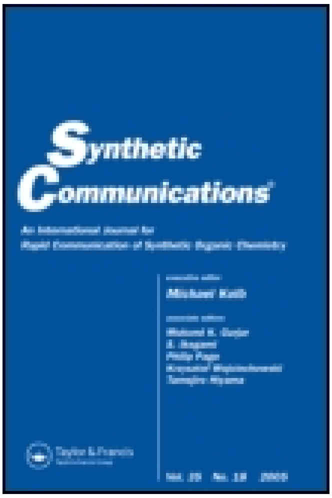
This article was downloaded by: [Memorial University of Newfoundland]
On: 31 July 2014, At: 14:34
Publisher: Taylor & Francis
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Paal-Knorr Pyrrole Synthesis in Water

Dilek Akbaşlar [a], Onur Demirkol [a] & Sultan Giray [a]

[a] Department of Chemistry, Art and Science Faculty, Çukurova University, Adana, Turkey

Accepted author version posted online: 02 Dec 2013.Published online: 28 Mar 2014.

To cite this article: Dilek Akbaşlar, Onur Demirkol & Sultan Giray (2014) Paal-Knorr Pyrrole Synthesis in Water, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 44:9, 1323-1332, DOI: 10.1080/00397911.2013.857691

To link to this article: http://dx.doi.org/10.1080/00397911.2013.857691

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the "Content") contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

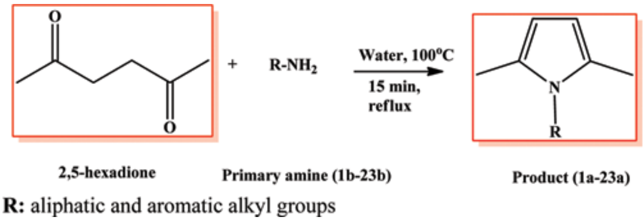
This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. Terms & Conditions of access and use can be found at http://www.tandfonline.com/page/terms-and-conditions

Synthetic Communications®, 44: 1323–1332, 2014
Copyright © Taylor & Francis Group, LLC
ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2013.857691

PAAL–KNORR PYRROLE SYNTHESIS IN WATER

Dilek Akbaşlar, Onur Demirkol, and Sultan Giray
Department of Chemistry, Art and Science Faculty, Çukurova University, Adana, Turkey.

GRAPHICAL ABSTRACT



Abstract *Water was a suitable medium for Paal–Knorr pyrrole cyclocondensation. Hexa-2,5-dione was reacted with several aliphatic and aromatic primary amines, affording N-substituted 2,5-dimethyl pyrrole derivatives in good to excellent yields. An efficient, green method using water either as environmentally friendly solvent or catalyst was presented.*

Keywords Green chemistry; hexa-2,5-dione; Paal–Knorr; pyrrole; water

INTRODUCTION

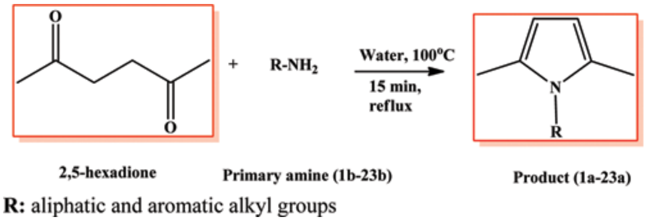
Green chemistry has become a crucial research area with the increasing interest in developing environmentally friendly reaction conditions, in particular, atom-economic catalytic processes or reactions without using any catalysts and organic solvents.[1] The use of water as solvent in organic reactions has attracted the attention of researchers because of the economic and environmental benefits of water, such as low cost and the lack of flammability, explosive, mutagenic, and carcinogenic properties. In addition, some unique properties, including high cohesive energy, large surface tension, high polarity, and high specific heat capacity, have led to use of water in many organic reactions instead of conventional organic solvents.[2,3]

Pyrrole and its derivatives are the heterocyclic compounds that are not only found in the structures of several drugs and natural compounds such as haem, chlorophyll, and B12 vitamin but also show some important pharmacological properties

Received September 12, 2013.

