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Rapid Ti(O*i*-Pr)$_4$ facilitated synthesis of α,α,α-trisubstituted primary amines by the addition of Grignard reagents to nitriles under microwave heating conditions

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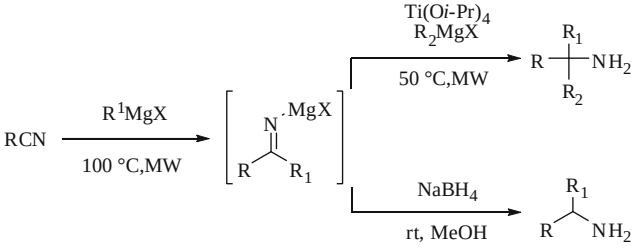
ABSTRACT

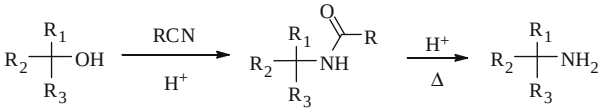
A series of carbinamines (α,α,α-trisubstituted amines) have been prepared in a simple and efficient one-pot procedure by the addition of Grignard reagents to a series of aliphatic, aromatic and heteroaromatic nitriles. The resulting magnesium imines are subsequently converted to the desired amine after treatment with Ti(O*i*-Pr)$_4$ and additional microwave heating. Key to this procedure is the use of microwave heating for both steps of the reaction protocol, which significantly improves both reaction yields and reduces reaction times. In general, the Grignard addition reaction is complete within 5–10 min at 100 °C followed by conversion with Ti(O*i*-Pr)$_4$ and additional microwave heating to give the target amines in good yields.

Considerable attention has been focused on the identification, preparation and use of 'privileged structures' in chemical library design. The use of novel and medicinally relevant fragments, which impart diversify on the core motif, are equally important for the success of the drug discovery effort. The use of α,α-disubstituted and α,α,α-trisubstituted amines (carbinamines) and amides thereof are excellent examples of compounds that have found much utility in pharmaceutical applications.[1] We have recently reported a rapid, one-pot synthesis of α,α-disubstituted primary amines by the addition of Grignard reagents to nitriles under microwave heating conditions followed by sodium borohydride reduction (Scheme 1).[2] Herein, we expand the scope of our work to the formation of α,α,α-trisubstituted amines. Both reactions rely upon the addition of a Grignard reagent to a nitrile, yielding a magnesium–imine intermediate. A key observation from our previous work was that microwave heating[3] significantly accelerated the formation of this magnesium–imine complex.

The classical method for the synthesis of this class of amines is the Ritter reaction of tertiary alcohols (Scheme 2).[4] This approach suffers from a number of drawbacks, including strongly acidic conditions for the carbocation addition to the nitrile as well as the harsh reaction conditions required to hydrolyze the intermediate amide to the amine. There are several alternate methods available for the synthesis of carbinamines, generally based on modification the procedure reported by Ciganek,[5,6] involving the addition of organocerium reagents (prepared by the addition of alkyllithium reagents to cerium(III) chloride) to nitriles and ketamines. An alternate approach reported by Sokolov, de Meijere[7] and co-workers uses Grignard reagents and Ti(O*i*-Pr)$_4$ to prepare carbinamines from nitriles. While both of these procedures reportedly worked well for some substrates, they also suffer from a number of drawbacks, including inconveniently long reaction times, low temperature conditions, poor to modest yields of product and/or limited substrate scope. We therefore set out to apply our recently reported optimized conditions for the formation of α,α-disubstituted



Scheme 1.



Scheme 2.

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amines to the Ti(O*i*-Pr)$_4$ mediated synthesis of α,α,α-trisubstituted amines.

We have previously disclosed the experiments used to optimize the synthesis of α,α-disubstituted amines.[2] In that manuscript, we concluded that the yield of the desired amine was dependent upon the extent of formation of the key magnesium–imine complex resulting from the addition of a Grignard reagent to a nitrile. Specifically, maximum yields were obtained with microwave heating at 100 °C for 5–10 min after addition of the Grignard reagent. Additionally, we reported that THF was necessary due to its increased solvating ability and being able to safely achieve higher reaction temperatures when using microwave heating. We reasoned that our improved procedures would be applicable to this transformation as well. The overall transformation involves a two-step, one-pot synthesis. The first step is the Grignard addition to the nitrile substrate to yield a magnesium–imine complex. The following step is the Ti(O*i*-Pr)$_4$-mediated addition of a second equivalent of Grignard reagent to give the desired amine. In cases where excess Grignard reagent is used in the first step (R^1MgX), the resulting α,α,α-trisubstituted amines bear the same R^1 groups on the tertiary alpha-carbon ($R^1 = R^2$). Amines differentially substituted at the α-carbon ($R \neq R^1 \neq R^2$) are achieved by the addition of R^1MgBr (1.2 equiv) and followed by R^2MgBr (2.0 equiv) after the initial magnesium–imine complex formation.

