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A SIMPLE AND HIGHLY EFFICIENT SYNTHESIS OF QUINOLINE TERTIARY AMINES CATALYZED BY HUNIG'S BASE

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Abstract
Substituted 2-methyl-4-chloroquinoline 4**(a-d)** were treated with secondary amines in DMF at RT for 3hrs in the presence of Hunig's base to obtain quinoline tertiary amines **5(a-p).** The reactions went smoothly without forming any quaternary ammonium salt as side products.

Keywords
2-methyl-4-chloro quinoline tertiary amines, Hunig's base, cyclic amines, DMF, R.T

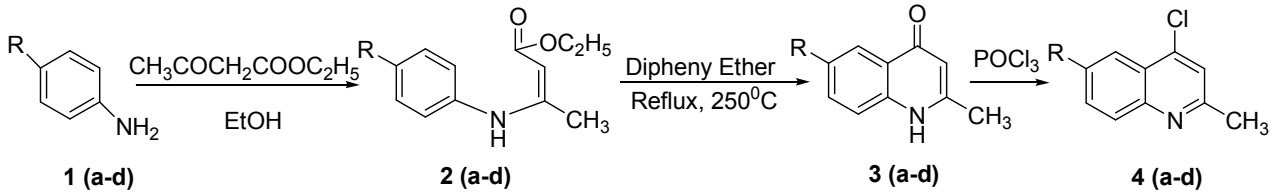
Introduction

Amines are of fundamental interest in many fields of chemistry, as evidenced by increase in modern methods now available for their synthesis[I]. Due to their unique fundamental and biological activities, amines have played a very important role in drug synthesis and are used to treat a variety of diseases.[II] Among amines, tertiary amines are prepared by N-alkylation of secondary amines using alkyl/aryl halides[III-V] and continues to be focus of numerous studies.[VI] However, this method has limitations since it results in the formation of quaternary ammonium salts as over alkylated products leaving behind the unconverted secondary amine.[VII-IX] Another method, reported in literature[IX] describes the use of excess triethylamine for N-alkylation of secondary amines with alkyl halides using metal amides. This method involving the use of metal amides is also problematic for the direct synthesis of highly functionalized tertiary amines, particularly if the secondary amine or alkyl halide contains acidic functional groups. Yet other alternative methods include reductive amination[X], reductive and catalytic alkylation[XI], Mannich and Petasis reactions[XII], and metal induced amination of alkenes and alkynes[XIII]. These methods, though they are useful, they suffer from some limitations like low catalytic activity, relatively lower yields and longer reaction times.

We now wish to report reaction of 4-chloro-2-methylquinolines with secondary cyclic amines in the presence of Hunig's base in DMF at RT.

