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Rapid, one-pot synthesis of α,α-disubstituted primary amines by the addition of Grignard reagents to nitriles under microwave heating conditions

Brian T. Gregg *, Kathryn C. Golden, John F. Quinn, Hong-Jun Wang, Wei Zhang, Ruifang Wang, Francis Wekesa, Dmytro O. Tymoshenko

AMRI, Medicinal Chemistry Department, 26 Corporate Circle, PO Box 15098, Albany, NY 12212-5098, USA

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ABSTRACT

A series of α,α-disubstituted amines have been prepared in a simple and efficient one-pot procedure by the addition of Grignard reagents to a series of aliphatic, aromatic, and heteroaromatic nitriles. Key to this reported procedure is the unprecedented addition of the Grignard reagent to the nitrile under heating by microwave irradiation which both significantly improves reaction yields and reduces reaction times. In general, the Grignard addition reaction is complete within 5–10 min at 100 °C followed by rapid reduction with sodium borohydride to give the target amines.

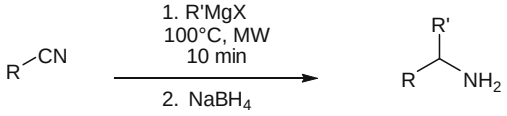
The importance of α,α-disubstituted amines and amides in biologically relevant pharmaceutical and agricultural compounds is well documented in the literature.[1] While there is a variety of commercially available α,α-disubstituted amines, we recently needed a set of non-commercially available compounds. Our motivation for preparing these unique amines stems from our on-going efforts to synthesize chemical libraries of medicinally relevant compounds.[2]

Among the myriad of synthetic methods for the preparation of amino groups, the reaction of nitriles with organometallics, followed by the reduction of the intermediate imine was first reported by Weiberth and Hall[3] and later modifications were reported by subsequent research groups.[4,5] While these procedures were adequately used to prepare a limited number of final targets, it became clear that the current state-of-the-art did not meet our needs. Due to the number of analogs that we needed to prepare (in excess of 25 novel α,α-disubstituted amines) we needed to avoid inconveniently long reaction times, the need for solvent exchange before the reduction step, poor to modest yields of product and/or limited substrate applicability. We therefore set out to develop and refine reaction protocols that allowed for the facile preparation of these amines. The procedures that we developed needed to be robust, tolerate a wide range of functionalities and, due to the number of entities to be prepared, operationally safe and simple.

As has been well documented over the last several years, microwave heating technology has revolutionized many synthetic procedures in the lab, enabling access to high temperatures and pressures that can dramatically shorten reaction times.[6] Additionally, microwave reactors are designed to work at high pressures and engineered to contain debris in the event of a failure. While the reaction of Grignard reagents with nitriles tends to proceed safely, we felt that microwave technology, with its inherent ability to increase reaction rates due to safely achieving higher reaction temperatures and pressures, would prove to be an asset for this work.

We report herein a one-pot, operationally simple, safe, and rapid protocol for the preparation of α,α-disubstituted primary amines from a wide range of substituted nitriles and Grignard reagents (Scheme 1). The Grignard reagents may be either commercially available or prepared in situ by metalation of aryl halides under microwave heating conditions.

Our initial experiments focused on the α-methylation of 2-naphthonitrile (**1**). Initially, the conditions reported by Prim and co-workers for the synthesis of heterobiarylmethylamines appeared promising.[5] After consulting the pertinent literature references, the most prevalent methodology for this conversion was low temperature addition of methylmagnesium bromide to 2-naphthonitrile, followed by replacement of the ethereal solvent with methanol and reduction with sodium borohydride. Initially we performed the reaction in diethyl ether at 0 °C, warmed to room temperature, and stirred for 4 h. Subsequent reduction was carried out with sodium borohydride in methanol at 0 °C overnight. Finally, after standard reaction workup the desired compound was isolated in 35% yield (Table 1, entry 1). Due to the number of amines that we wanted to prepare we felt that such a



Scheme 1.