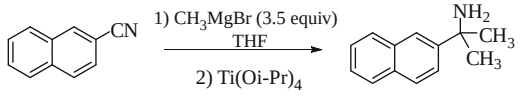
Optimization of the reaction conditions was conducted using 2-naphthonitrile (**1**) and methyl magnesium bromide in THF. It was previously reported[7] that diethyl ether was the solvent of choice for the Ti(O*i*-Pr)$_4$-mediated addition of Grignards to nitriles and that with THF products 'formed in very low yield, if at all.' Indeed in some instances diethyl ether is an acceptable solvent for this transformation; however the utility of Et_2O is limited to the simplest of organic molecules due to its poor solvating capability and inability to achieve high reaction temperatures that are required. Fortunately, we have demonstrated the THF is an acceptable reaction solvent substitute.

The effect of time and temperature (using both traditional and microwave heating) on the extent of conversion of 2-naphthonitrile (**1**) to α,α-dimethylnaphthylamine (**2**) are summarized in Table 1. At room temperature conditions, a modest 40% yield of **1** to **2** was observed (Table 1, entry 1). Yields steadily increased up to 77%, (Table 1, entry 5) when microwave heating was utilized. It is especially important to note that conducting the first step at a higher temperature available only with microwave heating was critical to achieving improved yields. Conventional heating at reflux for 3 h (step 1) followed by the addition of Ti(O*i*-Pr)$_4$ and further conventional heating for 12 h at 50 °C (step 2) afforded a 63% yield of **2** (Table 1, entry 3). Repeating the same reaction with microwave heating at 100 °C for 10 min (step 1), followed by heating at 50 °C for 1 h after Ti(O*i*-Pr)$_4$ addition (step 2), showed a significant yield improvement (77%, Table 1, entry 5).

Microwave heating is less crucial for the second step. Use of either microwave or traditional oil-bath heating at 50 °C gave comparable results (Table 1, entries 5 and 6). As expected, if no heating was applied during the Ti(O*i*-Pr)$_4$ step, a diminished yield was obtained (<70%, Table 1, entries 4 and 7). While the reaction of Grignard reagents with nitriles generally proceeds without incident, we chose to conduct all of our reactions under microwave heating for reasons of convenience and safety.[8]

Significant advantages with our reported procedures over previous reports[6b] are that not only increased isolated yield is obtained, but also a significant reduction in overall process time (from in excess of 12 h to less than 1.5 h) is achieved allowing for a more rapid

Table 1
Effect of time and temperature (both thermal and microwave irradiation) on the extent of conversion of 2-naphthonitrile (**1**) to α,α-dimethylnaphthyl amine (**2**)

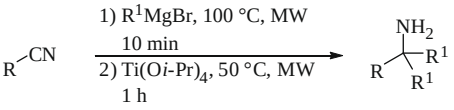


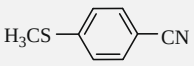
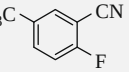
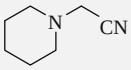
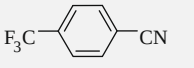
1 **2**

Entry	Time, temp (°C) *Step 1*[a]	Time, temp (°C) *Step 2*[a]	% Yield[b]
1	3 h, rt	12 h, rt	40
2	3 h, rt	1 h, MW[c] 50 °C	46
3	3 h, bath reflux[d]	12 h, bath 50 °C[d]	63
4	10 min, MW[c] 100 °C	12 h, rt	68
5	10 min, MW[c] 100 °C	1 h, MW[c] 50 °C	77
6	10 min, MW[c] 100 °C	1 h, bath 50 °C[d]	75
7	10 min, MW[c] 100 °C	1 h, rt	60

[a] Time and temperature for each step of the synthesis are reported. Step 1 refers to the CH_3MgBr (3.5 equiv) addition to **1**, Step 2 refers to the subsequent addition of Ti(O*i*-Pr)$_4$.
[b] Isolated yields reported.
[c] Reaction heated using microwave irradiation.
[d] Reaction heated by oil bath.