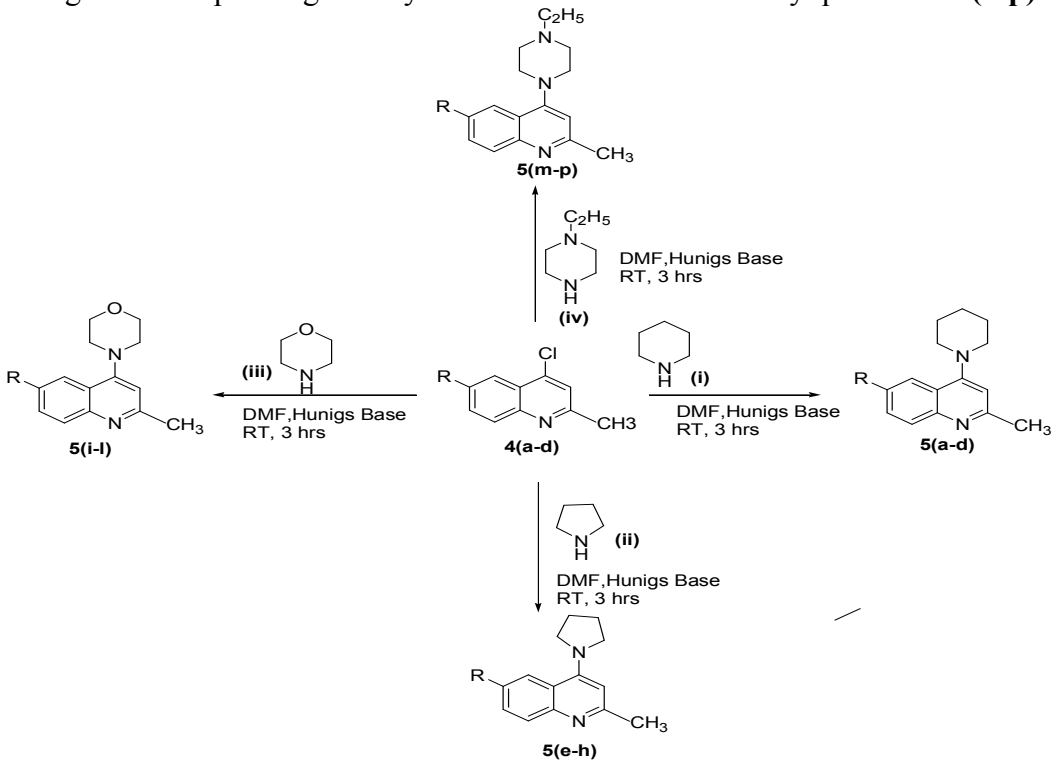
Results and Discussions

Anilines **1(a-d)** were treated with ethyl acetoacetate in refluxing ethanol to obtain enamine derivatives **2(a-d)** which were cyclized in refluxing diphenylether at 250^0C resulting in 2-methylquinoline-4-ones **3(a-d)**. The latter on reaction with $POCl_3$ at 100^0C gave the previously reported[XVII] 4-chloro-2-methylquinolines **4(a-d) (Scheme I).**



Scheme – I

In a typical experiment an equimolar mixture of **4(a-d)** and different secondary amines were mixed with catalytic amounts of Hunig's base in DMF at room temperature but the reaction did not complete even after 5 hrs. However, reactions were completed smoothly when 1mmol of Hunig's base (diisopropylethylamine) was used **(Table 1).** The progress of the reaction was monitored by TLC. Hunig's base was earlier used for Heck reaction[XIV] synthesis of indolizidines[XV] and for direct N-alkylation of secondary amines with alkyl halides[XVI]. The significance of Hunig's base in comparison to use of other bases like, triethylamine, trimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline is showed in **Table 2**. Different solvents were also evaluated including methylene dichloride, acetonitrile, acetone and methanol (**Table 3**). The present method is highly efficient and fast, ran smoothly at room temperature for 3 hrs yielding the corresponding tertiary amino derivatives of 2-methylquinolines **5(a-p)**.



Scheme – II

It may be mentioned here that most of the N-alkylation reactions utilized phase transfer catalysts like TBAB, here in this method there is no need to use biphasic systems with TBAB. Hunig's base acts as an auxiliary base whose nucleophilicity is low due to steric hindrance, enabling its use in chemical reactions as a good base or as "proton sponge". Unwanted secondary reactions do not occur because, unlike similar reagents such as di- and triethylamine which have both nucleophilic and basic properties, Hunig's base is not capable of replacing the intended reaction partner due to its built-in steric hindrance (**Table 2**). The auxiliary base must not be nucleophilic enough to act on the alkylating agent. Another advantage of Hunig's base for its applications in chemical synthesis is that it is readily soluble in many organic solvents. Thus, this low-nucleophilic strong base (**Table 4**) forms a salt with the released hydrogen chloride allowing the reaction to proceed under mild reaction conditions.

Table 1. Synthesis of Quinoline tertiary amines **5 (a-p)** from **4(a-d)** using Hunig's base at R.T

S.No	Reactant (R)	Secondary amine	Product	Yield (%)
1.	**4a** (**R** = OMe)	Pyrrolidine	**5a**	95
2.	**4b (R** = Cl)	Pyrrolidine	**5b**	92
3.	**4c (R** = F)	Pyrrolidine	**5c**	94
4.	**4d (R** = CH_3)	Pyrrolidine	**5d**	90
5.	**4a** (**R** = OMe)	Piperidine	**5e**	91
6.	**4b (R** = Cl)	Piperidine	**5f**	88
7.	**4c (R** = F)	Piperidine	**5g**	90
8.	**4d (R** = CH_3)	Piperidine	**5h**	86
9.	**4a** (**R** = OMe)	Morpholine	**5i**	85
10.	**4b (R** = Cl)	Morpholine	**5j**	84
11.	**4c (R** = F)	Morpholine	**5k**	88
12.	**4d (R** = CH_3)	Morpholine	**5l**	85
13.	**4a** (**R** = OMe)	N-Ethylpiperazine	**5m**	84
14.	**4b (R** = Cl)	N-Ethylpiperazine	**5n**	80
15.	**4c (R** = F)	N-Ethylpiperazine	**5o**	83
16.	**4d (R** = CH_3)	N-Ethylpiperazine	**5p**	84

