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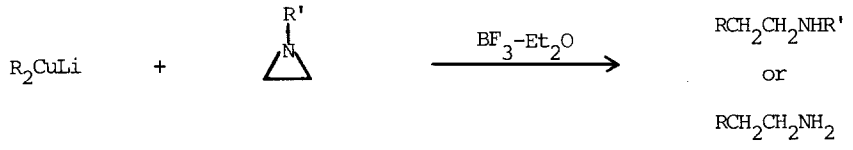
BF_3-ETHERATE PROMOTED ALKYLATION OF AZIRIDINES WITH ORGANOCOPPER REAGENTS: A NEW SYNTHESIS OF AMINES

Michael J. Eis and Bruce Ganem*
Department of Chemistry
Baker Laboratory
Cornell University
Ithaca, NY 14853

Summary: Boron trifluoride etherate promotes nucleophilic ring opening of a variety of substituted aziridines by diorganocopperlithium reagents leading to both primary and secondary amines.

Recent work by us[1] and Brown et al.[2] has elucidated the mechanism of BF_3-etherate promoted organolithium additions to epoxides, oxetanes and other oxygenated electrophiles. Extension of this methodology to appropriately protected aziridines would constitute overall a two-carbon aminoethylation of nucleophiles, thus complementing one and three-carbon aminoalkylations with tosyl cyanide[3] and acrylonitrile, respectively. N-Acylated aziridines and aziridinecarbamates usually undergo only carbonyl addition reactions with organolithium and magnesium reagents.[4-6] In 1975 the successful alkylation of a strained tricyclic N-acylaziridine was achieved by Aratani et al. using a cuprate, albeit in 15% yield.[7] We now report that BF_3--etherate promotes the ring-opening addition of organocopper reagents to N-substituted aziridines in a general new synthesis of primary and secondary amines.



The addition of trityllithium to aziridinecarbamates has been reported to afford the carbamate of 3,3,3-triphenylpropylamine in 35% yield.[5] The same reaction in the presence of BF_3-Et_2O (5 min,-78°) afforded a 74% yield of product. However similar openings of N-methyl, N-benzyl or N-silylaziridines could not be achieved at -78°, above which temperature mixtures of organolithiums and BF_3-Et_2O are not very stable. Only the addition of phenyllithium to N-(t-butyldimethylsilyl)aziridine in the presence of BF_3-Et_2O gave the desired β-phenethylamine in modest yield (19%). Alkylcopper(I) compounds, although more compatible with Lewis acids,[8] manifested little improvement. Lithium diorganocuprates in THF, on the other hand, demonstrated just the right balance of stability to BF_3-Et_2O and nucleophilicity to a range of N-substituted aziridines. The Table summarizes our findings.

Most N-substituted aziridines were prepared either by N-alkylation or by the method of Wenker.[9] Reaction with cuprates afforded N-methyl or N-benzylamines in good yield. Since ethyleneimine itself could not be alkylated, an easily removed N-substituent was required to synthesize primary amines directly.[10] Reactions of N-t-butyldimethylsilylaziridine[11] with cuprates were only moderately successful (entries 5,9). Ultimately the 4,4'-dimethoxybenzhydryl (DMB) group[12] proved superior (entries 2, 10). Several attempts to alkylate DMB-substituted-2,2-dimethylaziridine failed, even using $Ph_2CuCNLi_2$, however the less hindered N-benzyl derivative did react (entries 6, 11) making it possible to prepare the N-benzyl analog of the appetite suppressant phentermine.[13] The methodology could not be extended to azetidines.[14]

Preparation of N-(4,4'-Dimethoxybenzhydryl)aziridine — To a mixture of DMB chloride (3.8 mmol) and triethylamine (12.8 mmol) in THF (5 mL) at 0°C was added ethyleneimine (.33 mL). After stirring 5 min at 0°C and 8h at rt, anhydrous ether (10 mL) was added and the precipitated solids filtered. The supernatant was dried over Na_2SO_4 and concentrated in vacuo to afford the crude product which crystallized after chromatography (silica, 4:1 hexane:ethyl acetate) in 67% yield, mp 58-61°C.

Synthesis of β-Phenethylamine — A 50 mL roundbottom flask charged with CuI (1.5 mmol) and THF (6 mL) was cooled under Ar to -40°C and treated with phenyllithium (3 mmol in 7:3 cyclohexane:ether). The resulting black mixture was stirred 15 min, then cooled to -78°C. To it was rapidly added the DMB-protected aziridine (.5 mmol) in THF (.5 mL) followed by BF_3-Et_2O (1.5 mmol). After warming the mixture to rt, 14% NH_4OH (15 mL) was added along with ether (10 mL) and solid NH_4Cl (1g). The resulting dark blue aqueous layer was extracted three times with 1:1 hexane:ether. The combined extracts dried (K_2CO_3), filtered and concentrated to afford the N-DMB derivative of β-phenethylamine in 95% after flash chromatography (4:1 hexane:ethyl acetate).

This sample was deprotected according to the procedure of Trost[12b] by stirring in 88% formic acid (5 mL) at 80-85°C for 90 min. After removing the solvent as described, the amine was partitioned between 5% aqueous HCl and ether to furnish pure β-phenethylamine (44 mg, 80%).

TABLE

ALKYLATION OF AZIRIDINES WITH ORGANOCUPRATES

Entry	Nucleophile[a]		Product[b] (Yield)
1	$(CH_3)_2CuLi$	R=Bn, R'=H	C_3H_7NHBn (80%)
2	"	R=DMB, R'=H	C_3H_7NHDMB (97%)
3	$(Bu)_2CuLi$	R=CH_3, R'=H	$C_6H_{13}NHCH_3$ (94%)
4	"	R=Bn, R'=H	$C_6H_{13}NHBn$ (75%)
5	"	R=TBDMS, R'=H	$C_6H_{13}NH_2$ (30%)
6	"	R=Bn, R'=CH_3	$C_5H_{11}C(CH_3)_2NHBn$ (92%)
7	$(Ph)_2CuLi$	R=CH_3, R'=H	$Ph(CH_2)_2NHCH_3$ (56%)
8	"	R=Bn, R'=H	$Ph(CH_2)_2NHBn$ (92%)
9	"	R=TBDMS, R'=H	$Ph(CH_2)_2NH_2$ (45%)
10	"	R=DMB, R'=H	$Ph(CH_2)_2NH_2$ (80%)
11	"	R=Bn, R'=CH_3	$PhCH_2C(CH_3)_2NHBn$ (50%)[c]
12	$(Ph)_3CLi$	R=t-BOC, R'=H	$(Ph)_3C(CH_2)_2NHBOC$ (74%)

(a) Except as noted, all alkylations were carried out using a 3:3:1 ratio of cuprate:BF_3-Et_2O: aziridine. THF was preferred as solvent over ether. Lesser quantities of BF_3 or cuprate resulted in 10-35% recovered starting material.

(b) All products were isolated as described in the representative procedures and characterized by comparison with authentic samples.

(c) A 7:7:1 ratio of reactants was used in this experiment.

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