Table 2
Amine formation from double Grignard addition to nitriles under microwave heating



Entry	Substrate (1 equiv)	R^1MgBr (3.5 equiv)	Product	Isolated yield[a]
1	2-Naphthonitrile **1**	Me	**2**	77%
2	Benzonitrile **3**	Me	**4**	65% (44%)[b]
3	**3**	Ph	**5**	57% (55%)[b] (36%)[c]
4	**3**	Et	**6**	30% (60%)[b] (35%)[c]
5	 **7**	Me	**8**	78%
6	2-Furonitrile **9**	Me	**10**	80% 76%[d]
7	 **11**	Me	**12**	79%
8	2-Fluorobenzonitrile **13**	Me	**14**	69%
9	2-Thiophenecarbonitrile **15**	Me	**16**	82% (25%)[b]
11	 **17**	Me	**18**	35%
12	 **19**	Me	**20**	61%
13	4-Cyanopyridine **21**	Me	**22**	72%
14	Isopropylnitrile **23**	Me	**24**	59% (27%)[b]
15	Cyclohexylnitrile **25**	Me	**26**	75%

[a] Unless otherwise noted, all reactions performed in tetrahydrofuran (5 mL), 1 mmol substrate, product was isolated as hydrochloride.
[b] Reported yield in reference.
[c] Observed yield using reference procedure.
[d] 5 mmol substrate scale.

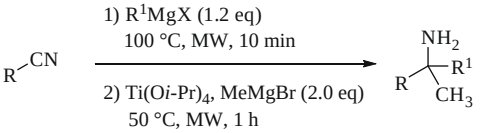
synthesis of multiple analogues. Rigorous air and moisture sensitive handling techniques are not necessary due to the rapid reaction times and sealed atmosphere achieved when using microwave vials as the reaction apparatus. Table 2 summarizes the scope of substrates and Grignards that can be used within the scope of this reaction protocol.[9] The substrates include a wide range of aromatic and heteroaromatic nitriles and nitriles with electron-withdrawing as well as electron-donating groups. Likewise, for all symmetrical amines ($R^1 = R^2$) our set of Grignard reagents gave acceptable yields and purity.[10] When compared to previously reported literature results, our procedure showed significant improvements in yield; conversion of **3** to **4** was achieved in 65% compared to 44%[7b] yield in the literature. Similarly, improved yields were achieved for **15** to **16** (82% vs 25%[11]) and **23** to **24** (59% vs 27%[12]) (Table 2, entries 2, 9 and 14). Disappointingly, benzylmagnesium bromide failed to generate any desired product upon reaction with **1**. Additionally, we observed a 30% isolated yield of **6** from the addition of ethylmagnesium bromide to benzonitrile (Table 2, entry 4); the reported literature yield for this transformation (utilizing diethylether, not THF) is 60%.[7a] Even using diethyl ether as a solvent we were unable to reproduce this result; obtaining a modest 35% yield of product. Both Szymoniak[13] and de Meijere reported that ethylmagnesium Grignard reagents in the presence of Ti(O*i*-Pr)$_4$ may form cyclopropyl species under certain conditions which may account for our observations.

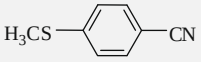
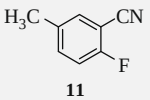
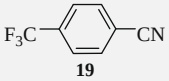
The developments of procedures that are not only reproducible, but also scalable were paramount to our reaction protocol development. It was successfully demonstrated that the scale of the reaction was limited only by the constraints of the microwave reactor. Specifically, the reaction of 2-furonitrile **9** to **10** was increased from 1 mmol to 5 mmol scale under identical reaction conditions, giving comparable yield and purity results (Table 2, entry 6).

Access to differentially substituted α,α,α-trisubstituted amines ($R \neq R^1 \neq R^2$) is also possible by careful control of Grignard addition and stoichiometry (Table 3). Specifically, R^1MgBr (1.2 equiv) is first added to the nitrile substrate. After microwave heating for 10 min at 100 °C, both Ti(O-*i*Pr)$_4$ and R^2MgBr (2.0 equiv) are added and the reaction mixture was heated for an additional 1 h at 50 °C.[14] Using this procedure, a wide array of carbinamines are accessible (Table 3) in moderate to high yield (25–71%).

