide proved to be unreactive towards **7b** and **8**/**9**, with none of the expected product observed even after 48 h reaction time at 40°C.

In summary, we have explored the formation, stability and reactivity of aziridinium ions **3** towards organometallic reagents and identified the optimum reaction conditions necessary for the preparation of ecopipam intermediate **5c** in high yield and stereoselectivity. Existing in equilibrium with chloroamines **8**/**9**, aziridinium chloride **3c** proved superior to unstable dimerization-prone 'naked' aziridinium triflate and tetrafluoroborate. Efficient generation of aziridinium chloride **3c** in solution from β-amino alcohol **6** was achieved using HexLi/$ClPO(OPh)_2$ method. While reactive organomagnesium reagents added to aziridinium chloride **3c** quantitatively, the use of catalytic amounts of copper(I) salts was necessary to accelerate the addition of deactivated *p*-chloro-*m*-methoxyphenylmagnesium bromide and minimize the amount of radical byproducts. Reaction of aziridinium precursors **7b** and **8**/**9** with aryllithium and arylzinc reagents failed to provide any of the expected product. Further investigations of this interesting and useful reaction are currently underway and will be reported in due course.

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6. Compound **9** data: ^{1}H NMR (THF-d_8, 400 MHz) δ: 7.60–7.10 (m, 4H), 4.55 (m, 1H), 4.45 (m, 1H), 4.05 (d, $J=6.5$ Hz, 1H), 3.30 (s, 3H), 3.25 (s, 3H), 3.00–2.90 (m, 4H), 2.31 (s, 3H), 2.28 (m, 1H), 2.15 (m, 1H). ^{13}C NMR (THF-d_8, 100.6 MHz) δ: 137.4, 130.6, 129.6, 128.9, 127.7, 125.8, 104.8, 70.7, 59.3, 58.3, 53.3, 53.2, 38.2, 32.5, 28.1. HRMS-FAB calcd for $C_{15}H_{23}ClNO_2$ 284.1417, found 284.1411.
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9. Compound **11** data: ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.38 (m, 1H), 7.18 (m, 2H), 7.05 (m, 1H), 4.50 (d, $J=7.0$ Hz, 1H), 4.50 (m, 1H), 3.41 (s, 3H), 3.40 (s, 3H), 3.38 (s, 3H), 3.05 (ddd, $J=10.5$ Hz, 7.0 Hz, 4.5 Hz, 1H), 2.78 (m, 2H), 2.70 (m, 2H), 2.41 (s, 3H), 2.05 (m, 1H), 1.65 (m, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 138.1, 136.5, 128.6, 128.0, 127.1, 125.7, 103.6, 78.1, 63.6, 56.2, 55.7, 53.7, 53.2, 38.7, 28.2, 22.7. HRMS-FAB calcd for $C_{16}H_{26}NO_3$ 280.1913, found 280.1910.
10. Impurity **12** was obtained as a single *trans*-diastereomer, while impurity **13** was a mixture of three diastereomers. Formation of impurity **14** was strongly enhanced when TsCl was used in place of $ClPO(OPh)_2$.
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12. (a) Calculations performed using Spartan'02; Wavefunction Inc., Irvine, CA. We employed the procedure described in Ref. 12b with the following modifications: global conformation minima were located using MMFF conformational driver and their geometries optimized at HF/3-21G(*) level; B3LYP/6-31G(d) method was used for final single-point energy calculations; (b) Beveridge, A. J.; Williams, M.; Jenkins, T. C. *J. Chem. Soc., Faraday Trans.* **1996**, *92*, 763–768.
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17. We have also examined a range of other substituted phenylmagnesium bromides in reaction with **7b**. Overall, good Hammett correlation of relative rates $\log k_{rel}$ with $\Sigma\sigma$ was obtained ($\rho=-1.7$). Increase in respective reaction yields generally paralleled the increase in $\log k_{rel}$.
18. **Typical experimental procedure**: To compound **6** (10.0 g, 37.7 mmol, 1 equiv.) were added 1,10-phenanthroline (5 mg) and anhydrous THF (60 mL). The solution was cooled to −20°C and *n*-hexyl lithium (16 mL, 2.5 M solution in hexanes, 40 mmol, 1.05 equiv.) was added dropwise. Towards the end of addition, the red-brown colored reaction mixture turned dark red in color. After stirring the reaction mixture at −20°C for 10 min, diphenyl chlorophosphate (8.6 mL, 41.5 mol, 1.1 equiv.) was added dropwise and the reaction mixture was held at −20°C for 1 h. Separately, a solution of CuCl·2LiCl was prepared by adding anhydrous THF (5 mL) to a mixture of copper(I) chloride (0.19 g, 1.9 mmol, 0.05 equiv.) and lithium chloride (0.16 g, 3.8 mol, 0.10 equiv.) and this solution was cannulated to the *p*-chloro-*m*-methoxyphenylmagnesium bromide (54 mL, 56.6 mmol, 1.5 equiv., 1.05 M in THF) held at 25°C. The mixture was stirred for 5 min, and the aziridinium ion solution held at −20°C was added to the Grignard solution via a cannula and then heated to 40–45°C for 1 h. The reaction mixture was cooled to 0°C, quenched with aqueous ammonium chloride solution, extracted with methyl *tert*-butyl ether and subjected to acid–base workup. Crude product was purified by chromatography to provide analytical sample of **5c** (12.1 g, 75.0% isolated yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.30–6.65 (m, 7H), 4.12 (t, $J=5.6$ Hz, 1H), 4.09 (d, $J=11.3$ Hz, 1H), 3.82 (s, 3H), 3.21 (s, 3H), 3.12 (s, 3H), 2.95 (m, 3H), 2.60 (dd, $J=5.6$, 11.3 Hz, 2H), 2.31 (s, 3H), 2.08 (m, 1H), 1.80–1.70 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 154.3, 146.3, 139.2, 136.5, 130.2, 129.2, 128.1, 125.7, 125.6, 122.2, 119.5, 113.3, 103.7, 67.2, 56.3, 55.8, 53.9, 52.6, 49.2, 37.7, 29.6, 22.3; FABMS: 235, 271, 314, 358, 390. Anal. calcd for $C_{22}H_{28}ClNO_3$: C, 67.77; H, 7.24; N, 3.59. Found: C, 67.77; H, 7.29; N, 3.69.
19. *p*-Chloro-*m*-methoxyphenyllithium was found to undergo facile dimerization even at low temperatures and was utilized immediately on preparation.