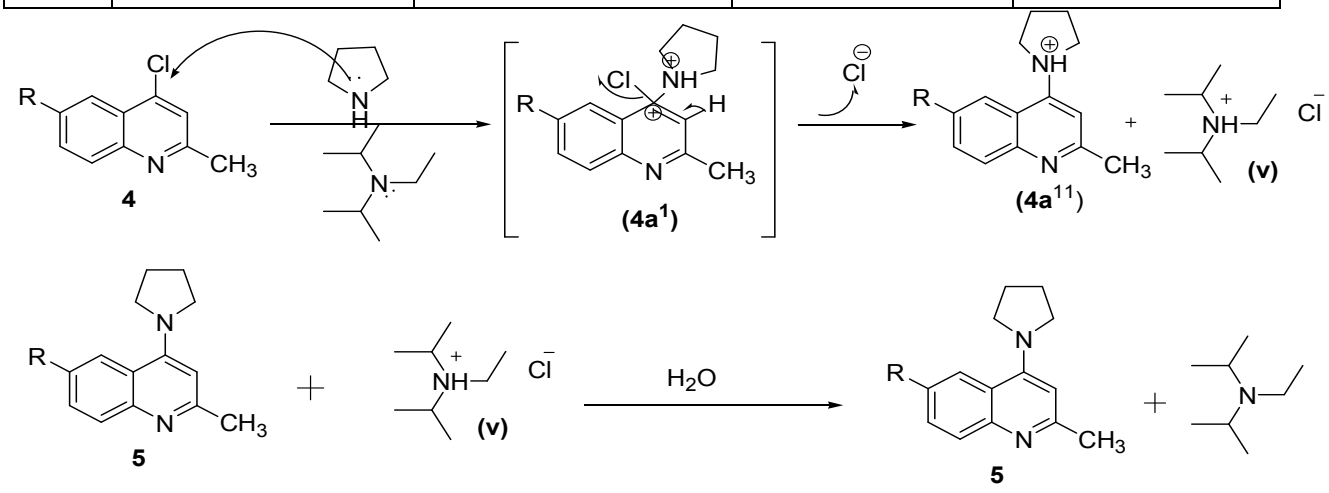
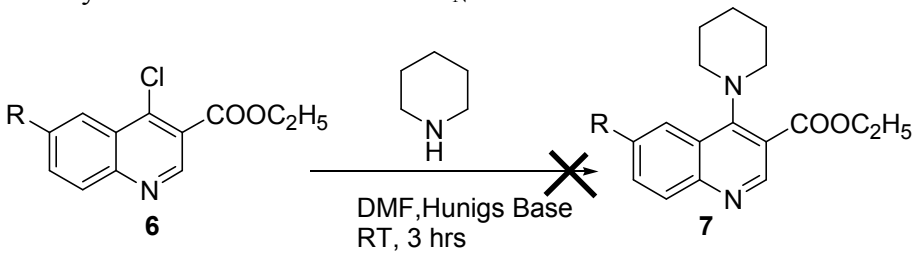


Fig 1: *Plausible mechanism for the formation of tertiary amines* ***5(a-p)***

There are two possibilities in the mechanism; the reaction can proceed via aromatic S_N1 or S_NAr (addition-elimination) mechanism. The former is also a two-step mechanism involving reversible dissociation of **4a** into the chloride ion & the quinolinyl carbocation in the first step. The latter then undergoes combination, in the second step with the secondary amine forming **5a** with the concomitant, loss of proton to the Hunigs's base. But this mechanism, in the present case, is considered to be less probable since when an alcoholic solution of **4a** was treated at RT with an alcoholic solution of $AgNO_3$, no precipitate of AgCl was formed even after 3 hrs. In the second mechanism, i.e. the S_NAr type, the secondaryamine (ii) attacks the substrate **4a** forming the dipolar adduct **4a**[1] which losses the chloride ion to form the intermediary ammonium ion **4a**[XI] that gives up the proton to the resulting Hunig's base resulting in **5** in an overall addition-elimination pathway. Indirect evidence for the S_NAr mechanism comes from the following fact,