Address correspondence to Elife Sultan Giray, Department of Chemistry, Art and Science Faculty, Çukurova University, 01330 Adana, Turkey. E-mail: esgiray@cu.edu.tr

Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/lsyc.



Scheme 1. Synthesis of N-substituted-2,5-dimethyl pyrrole in water.

such as antibacterial, antiviral, and antitumor activities. Because of these properties, the synthesis of pyrrole derivatives has an important role in heterocyclic chemistry and there is increasing interest in the synthesis of this kind of compounds.

There are several methods for the synthesis of many pyrrole derivatives. Generally, these methods are based on the cyclocondensation reactions. Classical methods for their preparation include Knorr, Hantzsch, and Paal–Knorr condensation reactions. In the Paal–Knorr reaction, 1,4-dicarbonyl compounds are converted to pyrroles in the presence of ammonia or primary amines. Recently, many catalysts have been used for this conversion such as montmorillonite KSF,[4] microwave irradiation,[5] $Bi(NO_3)_3 \cdot 5H_2O$,[6] $Sc(OTf)_3$,[7] and layered zirconium phosphate and zirconium sulfophenyl phosphonate.[8] Some other methods for synthesis of pyrroles include conjugate addition reactions,[9] annulations reactions,[10,11] multicomponent reactions,[12] and aza-Wittig reactions.[13] However, several of these methods suffer from certain drawbacks such as prolonged reactions times, use of volatile or hazardous organic solvents, tedious workup conditions, use of extra energy source, and toxic metals.[4,5]

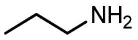
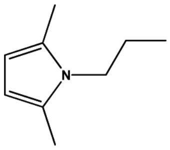
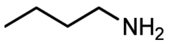
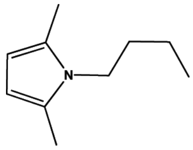
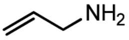
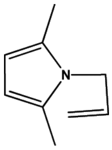
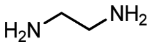
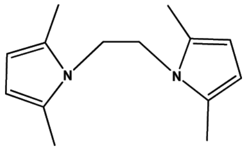
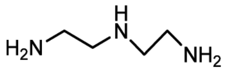
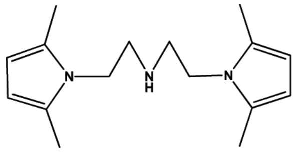
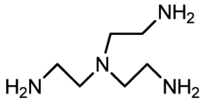
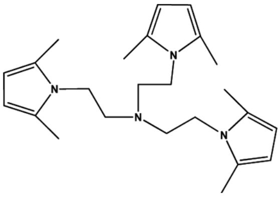
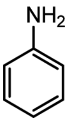
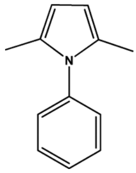
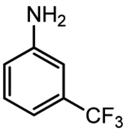
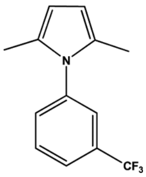
In continuation of our efforts toward the development of greener methodologies,[14] we report herein a simple, clean, and environmentally friendly process for the synthesis of *N*-substituted pyrrole derivatives by reaction of various aliphatic and aromatic amines with hexa-2,5-dione for the first time in water (Scheme 1).

RESULTS AND DISCUSSION

At the onset of this work, we have investigated the optimum conditions for the synthesis of 1-benzyl-2,5-dimethyl-1*H*-pyrrole as a model compound for conducting the reactions in water at different temperatures. At room temperature, the condensation reaction between benzyl amine (10 mmol) and hexa-2,5-dione (10 mmol) in 5 mL water in 15 min resulted in poor yields (45%). When further prolonging the reaction time to 3 h, no remarkable change was observed in yield. At 50 °C, the same reaction required 3 h of reaction time for excellent yields (95%). When the reaction took place at the boiling point of water, the product was also obtained in excellent yields (96%) but in a short time (15 min). Moreover, we also studied influence of the amount of water used on the reaction yields. We found that the yield was not dramatically affected by adding different amounts of water (5, 10, and 15 mL). Five mL of water was enough; an excessive amount of it did not increase the yield remarkably.