To further expand the scope of accessible α,α,α-trisubstituted amines beyond those obtained when using commercially available Grignard reagents we successfully employed the methodology described by Prim[15] to prepare in situ generated Grignard reagents. Specifically, 2-bromothiophene (**44**) was pre-treated with *iso*-propylmagnesium chloride in THF for 30 min at 0 °C. 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[16] 1-(naphthalen-2-yl)-1-(thiophen-2-yl)ethanamine (**47**) was cleanly isolated in moderate yield (42%, Table 4, entry 1).

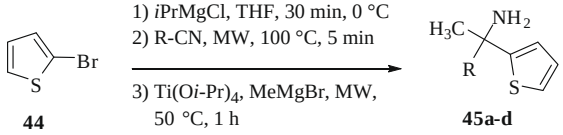
Table 3
Amine formation from admixed Grignard addition to nitriles under microwave heating



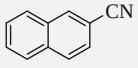
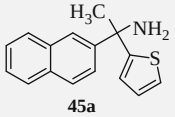
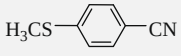
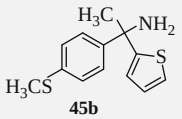
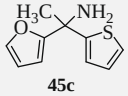
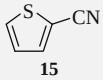
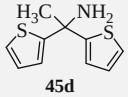
Entry	Substrate	R^1MgBr	Product	Isolated yield[a] (%)
1	2-Naphthonitrile **1**	Ph	**27**	70
2	**1**	Et	**28**	36
3	**1**	*i*-Pr	**29**	39
4	**1**	Benzyl	**30**	25
5	**1**	Cyclopropyl	**31**	43
6	Benzonitrile **3**	Ph	**32**	62
7	**3**	Et	**33**	40
8	 **7**	Ph	**34**	42
9	**7**	Et	**35**	41
10	2-Furonitrile **9**	Ph	**36**	51%
11	**9**	Et	**37**	38
12	 **11**	Ph	**38**	48
13	2-Thiophenecarbonitrile **15**	Ph	**39**	71
14	**15**	Et	**40**	47
15	 **19**	Ph	**41**	60
16	Isopropylnitrile **23**	Ph	**42**	64
17	Cyclohexylnitrile **25**	Ph	**43**	58

[a] All reactions performed in tetrahydrofuran (5 mL), 1 mmol substrate, product was isolated as hydrochloride.

Table 4
Amine formation from the in situ generated Grignard addition to nitriles under microwave heating



44 **45a-d**

Entry	Substrate	Product	Isolated yield[a] (%)
1	 **1**	 **45a**	42
2	 **7**	 **45b**	32
3	 **9**	 **45c**	61
4	 **15**	 **45d**	44

[a] All reactions performed in tetrahydrofuran (5 mL), 1 mmol substrate, product was isolated as hydrochloride.

In summary, we report herein the feasible and scalable procedure for the formation of α,α,α-trisubstituted amines and the first application of microwave irradiation heating to facilitate the product formation. Our procedure utilizes both commercially available Grignard reagents as well as those generated in situ from heteroaromatic halides. Reactions are highly reproducible, afford moderate to high yields of the desired products, typically better than previously reported for a number of different substrates. Additionally, overall reaction times have been dramatically decreased from in excess of 12 h to less than 2 h for even the most difficult of substrates. 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 key magnesium–imine intermediate complex, and the observation that all steps of the reaction can be conducted in a one-pot two-step synthetic procedure.