Scheme - III

Similar strategy, we tried to apply to the other moiety like ethyl-4-chloroquinoline-3-carboxylate **6,** which prepared from the literature reported[XVIII] procedure. But unfortunately the reaction was not succeeded and we could not get the desired products. Hence this may be concluding that due to the steric hinderence of secondary amines and carboxylate group of ethyl-4-chloroquinoline-3-carboxylate. (Scheme - III)

Table 2. Comparison & Optimization data of bases at room temperature for **4a & i**

S.No	Solvent	Base	Time (h)	Yield (%)
1	DMF	Hunig's base	**3 hrs**	**90**
2	DMF	Triethylamine	**6 hrs**	**55**
3	DMF	Trimethylamine	**6 hrs**	**50**
4	DMF	4-dimethylaminopyridine	**6 hrs**	**50**
5	DMF	N,N-dimethylaniline	**6 hrs**	**45**

Table 3: Comparison and optimization data of solvent systems for **4a & i**

S.No	Solvent	Base	Time (h)	Yield (%)
1	Methylene Chloride	Hunig's Base	4 hrs	65
2	Acetonitrile	Hunig's Base	5 hrs	75
3	Acetone	Hunig's Base	3 hrs	70
4	Methanol	Hunig's Base	4 hrs	70
5	**DMF**	**Hunig's Base**	**3 hrs**	**90**

Table 4: Comparison of basic strength based on pKa Values

S.No	Base	pKa Value
1	Hunig's base	11.4
2	Triethylamine	10.7
3	Trimethylamine	9.87
4	4-dimethylaminopyridine	9.7
5	N,N-dimethylaniline	5.1

Experimental Section

General

All the reagents used in this work were obtained from commercial suppliers. Solvents were freshly distilled before being used. Melting points were determined using a Buchi Melting Point apparatus and are uncorrected. The progress of the reaction was monitored by Thin-layer chromatography (TLC) performed on silica gel G (Merck), and spots were exposed to iodine vapour or UV light. IR spectra were recorded by using KBr disc on a Perkin-Elmer 240c analyzer. ^{1}H NMR spectra were recorded on Brucker DPX-400 at 400-MHz (chemical shifts in δ, ppm) and Mass spectra on an Agilent LC-MS instrument giving only M+ values in Q+1 mode.

General Procedures.

Secondary amine (1mmol), *N,N*-diisopropylethylamine (1 mmol), 4-chloro-2-methylquinoline (1mmol) and 10ml of DMF were placed in a round bottom flask and stirred at room temperature for 3 hr. After completion of the reaction (which was monitored by TLC) the reaction mixture was poured on ice-cold water and neutralized with NH_3 solution, further stirred well for 10 more minutes. The solid which is precipitated out is filtered and dried which is further recrystallized from ethanol.

5a: ^{1}H- NMR (DMSO-d_6, 400 MHz): δ 1.8(s, 3H, -C**H$_3$**), 2.2-2.4 (m, 10H, -$(CH_2)_5$), 3.9 **(**s**,** 3H, -OCH3), 6.8-7.8(4H, Ar-H, m) ; $[M+H]^+$:. **256**

5b: ^{1}H- NMR (DMSO-d_6, 400 MHz): δ 1.9(s, 3H, -C**H$_3$**), 2.1-2.2 (m, 10H, -$(CH_2)_5$), 6.9-7.6(4H, Ar-H, m) ; $[M+H]^+$:. **260**

5c: ^{1}H- NMR (DMSO-d_6, 400 MHz): δ 1.7(s, 3H, -C**H$_3$**), 2.3-2.4 (m, 10H, -$(CH_2)_5$), 6.7-7.9(4H, Ar-H, m) ; $[M+H]^+$:. **244**

5d: ^{1}H- NMR (DMSO-d_6, 400 MHz): δ 1.8(s, 3H, -C**H$_3$**), 2.5-2.7 (m, 10H, -$(CH_2)_5$), δ 1.9(s, 3H, -C**H$_3$**), 6.8-7.7(4H, Ar-H, m) ; $[M+H]^+$:. **240**

5e: ^{1}H- NMR (DMSO-d_6, 400 MHz): δ 1.7(s, 3H, -C**H$_3$**), 2.4-2.6 (m, 8H, -$(CH_2)_4$), 3.7 **(**s**,** 3H, -OCH3), 6.6-7.5(4H, Ar-H, m) ; $[M+H]^+$:. **242**