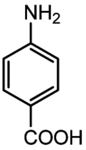
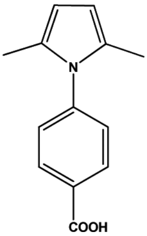
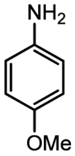
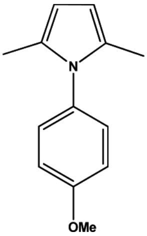
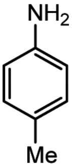
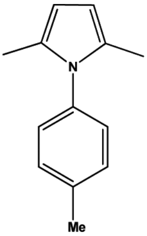
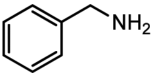
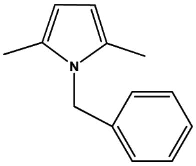
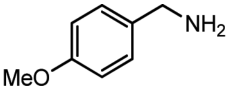
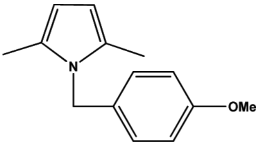
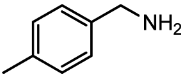
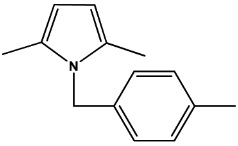
Having the established the reaction conditions, various aliphatic and aromatic amines were reacted with hexa-2,5-dione to investigate the reaction field, and the results are displayed in Table 1. In all cases, the Paal–Knorr reaction proceeded smoothly and gave the corresponding *N*-substituted 2,5-dimethyl pyrroles in good to excellent yields.

Table 1. Synthesis of N-substituted 2,5-dimethyl pyrroles in water

Entry	Amine (**1b**–**23b**)	Product (**1a**–**23a**)	Yield (%)
1			96
2			95
3			98
4			94[a]
5			96[a]
6			97[b]
7			96
8			75

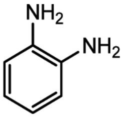
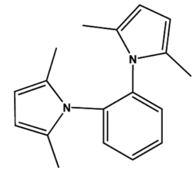
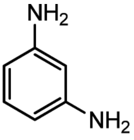
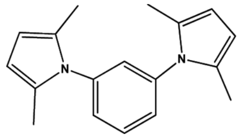
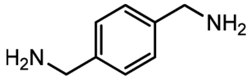
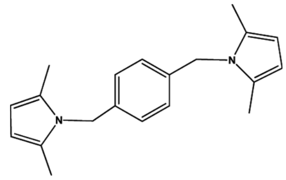
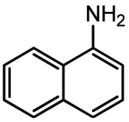
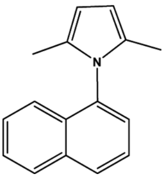
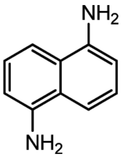
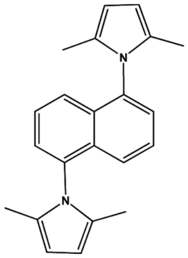
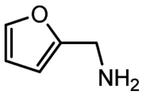
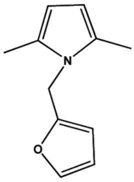
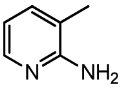
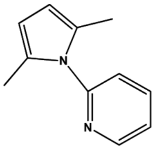
(*Continued*)

Table 1. Continued

Entry	Amine (**1b–23b**)	Product (**1a–23a**)	Yield (%)
9			n.o.
10			90
11			88
12			96
13			85
14			95

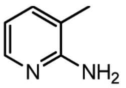
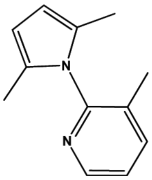
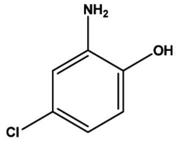
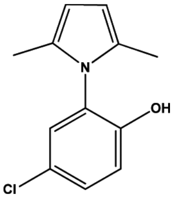
(*Continued*)

Table 1. Continued

Entry	Amine (**1b**–**23b**)	Product (**1a**–**23a**)	Yield (%)
15			75[a]
16			76[a]
17			78[a]
18			n.o.
19			n.o.
20			98
21			n.o.

