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A FACILE SYNTHESIS OF β-SUBSTITUTED-α-ALLENYL PRIMARY AMINES

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Abstract. Copper or nickel catalyzed substitution of Grignard reagents on the bis-trimethylsilyl protected 4-methoxy-2-butynylamine (2) provides β-substituted-α-allenyl primary amines (3) in high yield.

Several α-allenyl primary amines are of interest as mechanism-based enzyme inhibitors.[1-5] Although a useful synthesis of α-allenyl-α-alkyl primary amines has recently appeared,[4] routes to α-allenyl-β-substituted primary amines (3) generally are tedious and proceed in low yield.[6-8] There are few examples of the title compounds. β-Phenyl-α-allenylamine (3a) has been synthesized in 14% yield;[8] the β-benzyl, -methyl, and -n-butyl analogues were obtained by the same method in low yield. The same authors[7] have prepared tertiary α-allenyl amines in 20% to 70% yield by the reaction of acetylenic amino ethers with organocuprates. A single example of a trisubstituted primary α-allenylamine, 1,3-dimethyl-α-allenylamine, was reported, albeit in a 42% yield.

We desired a convenient synthesis of 3, particularly where the β-substituent was aryl--specifically thienyl, because of our interest in potential mechanism-based inhibitors of dopamine β-hydroxylase (DBH; EC 1.14.17.1).[9,10] We have recently demonstrated that the thiophene ring can be used as a bioisostere for phenyl for designing potent allylamine mechanism-based inhibitors of DBH. Enzymatic epoxidation of 3 by DBH would lead to the reactive and mechanistically interesting allene oxides.[11]

We wish to report a general, one step method for the preparation of β-substituted-α-allenyl-amines in high yield using the bis-trimethylsilyl protected synthon 2 as starting material. As part of an unrelated study, compound 2 has recently been reported without experimental details.[12] However, we have developed an alternate and convenient synthesis of 2 which can readily be carried out on a large scale.[13] Treatment of an aromatic or aliphatic Grignard reagent with 10 mole % of copper bromide-dimethyl sulfide in anhydrous ether at -25°C, followed

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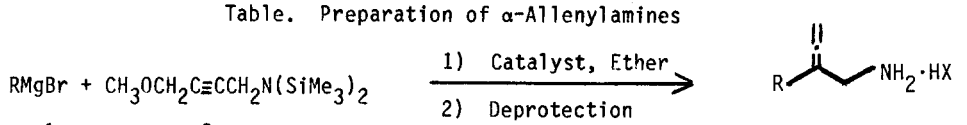
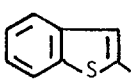
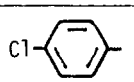
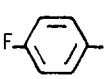
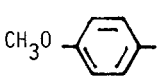
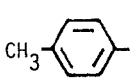
Table. Preparation of α-Allenylamines



1 2 3

Entry	R	Product	Catalyst[a]	Rxn Time, hrs.	Yield, %[b]	HX	mp°,C	Recryst Solvent
a		3a	Cu	1	86	oxalate	163-5(dec)[c]	CH_3CN
						TsOH	163-4	CH_3CN
b			Ni	6	44	HCl	229-30	EtOH
c		3b	Cu	20	0			
						oxalate	188-90(dec)	i-PrOH
d			Ni	20	87	TsOH	126-7	i-PrOH
e		3c	Cu	20	0			
						HCl	235(dec)	EtOH
f			Ni	4	72[d]			
g		3d	Cu	3	87	TsOH	159-60.5	i-PrOH
h		3e	Cu	18	86	oxalate	192-3	i-PrOH/H_2O
						TsOH	164-6	CH_3CN
i		3f	Cu	1.5	76	TsOH	166-8	CH_3CN
j		3g	Cu	18	98	TsOH	134-6	CH_3CN
						HCl	205-7(dec)	--
k			Ni	0.1	52			
	$n\text{-}C_6H_{13}$	3h				HCl	120-1	CH_3CN
l			Cu	18	82			

(a) Cu catalyst: CuBr Me_2S. Ni catalyst: $NiCl_2$(dppp). (b) All yields refer to isolated, chromatographically pure materials. Satisfactory NMR, IR, MS and elemental analysis obtained for all compounds. (c) Lit. (ref 8) mp 160° (dec). (d) Isolated by the addition of 0.95 equivalent of 1N ethanolic HCl to an etheral solution of the silylated allenylamine. Flash chromatography catalyzed a rearrangement of 3c.