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8. Microwave reactors are designed to work at high pressures and temperatures and are engineered to contain debris in the event of a reaction vessel failure.
9. *A representative procedure is as follows*: 2-(4-(Methylthio)phenyl)propan-2-amine hydrochloride (**8**): A 20 mL Biotage microwave process tube with stir bar was charged with 4-(methylthio)benzonitrile (0.149 g, 1.0 mmol) and tetrahydrofuran (5 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 Ti(O*i*-Pr)$_4$ (0.293 mL, 1.0 mmol) was carefully added. After heating under microwave irradiation at 50 °C for 1 h, brine (10 mL) was added. The mixture was extracted with CH_2Cl_2 (50 mL), the organic layer was washed with brine (20 mL × 2), separated, dried over Na_2SO_4 and filtered. 1 N HCl in diethyl ether (1 mL) was added to the filtrate and the filtrate was concentrated to dryness under reduced pressure. The crude product was triturated with diethyl ether to give the desired product (0.170 g, 78%) as off white solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.52 (3H, br s), 7.48 (2H, d, J = 8.7 Hz), 7.32 (2H, d, J = 8.7 Hz), 2.48 (3H, s), 1.61 (s, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 139.3, 137.8, 125.8, 125.7, 55.1, 27.4, 14.6; APCI MS m/z 165 $[M+1-NH_3]^+$; HPLC 95.3% (AUC).
10. All compounds were fully characterized by ^{1}H and ^{13}C NMR and HPLC/APCI-MS anaylses and compared to the literature results for known compounds.
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14. *A representative procedure is as follows*: 1-Phenyl-1-(thiophen-2-yl)ethanamine hydrochloride (**39**): A 20 mL Biotage microwave process tube with stir bar was charged with thiophene-2-carbonitrile (109 mg, 1.0 mmol) and tetrahydrofuran (5 mL) to which was added 1 M phenylmagnesium bromide in tetrahydrofuran (1.2 mL, 1.2 mmol). The resulting mixture was heated under microwave irradiation at 100 °C for 10 min after which time Ti(O*i*-Pr)$_4$ (0.293 mL, 1.0 mmol) and 3 M methylmagnesium bromide in diethyl ether (0.667 mL, 2.0 mmol) were carefully added. After heating under microwave irradiation at 50 °C for 1 h, brine (10 mL) was added. The mixture was extracted with CH_2Cl_2 (50 mL), the organic layer was washed with brine (20 mL × 2), separated, dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude product was purified by flash chromatography (12 g silica gel, methylene chloride to 95:5 methylene chloride/methanol), 1 N HCl/diethyl ether (1 mL) was added to the combined fractions and then concentrated to dryness under reduced pressure to give the desired product (0.170 g, 71%) as off white solid: ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.22 (3H, br s), 7.60 (1H, d, J = 5.0 Hz), 7.50–7.39 (5H, m), 7.25 (1H, d, J = 4.0 Hz), 7.10 (1H, dd, J = 5.0, 4.0 Hz), 2.09 (3H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 146.6, 142.1, 128.5, 128.3, 127.1, 126.7, 126.6, 125.8, 58.5, 28.3; APCI MS m/z 187 $[M+1-NH_3]^+$; HPLC 95.5% (AUC).
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16. *A representative procedure is as follows*: 1-(Furan-2-yl)-1-(thiophen-2-yl)ethanamine hydrochloride (**45c**): A 20 mL Biotage microwave process tube with stir bar was charged with 2-bromothiophene (0.245 g, 1.5 mmol) and tetrahydrofuran (5 mL) to which was added 2 M *iso*-propylmagnesium chloride in tetrahydrofuran (0.75 mL, 1.5 mmol). The resulting mixture was stirred at 0 °C for 30 min after which time furan-2-carbonitrile (93 mg, 1.0 mmol) was added. The resulting mixture was heated under microwave conditions at 100 °C for 10 min after which time Ti(O*i*-Pr)$_4$ (0.293 mL, 1.0 mmol) and 3 M methylmagnesium bromide in diethyl ether (0.667 mL, 2.0 mmol) were carefully added. After heating under microwave irradiation conditions at 50 °C for 1 h, brine (10 mL) was added. The mixture was extracted with CH_2Cl_2 (50 mL), the organic layer was washed with brine (20 mL × 2), separated, dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude product was purified by flash chromatography (12 g silica gel, methylene chloride to 95:5 methylene chloride/methanol), 1 N HCl/diethyl ether (1 mL) was added to the combined fractions and then concentrated to dryness under reduced pressure to give the desired product (0.140 g, 61%) as light brown solid: ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.28 (br, s, 3H), 7.80 (1H, d, J = 1.5 Hz), 7.60 (1H, dd, J = 5.0, 1.0 Hz), 7.28 (1H, dd, J = 3.5, 1.0 Hz), 7.09 (1H, dd, J = 5.0, 3.5 Hz), 6.60 (1H, d, J = 3.5 Hz), 6.56 (1H, dd, J = 3.5, 1.5 Hz), 2.05 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 153.0, 143.8, 143.6, 127.1, 126.7, 126.4, 110.8, 107.9, 54.4, 25.9; APCI MS m/z 177 $[M+1-NH_3]^+$; HPLC 95.9% (AUC).