Published in final edited form as:

Org Lett. 2016 November 18; 18(22): 5808–5811. doi:10.1021/acs.orglett.6b02719.

Organocatalytic Synthesis of Methylene-Bridged *N*-Heterobiaryls

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Abstract

A one-step synthesis of 1,1'- and 2,2'-methylene-bridged *N*-heterobiaryls directly from the corresponding *N*-heterocycles in a reaction with methylmagnesium chloride in the presence of catalytic amounts of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) under thermal and microwave conditions is reported. The split-and-merge methylenation of 2,2'-*N*-heterobiaryls and the direct *ortho*-alkylation of quinoline and isoquinoline with Grignard reagents have also been developed. Mechanistic studies identified several intermediates and provided insights into the formation and roles of magnesium hydride species in the process.

ortho-Methylene-bridged *N*-heterobiaryls **1** are an important class of nitrogenous heterocycles with applications in drug discovery,¹ catalyst and ligand design,² and materials science.³

ortho-Methylene-bridged *N*-heterobiaryls **1** were previously synthesized in several steps,^{2b} or at very high temperatures.⁴ We hypothesized that **1** could be accessed directly from the corresponding *N*-heterocycles **2** by a reaction with methylmagnesium halide (Scheme 1). In this case, addition of the Grignard reagent to **2** would produce intermediate **3** that could undergo elimination of HMgX. Disproportionation of MgHX produces magnesium hydride and magnesium halide, as previously observed in Singaram pinacolboronate ester synthesis.^{5,6} Deprotonation of 2-methylazine **4** would produce anionic species **5** that can add to **2** to give chelate **6**. Subsequent elimination of HMgX and deprotonation of the methylene group would furnish intermediate **7** that would produce *ortho*-methylene-bridged *N*-heterobiaryl **1** upon aqueous work-up.

We report herein that the scalable synthesis of *ortho*-methylene-bridged *N*-heterobiaryls **1** can be accomplished directly from the corresponding *N*-heterocycles in the presence of catalytic amounts of TMEDA (*N,N,N',N'*-tetramethylethylenediamine).

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The authors declare no competing financial interest.

Supporting Information

Experimental and spectral details for all new compounds and all reactions, as well as X-ray crystallographic data for compound **35** reported. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Initial experiments showed that di(isoquinolin-1-yl)methane (**9**) is produced in 7% yield on treatment of isoquinoline (**8**) with MeMgCl in hexane at 120 °C (Table 1, entry 1). Addition of TMEDA led to a significant improvement of the yield (entries 2 and 3).

The optimal temperature range was 120–140 °C, and hexane and toluene were both suitable solvents. Other amines were inferior to TMEDA (entries 4–6), and the starting material remained largely unconsumed. Further experiments showed that the reaction can be carried out efficiently with catalytic amounts of TMEDA (entries 7 and 8). Both methylmagnesium chloride and bromide worked well, while a lower yield was observed for MeMgI (entries 7–9).

The reaction tolerates a number of functional groups (Figure 1). Quinolines and isoquinolines with substituents in 3, 4, 5, 6 and 7 positions have produced corresponding *ortho*-methylene-bridged biquinolines and biisoquinolines (**8**, **10–21**) in good to excellent yields. The reaction was also successfully carried out under the microwave irradiation. Further, products **9** and **10** were synthesized on a preparative scale (6.3 g and 1.9 g, respectively).

Quinolines reacted regioselectively at C2 position, while isoquinolines produced the 1,1'-methylene-bridged products. C2-methylene-bridged bipyridines were not observed, when pyridines were subjected to the standard reaction conditions.

4,4'-Methylene-bridged biquinoline **22** was readily obtained by a reaction of 4-chloroquinoline **23** with MeMgCl in the presence of TMEDA (Scheme 2). 4-Hydroxyquinoline (**24**) also produced 4,4'-methylene-bridged biquinoline **22**, indicating that 4-hydroxy group can be readily displaced by a Grignard reagent under these conditions.

Interestingly, 1,1'-biisoquinoline and 2,2'-biquinoline underwent a C–C bond cleavage with subsequent formation of the methylene-bridged products **9** and **10** in excellent yields, indicating that an unusual and facile *C*-nucleophile/*C*-nucleofuge displacement takes place under the reaction conditions (Scheme 3). Since substituted 1,1'-biisoquinolines and 2,2'-biquinolines can be prepared in a scalable manner from the corresponding *N*-oxides,⁷ this route offers additional flexibility in the synthesis of *ortho*-methylene-bridged *N*-heterobiaryls.

