Synthesis of Substituted Benzhydrylamines

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Abstract: The synthesis of *para* di- and monosubstituted benzhydrylamines by addition of Grignard reagents to benzonitriles and subsequent reduction, is evaluated and discussed. The reduction step with sodium borohydride allows simple handling and mild conditions. An optimized synthesis of 4,4'-dimethoxybenzhydrylamine by this method is disclosed.

Key words: benzhydrylamines, Grignard reactions, diphenylmethylidenamines, diarylketimines, reductions, protecting groups

Benzhydrylamine and its substituted derivatives form an important class of compounds in organic synthesis because of their use as protecting groups.¹ The benzhydrylamine moiety can be cleaved by hydrogenation, acid hydrolysis or radical reaction with ceric ammonium nitrate (in the case of 4,4'-dimethoxybenzhydrylamine). Furthermore, these diarylmethylamines are present in a wide variety of physiologically interesting compounds.²

A wide array of syntheses of benzhydrylamines are known, based on transformations of the corresponding benzhydrols,^{1a,b,3} reduction of the oxime derivatives,⁴ reductive amination of benzophenone precursors,^{1c,5} and addition of organometallic reagents to either aldimines,⁶ *N*boryl imines,⁷ quaternary hydrazonium salts⁸ or nitriles.⁹

However, while using the latter method in our own research, we found some inadequacies in the literature concerning this topic. In most of the papers discussing Grignard addition of bromobenzene derivatives to substituted benzonitriles, the synthesis of bis(4-methoxyphenyl)methylidenamine (precursor to the more interesting 4,4'-dimethoxybenzhydrylamine) is not performed nor discussed.⁹ In other papers, this latter experiment has been performed, but only with very low or moderate yields $(10-20\%, ^{10} 54\%^{11})$. In this letter, the synthesis of *para* di- and monosubstituted benzhydrylamines, including an optimized procedure for the synthesis of 4,4'-dimethoxybenzhydrylamine, by reaction of bromobenzene derived Grignard reagents with benzonitriles and subsequent reduction with sodium borohydride, is disclosed. A one-pot synthesis of 4,4'dimethoxybenzhydrylamine is also described.

For the synthesis of the diphenylmethylidenamine derivatives **2**, the work published by Pickard et al. was used as a starting point.^{9a,b} To an ethereal solution of the Grignard reagents, derived from bromobenzenes **1**, benzonitriles, dissolved in diethyl ether, were added. After 5 hours of reflux, the mixture was cooled and dry methanol was added. Filtration and evaporation of the solvent yielded the diphenylmethylidenamine derivatives **2** in good yields and purity (see Scheme and Table). Although further purification was not really necessary to perform the reduction step, this could be performed either by distillation (entry a, c, d) or crystallization from toluene (entry b, e) or from hexane/cyclohexane (1:1) (entry e).

In the case of bis(4-methoxyphenyl)methanimine 2e, a precipitate was formed directly after the addition of the 4-methoxybenzonitrile to the corresponding Grignard reagent, derived from 1-bromo-4-methoxybenzene. During further reflux, this precipitate dissolved. It is believed that this possibly accounted for the lower yield observed in this case, corresponding to literature data.^{10,11} Performing the reaction in tetrahydrofuran, there was no precipitate formed. However, after quenching with methanol, partial evaporation of tetrahydrofuran and addition of diethyl ether, a precipitate was formed, that we assumed to be methoxymagnesium bromide. After filtration and evaporation of the solvent, the imine 2e was obtained in only 45% yield. It was observed that the solubility of 2e in di-



Scheme

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TableSubstitution Pattern and Yields of Imines 2 and Amines 3

R ¹	R ²	Yield 2 (%)	b.p. (°C/mmHg)	Yield 3 (%)
Н	Н	70 ^a	166 / 11.5	99
Me	Me	75 ^b	-	95
Н	Me	50 ^a	91/0.04	98
MeO	Me	50 ^a	135/0.08	98
MeO	MeO	51°	_	94
	R ¹ H Me H MeO MeO	R ¹ R ² H H Me Me H Me MeO Me MeO MeO	R^1 R^2 Yield 2 (%) H H 70^a Me Me 75^b H Me 50^a MeO Me 50^a	R ¹ R ² Yield 2 (%) b.p. (°C/mmHg) (°C/mmHg) H H 70 ^a 166 / 11.5 Me Me 75 ^b - H Me 50 ^a 91/0.04 MeO Me 50 ^a 135/0.08 MeO MeO 51 ^c -

^a Yields before distillation were 90-95% with > 90% purity based on ¹H NMR; yields dropped because of small scale distillation.

^b Yield after crystallization from toluene.