* Corresponding author. Tel.: +1 518 512 2000; fax: +1 518 512 2079.
E-mail address: Brian.Gregg@amriglobal.com (B.T. Gregg).

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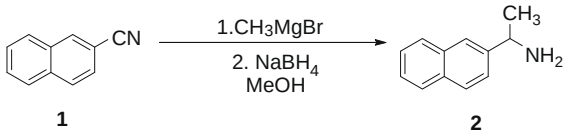
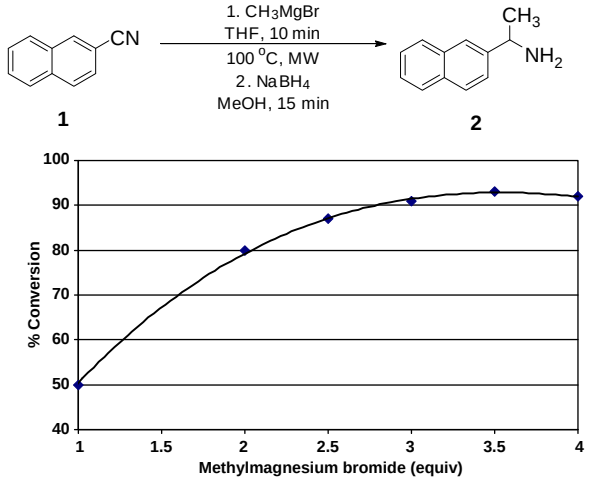
Table 1
Effect of reaction solvent and temperature on the extent of conversion of 2-naphthonitrile (**1**) to 1-(naphthalen-2-yl)ethanamine (**2**)



1 **2**

Entry	CH_3MgBr (equiv)	Solvent	Time (h)	Temp (°C)	Yield (%)
1	2.5	Et_2O	4 h, 12 h[a]	0 °C to rt	35
2	2.5	Et_2O	4 h, 12 h[a]	Reflux[b], rt	61
3	2.5	THF	4 h, 12 h[b]	Reflux[b], rt	74
4	2.5	THF	15 min, 5 min[c]	MW[d], 100 °C	88

[a] 4-h reaction time for CH_3MgBr addition to **1** followed by 12 h $NaBH_4$/MeOH reduction.
[b] Reaction heated by oil bath.
[c] 15-min reaction time for CH_3MgBr addition to **1** followed by 5 min $NaBH_4$/MeOH reduction.
[d] Reaction heated using microwave irradiation.



1 **2**

Graph 1. Effect of methylmagnesium bromide equivalents on the extent of conversion of 2-naphthonitrile (**1**) to 1-(naphthalen-2-yl)ethanamine (**2**). Conversion (%) determined from HPLC analysis (210 and 254 nm AUC) of crude reaction mixture.

low yielding procedure would be problematic; we therefore set out to develop a more robust and higher yielding reaction protocol.

In our first attempt at optimization, we choose to investigate the effect of temperature on the formation of the magnesium imine complex. After addition of the Grignard reagent to nitrile **1**, the reaction mixture was heated at reflux (35 °C) for 4 h. The reduction and workup were carried out as previously described to give **2** in a much higher yield (61%, Table 1, entry 2). This promising result led us to conclude that higher reaction temperatures may be key to obtaining improved yields. Substitution of THF (reflux at 67 °C) for diethyl ether (reflux at 35 °C) gave an additional improvement in yield (74%, Table 1, entry 3). A further convenience of this protocol is that the THF is not needed to be removed and replaced with methanol for the reduction step. The crude THF solution from the magnesium imine formation could simply be poured into a cooled methanol solution of sodium borohydride. This finding considerably simplified the reaction protocol.

Concurrent with investigating the use of THF, the effect of microwave heating on the magnesium imine formation reaction was explored. A significantly improved yield (88%) was observed for the conversion of **1** to **2** in THF under microwave heating (100 °C for 15 min prior to sodium borohydride reduction) (Table 1, entry 4).