by the addition of 2, gave bis-trimethylsilylated 3 in essentially quantitative yield after stirring at room temperature. The only side product observed was the biaryl or bis-alkane of the Grignard reagent. Flash chromatography provided the deprotected amines 3 usually in greater than 80% yield (see Table). A control experiment with phenylmagnesium bromide without copper catalyst provided none of the desired allene 3a.[15]

Attempts to apply this methodology with the heteroaromatic 2-thienyl Grignard reagent (1b) to obtain the allenylamine of most interest (3b) were unsuccessful. Lipshutz and co-workers have noted a similar lack of transfer of the 2-thienyl group in mixed higher order cuprate reactions.[16] Since various transition metals are known to catalyze the S_N2' substitution of Grignard reagents to propargyl halides,[17,18] we investigated 1,3-bis(diphenylphosphinopropane)-nickel (II) chloride[19] ($NiCl_2$(dppp)) as a catalyst. Indeed, the difference in results was dramatic. Addition of synthon 2 to 3 mole % $NiCl_2$(dppp) in ether followed by 2-thienyl-magnesium bromide at room temperature provided the desired allenyamine 3b in 87% yield. It should be noted that 2-benzothienylmagnesium bromide (prepared by lithiation of benzothiophene followed by addition of $MgBr_2$ etherate) also required $NiCl_2$(dppp) (entries e and f). The nickel catalyzed addition of n-hexylmagnesium bromide was notably exothermic and complete in a few minutes as determined by GC. However, the isolated yield of allene was considerably lower than with the copper catalyst (see entries k and l). The nickel catalyst also proved less satisfactory for phenyl (entry b).

An illustrative example is as follows: In a dry 3-necked 100 mL flask with stirring bar, N_2 bubbler, thermometer and septum was added $CuBr \cdot Me_2S$ (200 mg, 1 mmol) and dry ether (30 mL). The mixture was cooled to -25°C and 3M phenylmagnesium bromide in ether (6.7 mL, 20 mmol) was added *via* syringe. The mixture was stirred at -25°C for ca. 2 min and 2[13] (2.43 gm, 10 mmol) was added slowly *via* syringe. The reaction was allowed to warm to room temperature and its progress monitored by GC. After 1 hour, the mixture was poured into dilute ammonium hydroxide (100 mL) and extracted with ethyl acetate. The combined organic layers were dried and evaporated to a colorless oil. Purification by flash chromatography ($CHCl_3$ then $CHCl_3$:MeOH:NH_4OH (100:8:1)) gave 3a as a colorless oil (1.25 gm, 86%). Dilution with ether and treatment with an ethanolic solution of oxalic acid (775 mg, 8.6 mmol) gave the oxalate salt as a white precipitate (1.9 gm). Recrystallization of a small sample from CH_3CN gave material with mp 163-165°C (dec) (Lit[8] mp 160°C (dec)) IR(KBr) 1955 cm-1; NMR of free base ($CDCl_3$) δ 1.5 (s, 2H), 3.62 (t, J=3.5 Hz, 2H), 5.15 (t, J=3.5 Hz, 2H), 7.28 (s, 5H); MS (CI) m/z 146 (MH+). Alternatively, treatment of an etheral solution of the free base with one equivalent of 1M ethanolic p-toluenesulfonic acid provided the tosylate salt as shiny white crystals, mp 163-164°C (CH_3CN) Anal. Calcd for $C_{10}H_{11}N\ C_7H_8SO_3$; C, 64.33; H, 6.03; N, 4.41. Found: C, 64.18; H, 6.06; N, 4.22. Hydrochloride salt obtained from oxalate salt by anion exchange chromatography (AG3-X4A Cl-form), (MeOH:H_2O) (9:1) mp 229-230°C (dec) (EtOH).

Further investigation on the contrasting effects of the nickel (0) and copper (I) catalysts, particularly for the thienyl allenylamine 3b, and its implication on the mechanism of the reported reaction are underway. The mechanism-based inhibition of DBH by these compounds will be reported separately.

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