5f: ^{1}H- NMR (DMSO-d_6, 400 MHz): δ 1.6(s, 3H, -C**H$_3$**), 2.1-2.2 (m, 8H, -$(CH_2)_4$), 6.9-7.2(4H, Ar-H, m) ; $[M+H]^+$:. **246**

5g: ^{1}H- NMR (DMSO-d_6, 400 MHz): δ 1.4(s, 3H, -C**H$_3$**), 2.4-2.5 (m, 8H, -$(CH_2)_4$), 6.4-7.5(4H, Ar-H, m) ; $[M+H]^+$:. **230**

5h: ^{1}H- NMR (DMSO-d_6, 400 MHz): δ 1.8(s, 3H, -C**H$_3$**), 2.7-2.9 (m, 8H, -$(CH_2)_4$), δ 1.9(s, 3H, -C**H$_3$**) 6.6-7.8(4H, Ar-H, m) ; $[M+H]^+$:. **226**

5i: ^{1}H- NMR (DMSO-d_6, 400 MHz): δ 1.9(s, 3H, -C**H$_3$**), 2.5-2.8 (m, 8H, -$(CH_2)_4$), 3.8 **(**s**,** 3H, -OCH3), 6.4-7.6(4H, Ar-H, m) ; $[M+H]^+$:. **258**

5j: ^{1}H- NMR (DMSO-d_6, 400 MHz): δ 1.5(s, 3H, -C**H$_3$**), 2.3-2.7 (m, 8H, -$(CH_2)_4$), 6.7-7.8(4H, Ar-H, m) ; $[M+H]^+$:. **262**

5k: ^{1}H- NMR (DMSO-d_6, 400 MHz): δ 1.6(s, 3H, -C**H$_3$**), 2.6-2.7 (m, 8H, -$(CH_2)_4$), 6.5-7.9(4H, Ar-H, m) ; $[M+H]^+$:. **246**

5l: ^{1}H- NMR (DMSO-d_6, 400 MHz): δ 1.9(s, 3H, -C**H$_3$**), 2.5-2.9 (m, 8H, -$(CH_2)_4$), δ 1.7(s, 3H, -C**H$_3$**) 6.6-7.4(4H, Ar-H, m) ; $[M+H]^+$:. **242**

5m: ^{1}H- NMR (DMSO-d_6, 400 MHz): δ 1.7(s, 3H, -C**H$_3$**), δ 1.9(t, 3H, -C**H$_3$**), δ 2.0(q, 2H, -C**H$_2$**), 3.7 **(**s**,** 3H, -OCH3), 2.2-2.6 (m, 8H, -$(CH_2)_4$), 3.7 **(**s**,** 3H, -OCH3), 6.6-7.8(4H, Ar-H, m) ; $[M+H]^+$:. **285**

5n: ^{1}H- NMR (DMSO-d_6, 400 MHz): δ 1.6(s, 3H, -C**H$_3$**), δ 1.8(t, 3H, -C**H$_3$**), δ 2.2(q, 2H, -C**H$_2$**), 2.3-2.5 (m, 8H, -$(CH_2)_4$), 6.7-7.5(4H, Ar-H, m) ; $[M+H]^+$:. **289**
5o: ^{1}H- NMR (DMSO-d_6, 400 MHz): δ 1.8(s, 3H, -C**H$_3$**), δ 1.7(t, 3H, -C**H$_3$**), δ 2.4(q, 2H, -C**H$_2$**), 2.1-2.3 (m, 8H, -$(CH_2)_4$), 6.5-7.8(4H, Ar-H, m) ; $[M+H]^+$:. **273**
5p: ^{1}H- NMR (DMSO-d_6, 400 MHz): δ 1.7(s, 3H, -C**H$_3$**), δ 1.9(t, 3H, -C**H$_3$**), δ 2.3(q, 2H, -C**H$_2$**), δ 1.9(s, 3H, -C**H$_3$**), 2.4-2.6 (m, 8H, -$(CH_2)_4$), 6.6-7.9(4H, Ar-H, m) ; $[M+H]^+$: **269**

Conclusion

The formation of quinoline tertiary amines by using Hunig's base (*N, N*-diisopropylethylamine) as catalyst is proven as highly efficient and fast. Compounds like 2-methyl-4-chloroquinmolines reacts smoothly with various secondary cyclic amines at RT gave good yields were developed shows the simplicity and generality of the reactions and avoiding of using other heavy metal catalysts and solid supports are the advantages of the current procedure for the syntheses of tertiary amines.