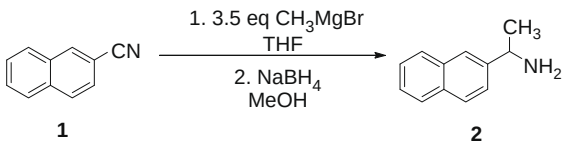
Next we determined the optimum amount of Grignard reagent. Our initial reaction conditions utilized 2.5 equiv of methylmagnesium bromide, giving, in the best case, an 88% isolated yield (Table 1, entry 4). Plotting the % conversion of **1** to **2** versus methylmagnesium bromide equivalents from 1.0 to 4.0 (Graph 1) clearly demonstrates that the maximum yield of **2** corresponds to 3.5 equiv of Grignard. Additional Grignard reagent (>3.5 equiv), was not detrimental to the reaction, but made isolation of the final material more problematic and was therefore avoided.

Having established the optimal solvent and number of equivalents of Grignard reagent for the formation of 1-(naphthalen-2-yl)ethanamine (**2**) from 2-naphthonitrile (**1**) we decided to re-examine the optimal time and temperature for the reaction. As shown in Table 2, optimal reaction conditions were determined to be heating under microwave irradiation at 100 °C for 10–15 min (Table 2, entry 2). It is noteworthy to stress that this not only represents a significant increase in overall isolated yield as compared to traditional reaction conditions, but also represents a dramatic reduction in overall reaction time; from in excess of 12 h to less than 30 min—including reaction workup. An added benefit of the protocol reported herein is that the air- and moisture-sensitive Grignard reagents undergo negligible decomposition, presumably due to the short reaction times, thereby negating the need for rigorous air- and moisture-sensitive handling techniques; no special precautions were taken for these reagents.

With optimized reaction conditions being obtained for the conversion of **1** to **2** (3.5 equiv Grignard reagent, microwave irradiation at 100 °C for 10 min with THF as reaction solvent),[7] we set out to explore the scope of this transformation with respect to substrate and reagents.

As shown in Table 3, the microwave enhanced reaction conditions work well for a wide range of aromatic and heteroaromatic nitriles including those possessing electron-withdrawing as well as electron-donating groups. Likewise, a wide array of Grignard reagents gave excellent results.[8] As a general rule, Grignard bromides gave higher yields than their chloride analogs. The nature of the Grignard reagent also showed some interesting results. The reaction of 4-fluorobenzyl magnesium chloride with **1** gave lower yields (50% and 15%, respectively, Table 3 entries 2 and 15) compared to that of benzylmagnesium chloride (87% and 60%, Table 3 entries 3 and 14). Regardless of the lower reactivity of 4-fluorobenzylmagnesium chloride, microwave heating conditions proved critical for the conversion of **10** to **17**, resulting in an isolated yield of 15% (Table 3, entry 15) compared to 0% at room temperature.

Table 2
Effect of time and temperature (both thermal and microwave irradiations) on the extent of conversion of 2-naphthonitrile (**1**) to 1-(naphthalen-2-yl)ethanamine (**2**)

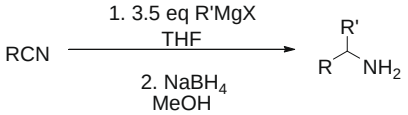


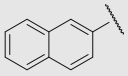
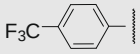
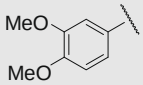
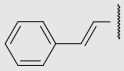
1 **2**

Entry	Grignard (equiv)	Time (min)	Temp (°C)	Conversion[a] (%)
1	3.5	5	MW 100 °C	78
2	3.5	10	MW 100 °C	97
3	3.5	15	MW 100 °C	93
4	3.5	120	25 °C	55
5	3.5	15	MW 60 °C	88
6	3.5	120	60 °C	85

[a] Determined by HPLC (210 and 254 nm AUC) of crude reaction mixture.