^c Yield of the crude reaction product.

ethyl ether is very low, so bis(4-methoxyphenyl)methylidenamine 2e was probably also partially precipitated after the removal of tetrahydrofuran and addition of diethyl ether. For this reason, the application of an alternative work-up procedure (extraction with water/diethyl ether or dichloromethane) was performed. Now, it was observed that the crude yields of the reaction product 2e improved to almost 100%, either using diethyl ether or tetrahydrofuran as solvent. However, recrystallization from toluene or hexane-cyclohexane (1:1) decreased the yield of the pure product to 50%, as was already observed in the aforementioned publications. Taking advantage of observing the low solubility of the imine 2e in diethyl ether, the latter compound was dissolved in a minimal amount of dichloromethane and diethyl ether was added until precipitation started. This increased the overall yield of the reaction to 80% after purification. In conclusion, changing the workup procedure and solvents for crystallization allowed to increase the yield of bis(4-methoxyphenyl)methanimine **2e** from 51% to 80% for the pure compound.

The subsequent reduction of the diphenylmethanimine derivatives 2 with sodium borohydride in methanol is very mild and effective (see Scheme). The resulting benzhydrylamines 3 were obtained in excellent yields (see Table). Previously, reduction of substituted diphenylmethylidenamines 2 to the corresponding amines 3 had only been performed with less common and sometimes not easy-to-handle reductive systems, including zinc powder in aqueous sodium hydroxide solution,¹² diphenylsilane in the presence of various titanocene complexes,¹³ ytterbium in THF/HMPA,14 irradiation in isopropanol,15 lithium in HMPT¹⁶ and hydrogenation in the presence of nickel.17 Three tandem alkylation-reduction methods have also been described in the literature. The reduction was performed with lithium in ammonia,^{9c,d} lithium aluminium hydride¹⁸ and zinc borohydride, respectively.¹⁹ However, none of these methods was performed towards the synthesis of amine 3e. Finally, this tandem arylation-reduction method was applied to the synthesis of bis(4methoxyphenyl)methylidenamine 2e.20 After the Grignard addition, the reaction mixture was cooled down to 0 °C, dry methanol was added, and after 20 minutes, also sodium borohydride (2 molar equiv) was added. After stirring for 1 hour at room temperature and 1 hour of reflux, the amine **3e** was obtained with an overall yield of 85%. Accordingly, this highly valuable amine **3e** in N-protection/N-deprotection protocols becomes now readily available.

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- (20) General Procedure for the one-pot synthesis of 4,4'-Dimethoxybenzhydrylamine 3e : In an oven-dry bulb, 1.01 g (43 mmol) of magnesium is suspended in 15 mL dry THF. At r.t., some drops of 4-bromoanisole are added. In order to initiate the reaction, the resulting mixture is scratched with a spatula. If necessary, a crystal of iodine might be added, and the solution might be heated. Once initiated, the remaining of 7.73 g (41 mmol) of 4-bromoanisole were added in 8 mL THF, in order to maintain gentle reflux. When the addition is completed, the mixture is refluxed for another 45 min. After cooling to r.t., 5 g (37.5 mmol) of anisonitrile in 8 mL dry THF is added over 20 min. After additional reflux for 5 h, the reaction mixture is cooled in an ice bath and 30 mL dry methanol is carefully added. After stirring for 20 min, 2.86 g (75 mmol) sodium borohydride is added in portions.

The solution is stirred for 1 h at r.t. and 1 h reflux. Subsequently, the mixture is filtered over Celite and the filtrate partially evaporated. The remaining liquid is poured into 200 mL 0.5 N HCl solution and extracted 3 times with 25 mL diethyl ether. After addition of 2 N NaOH untill pH 9-10, the water phase is extracted with 3 times 50 mL CH₂Cl₂. The combined organic phases are dried (MgSO₄). After filtration and evaporation of the solvent, 7.71 g of amine 3e is obtained. Yield: 85%. Spectroscopic data for compound **3e**: ¹H NMR (270 MHz, CDCl₃): δ = 1.79 (2 H, br s, NH₂); 3.78 (6 H, s, 2 × OMe); 5.13 (1 H, s, CHNH₂); 6.84 and 7.27 (4 H each, d each, J = 8.6 Hz, CH_{ar}); ¹³C NMR (68 MHz, CDCl₃): δ = 55.24 (2 × OMe); 58.45 (CHNH₂); 113.76 and 127. 83 (CH_{ar}); 138.15 and 158.45 ($C_{ar,quat}$); IR (KBr, cm⁻¹): 3370, 1608, 1585, 1509, 1466;^{3c} MS (70eV): m/z (%) = 243(10) [M⁺], 242(54), 241(34), 227(9), 226(39), 211(14), 183(6), 135(81), 134(100), 133(47), 109(9); mp (Büchi 540 melting point apparatus, uncorrected): 58-59 °C.