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References:

I. Berman A M, Johnson J S. J Am Chem Soc, 2004, 126, 5680.

II. (a) Bradshaw, J. S.; Krakowiak, K. E.; Izatt, R. M. *Tetrahedron* **1992**, *48*, 4475.
(b) Blagbrough, I. S.; Carrington, S.; Geall, A. *J. Pharm. Sci.* **1997**, *3*, 223.
(c) Bergeron, R. J.; Feng, Y.; Weimer, W. R.; McManis, J. S.; Dimova, H.; Porter, C.; Raisler, B.; Phanstiel, O. *J. Med. Chem.* **1997**, *40*, 1475.

III. Varma RS & JU Y, *Green. Chem.* 2004, 6, 219.

IV. Salvatore R N, Nagle A S & Jung K W, *J Org Chem,* **2002,** 67, 674.

V. Zaragoza F & Stephensen H, *J Org Chem.* **2001**, 66, 2518.

VI. Roundhill D M, *Chem Rev,* **1992**, 92, 1.

VII. (a) Salvatore, R. N.; Nagle, A. S.; Jung, K. W. *J. Org. Chem.* **2002**, *67*, 674.
(b) Zaragoza, F.; Stephensen, H. *J. Org. Chem.* **2001**, *66*, 2518.
(c) Zanetti, J. E.; Bashour, J. T. *J. Am.Chem. Soc.* **1940**, *62*, 741. (d) Shi, M.; Shen, Y. *Helv.Chim. Acta* **2001**, *84*, 3357.

VIII. Varma, R. S.; Ju, Y. *Green Chem.* **2004**, *6*, 219.

IX. Mohri, K.; Suzuki, K.; Usui, M.; Isobe, K.; Tsuda, Y. *Chem. Pharm. Bull. Jpn.* **1995**, *43*, 159.

X. (a) Sato, S.; Sakamato, T.; Miyazawa, E.; and Kikugawa, y *Tetrahedron*, **2004**, 60, 7899.
(b) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, R. J.; and Shah, R. D. *J. Org. Chem*, **1996**, 61, 3849.
(c) Mattson, R. J.; Pham, K. M.; Leuck, D. J.; and Cowen, K. A. *J. ,Org. Chem*, **1990**, 55, 2552.

XI. (a) Sajiki, H.; Ikawa, T.; Hirota, K. *Org. Lett.* **2004**, *6*, 4977.
(b) Mattson, R. J.; Pham, K. M.; Leuck, D. J.; Cowen, K. A. *J. Org. Chem.* **1990**, *55*, 2552.
(c) Roundhill, D. M. *Chem.Rev.* **1992**, *92*, 1.

(d) Kuwano, R.; Kondo, Y.; Matsuyama, Y. *J. Am. Chem. Soc.* **2003**, *125*,12104.
XII. (a) Tremblay-Morin, J. P.; Raeppel, S.; Gaudette, F. *Tetrahedron Lett.* **2004**, *45*, 3471.
(b) Arend, M.; Westerman, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1045.
(c) Petasis, N.A.; Akritopoulou, I. *Tetrahedron Lett.* **1993**, *34*, 583. (d) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445.
(e) Petasis, N. A.; Goodman, A.; Zavialov, I. A. *Tetrahedron* **1997**, *53*, 16463.
(f) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798.
XIII. Muller, T. E.; Beller, M. *Chem. Rev*. **1998**, *98*, 675.
XIV. Srinivas, A.; Virginie, Liautard.; Robert, Paugh.; and Prof. Michael G. *Organ*. *Chemistry*. **2010,** 16(43), 12797–12800.
XV. Roger, H.; Sophie, C. M.; Rees-Jones and Hong Su. *Beilstein J. Org. Chem,* **2007**, 3, 38.
XVI. Varma, R. S.; Ju, Y. *Green Chem.* **2004**, *6*, 219.
XVII. Journal of Medicinal Chemistry, **1995**, 38(18), 3536-46;
XVIII. Shan K, Coats E. J. Med. Chem. **1977,** *20,* 1001.

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