Table 3
Amine formation from addition of Grignard to nitriles under microwave heating and subsequent sodium borohydride reduction



Entry	Substrate RCN	Grignard R′MgX[e]	Product	Isolated yield[a] (%)
1	 **1**	Me	**2**	89 (88)[b]
2		4-F-benzyl	**3**	50
3		Benzyl	**4**	87
4		Ph	**5**	93
5		Et	**6**	85
6		*i*-Pr	**7**	76
7		Cyclo-propyl	**8**	95
8		Vinyl	**9**	0
9	 **10**	Me	**11**	85
10		Et	**12**	85
11		*i*-Pr	**13**	90 (30)[c]
12		Cyclo-propyl	**14**	90 (60)[c]
13		Ph	**15**	75
14		Benzyl	**16**	60 (23)[c]
15		4-F-benzyl	**17**	15 (0)[c]
16	 **18**	Ph	**19**	87
17		Benzyl	**20**	76
18	 **21**	Phenyl	**22**	84
19		Benzyl	**23**	76
20		Me	**24**	95 (26)[d]
21	 **25**	Me	**26**	68
22	 **27**	Me	**28**	95
23	 **29**	Me	**30**	17

[a] Unless otherwise noted, all reactions performed in tetrahydrofuran (3 mL), 1 mmol substrate, heated under microwave conditions at 100 °C for 10 min. Methanol was used as solvent for sodium borohydride reduction step.
[b] 5 mmol substrate scale.
[c] Reaction conducted at room temperature for 4 h.
[d] Literature reference.
[e] All Grignard regents were magnesium bromides except for phenyl and 4-fluorophenyl which were magnesium chlorides.

Disappointingly, vinylmagnesium bromide failed to generate any desired product (Table 3, entry 8).

Other examples where microwave enhanced imine formation led to higher yields of α,α-disubstituted amines are shown in Table 3 entries 11, 12, and 14 where isolated yields increased up to 60%.

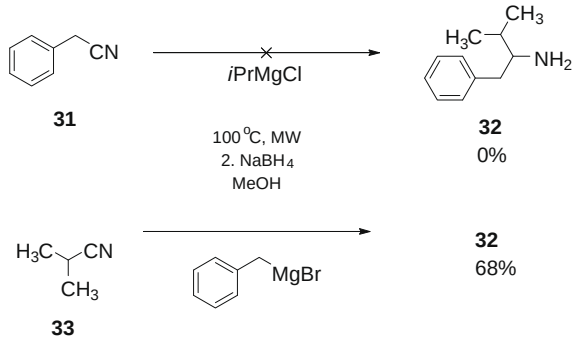
The preparation of 3,4-dimethoxy-α-methylbenzyl amine (**24**; Table 3, entry 20) was previously reported[9] to give 26% yield. With the conditions reported herein, a 95% yield was obtained. Cinnamonitrile (**29**), the double bond of which is known to react with Grignard reagents, was successfully converted, albeit in low yield (17%), to (*E*)-4-phenylbut-3-en-2-amine (**30**).

Furthermore, these reactions are amenable to scale-up. The conversion of **1** to **2** was increased from 1 mmol to 5 mmol under identical conditions, and gave comparable results.

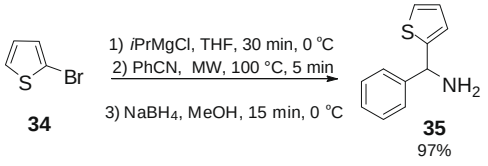
Unsurprisingly, the reaction between 2-phenylacetonitrile (**31**), and isopropylmagnesium chloride (**33**) failed to provide any 3-methyl-1-phenylbutan-2-amine (**32**). The reaction resulted in an intractable mixture, presumably due to the acidity of the benzylic position of **31** (Scheme 2). To access the substituted phenethylamine **32**, the functional groups were reversed; addition of benzylmagnesium bromide to isobutyronitrile gave **32** in a 68% yield.