We have further investigated the reactions of quinoline and isoquinoline with other alkylmagnesium halides (Figure 2). The reactions did not produce *ortho*-methylene-bridged *N*-heterobiaryls, but instead afforded the corresponding 2-alkylquinolines (**25** and **26**) and 1-isopropylisoquinoline (**27**). These results are in line with the observation of TMEDA-catalyzed arylation of azines with arylmagnesium bromides reported by Da.⁸ No functionalization of the distal positions⁹ was observed for quinolines and isoquinoline. This direct alkylation reaction is complimentary to the deoxygenative *ortho*-alkylation of heterocyclic *N*-oxides.¹⁰

Several experiments were carried out to clarify the mechanism of the reaction. First, monitoring of the reaction of isoquinoline with methylmagnesium chloride in the presence of TMEDA in C₆D₆ at 50 °C by means of ¹H NMR spectroscopy identified several

intermediates along the reaction pathway (Scheme 4). Formation of the Grignard addition product **28**, as well as 1-methylisoquinoline (**29**) that arises from the loss of HMgX was observed. Further, magnesiated di(isoquinolin-1-yl)methane intermediate **30** was also detected. Interestingly, formation of 1,2-dihydroisoquinoline intermediate **31** was also observed. Addition of magnesium hydride species to pyridines is a reversible process.¹¹ Indeed, when 1-*d*₇-isoquinoline was heated with 25 mol% MgH₂¹² in the presence of TMEDA (1 equiv) in *d*₈-toluene for 2 h at 110 °C, 20% H/D exchange (40% after 21 h) took place in C1 position of isoquinoline, indicating that magnesium hydride addition to isoquinoline is reversible under the reaction conditions. Intermediate **31** may serve as a pool of soluble magnesium hydride species in solution. It is also possible that a hydride transfer takes place directly to isoquinoline from 1,2-dihydroisoquinoline intermediates **28** and **32**,¹³ facilitating their aromatization. In order to further investigate the formation and roles of magnesium hydride species in the methylenation process, the amount of hydrogen produced in the reaction of quinoline with methylmagnesium chloride in the presence of TMEDA in hexane at 120 °C was determined by means of gas chromatography.

Interestingly, hydrogen was formed even before quenching the reaction mixture with methanol (0.45 mmol H₂ per 1 mmol of quinoline), indicating that magnesium hydride participates in the deprotonation of intermediates **9** and **29** en route to magnesiated species **30** and **33**. Addition of methanol after the reaction led to generation of 0.7 mmol of hydrogen per 1 mmol of quinoline, in agreement with the observed 73% conversion of quinoline.

ortho-Methylene-bridged *N*-heterobiaryls **1** can be readily oxidized to the corresponding ketones that are useful bidentate chelators.¹⁴ For example, diquinolinylmethanes **16** and **17** were oxidized by air in the presence of potassium *tert*-butoxide to give ketones **34** and **35** in 95% and 78% yields, respectively (Scheme 5).

In conclusion, a simple, one-step synthesis of *ortho*-methylene-bridged biquinolines and biisoquinolines has been developed. The reaction is catalyzed by an organic base (TMEDA). Furthermore, the efficient split and merge methylenation of biquinolines and biisoquinolines by methylmagnesium chloride in the presence of TMEDA as a catalyst has also been described. *ortho*-Alkylation of quinoline and isoquinoline has been observed with other alkylmagnesium reagents. Mechanistic studies point to a reversible elimination of magnesium hydride species en route to *ortho*-methylene-bridged *N*-heterobiaryls. The methylene bridge in the products of methylenation can be readily oxidized by air in the presence of potassium *tert*-butoxide.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support by the Welch Foundation (AX-1788), NIGMS (SC3GM105579), UTSA, and the NSF (CHE-1455061) is gratefully acknowledged. Mass spectroscopic analysis was supported by a grant from the NIMHD (G12MD007591). We thank Prof. Donald M. Kurtz, Jr (UTSA) for access to a gas chromatograph in his laboratory.

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Figure 1.
Organocatalytic Synthesis of *ortho*-Methylene-Bridged *N*-Heterobiaryls

Figure 2.
Synthesis of 2-Alkylquinolines and 2-Alkylisoquinolines

Scheme 1. Direct Synthesis of *ortho*-Methylene-Bridged *N*-Heterobiaryls from *N*-Heterocycles

Scheme 2.
Synthesis of 4,4'-Methylene-Bridged *N*-Heterobiaryls

Scheme 3.

Split and Merge Synthesis of *ortho*-Methylene-Bridged *N*-Heterobiaryls from 2,2'-Biquinoline and 1,1'-Biisoquinoline

Scheme 5.

Oxidation of the methylene group in diquinolinylmethanes **16** and **17**

Table 1Reaction Conditions for the Synthesis of *ortho*-Methylene-Bridged *N*-Heterobiaryl^a

Entry	Amine (equiv)	X	Solvent	Time (h)	Temp (°C)	Yield (%)
1	–	Cl	hexane	2	120	7
2	TMEDA (1.3)	Cl	toluene	2	120	93
3	TMEDA (1.3)	Cl	hexane	2	120	78
4	DABCO (1.3)	Cl	hexane	2	120	7
5	PMDTA (1.3)	Cl	hexane	2	120	15
6	DMEDA (1.3)	Cl	hexane	2	120	0
7	TMEDA (0.2)	Cl	toluene	14	140	95
8 ^b	TMEDA (0.1)	Br	toluene	14	140	97
9 ^b	TMEDA (0.1)	I	toluene	14	140	65

^a Isoquinoline (2 mmol), MeMgX (3 equiv), solvent (2 mL), 1,4-Dimethoxybenzene was used as an internal standard added prior to work-up.^b 1 mL of toluene was used. PMDTA = *N,N,N',N',N''*-pentamethyldiethylenetriamine. DMEDA = *N,N'*-dimethylethylenediamine.