While many Grignard reagents are commercially available, in order to prepare a set of truly unique α,α-disubstituted amines, the ability to incorporate in situ-generated Grignard reagents is essential. Using the methodology described by Prim[5] 2-bromothiophene (**34**) was pre-treated with isopropylmagnesium chloride in THF for 30 min at 0 °C (Scheme 3).[10] After allowing the metal–halogen exchange to occur, the in situ-generated reagent was added to benzonitrile and subjected to our standard microwave irradiation reaction protocol. Phenyl (thiophen-2-yl)methanamine (**35**) was cleanly isolated in excellent yield (97%).

In summary, we report herein the first application of heating with microwave irradiation to facilitate the formation of α,α-disubstituted amines. Our procedure utilizes widely available Grignard reagents and nitriles to prepare a wide range of α,α-disubstituted amines. Reactions are highly reproducible, afford moderate to high yields of the desired products for a number of different substrates, and have overall reaction times that have been dramatically decreased from several hours to less than 30 min. Key factors to the success of this protocol are the use of THF as a reaction solvent, using microwave heating conditions to rapidly generate the magnesium imine, and the observation that the THF need not be removed prior to the reduction of the imine with sodium borohydride in methanol. The utility of this procedure is greatly expanded by the ability to use Grignard reagents generated



Scheme 2.



Scheme 3.

in situ from heteroaromatic halides. A subsequent communication, which utilizes a similar procedure as described herein, involving microwave irradiation for the formation of α,α,α-trisubstituted amines is in preparation and will be reported on in due course.

Acknowledgments

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7. A representative procedure is as follows: 1-(Naphthalen-2-yl)ethanamine (**2**): A 5 mL Biotage microwave process tube with a magnetic stir bar was charged with 2-naphthonitrile (0.153 g, 1.0 mmol) and THF (3 mL) to which was added 3 M methylmagnesium bromide in diethyl ether (1.17 mL, 3.5 mmol). The resulting mixture was heated under microwave conditions at 100 °C for 10 min after which time it was carefully added to a freshly prepared solution of sodium borohydride (0.076 g, 2.0 mmol) in methanol (5 mL). After stirring for 5 min the reaction mixture was concentrated to dryness under reduced pressure onto silica gel (3 g). The crude product was purified by flash chromatography (20 g silica gel, methylene chloride to 80:20 methylene chloride/methanol) to give the desired product (0.152 g, 89%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (3H, d, J = 6.6 Hz), 4.29 (1H, q, J = 6.6 Hz), 7.41–7.51 (3H, m), 7.79–7.84 (4H, m); ESI MS m/z 172 $[M+H]^+$; HPLC >99% (AUC).
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10. *A representative procedure is as follows*: Phenyl(thiophen-2-yl)methanamine (**35**): A 5 mL Biotage microwave process tube with stir bar was charged with 2-bromothiophene (0.570 g, 3.5 mmol) and THF (3 mL) to which was added 2 M isopropylmagnesium chloride in THF (1.75 mL, 3.5 mmol). The resulting mixture was stirred at 0 °C for 30 min after which time benzonitrile (102 μL, 1.0 mmol) was added. The resulting mixture was heated under microwave conditions at 100 °C for 5 min after which time it was carefully added to a freshly prepared solution of sodium borohydride (0.076 g, 2.0 mmol) in methanol (5 mL) at 0 °C. After stirring for 15 min the reaction mixture was concentrated to dryness under reduced pressure onto silica gel (3 g). The crude product was purified by flash chromatography (20 g silica gel, methylene chloride to 80:20 methylene chloride/methanol) to give the desired product (0.183 g, 97%) as a light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.93 (2H, s), 5.41 (1H, s), 6.82 (1H, d, J = 3.5 Hz), 6.91 (1H, t, J = 3.5 Hz), 7.20 (1H, d, J = 3.8 Hz), 7.27 (1H, d, J = 7.1 Hz), 7.34 (2H, t, J = 7.0 Hz), 7.41 (2H, d, J = 6.9 Hz); ESI MS m/z 190 $[M+H]^+$; HPLC >99% (AUC).