(*Continued*)

Table 1. Continued

Entry	Amine (**1b–23b**)	Product (**1a–23a**)	Yield (%)
22			n.o
23			81

Note: Reaction conditions: amine (10 mmol), 2,5-hexadione (10 mmol), 5 mL water, 15 min, 100 °C.
[a]Amine (5 mmol), 2,5-hexadione (10 mmol), 5 mL water, 15 min, 100 °C.
[b]Amine (3.3 mmol), 2,5-hexadione (10 mmol), 5 mL water, 15 min, 100 °C.
n.o., not observed.

It is well known that the reactivity of aliphatic amine is more nucleophilic or more basic compared with that of aromatic amines.[15] Thus, it is obviously seen that aliphatic amines give greater yields than aromatic amines in water medium at 100 °C. Furthermore, the electronic effect of substituent on the aromatic rings of aryl amines in the Paal–Knorr condensation was not clear. The presence of either an electron-donating or an electron-withdrawing group in the aromatic ring prompted the reaction, with quantitative conversions being achieved after 15 min (Table 1, entries 8, 10, 11, 15, and 16).

It is important to note that the less nucleophilic aromatic amines and the ones less soluble in water were not coupled with hexan-2,5-dione in this condition (Table 1, entries 9, 18–21). Both prolonged reaction time and increase in amount of water could not further improve their reactivity.

With these results in hand, we subjected di- or tri-amino substrates to this methodology. Two or three equivalents of hexan-2,5-dione were required to have a complete conversion of di- or tri-amines. Bipyrrole or tripyrrole compounds were obtained in good to excellent yields (Table 1, entries 4–6, 15–17). Also, aliphatic diamines gave products in greater yields than those of aromatic diamines (Table 1, entries 4, 5, 15, 16).

The role of water was further explored for Paal–Knorr condensation by performing the reactions of benzylamine and aniline with hexa-2,5-dione as model reactions in various organic solvents at reflux temperatures (Tables 2 and 3).

After extensive screening, we found that the yields of both 2,5-dimethyl-1-phenyl-1*H*-pyrrole and 1-benzyl-2,5-dimethyl-1*H*-pyrrole, respectively, in different organic solvents were approximately the same as the ones obtained in water. Also, the corresponding products were obtained in only poor yields (25%, 30%) in the absence of solvent. Water is more preferable than the other solvents because it not only is an environmentally friendly and easily available solvent but also presents a simple product isolation procedure.

Table 2. Synthesis of 2,5-dimethyl-1-phenyl-1*H*-pyrrole in different solvents

Entry	Solvent	Temperature (°C)	Yield (%) for **7a**
1	Water	100	96
2	Methanol	65	95
3	Ethanol	78	93
4	Acetone	56	85
5	Chloroform	62	75
6	Ethyl acetate	77	90
7	THF	66	89
8	DCM	40	90
9	Toluene	110	87
10	Hexane	69	75
11	None	25	25

Note: Reaction conditions: Aniline (10 mmol), 2,5-hexzadione (10mmol), solvent (5 mL), 15 min.

At room temperature, because of the absence of the solute-water H-bonding, the water keeps the three-dimensional H–bonding network with increasing temperature. The H–bonds break down, the orientational preference of water molecules decrease, and then organic reactions take place in hot water. Water at the boiling point creates an ideal medium for the Paal–Knorr reaction proceeding in less acidic or neutral condition. A plausible mechanism is shown in Scheme 2.

To prove the benefit of our methodology, we collected in Table 4 results of 2,5-dimethylpyrrole synthesis under different conditions. As indicated in Table 4, this compound was synthesized in organic solvents in the presence of various catalysts or under solvent-free conditions using microwave irradiation with catalysts. In addition to having the general advantages attributed to green chemistry, our present method is better or comparable with others in terms of yields, reaction time, and environmental friendliness.

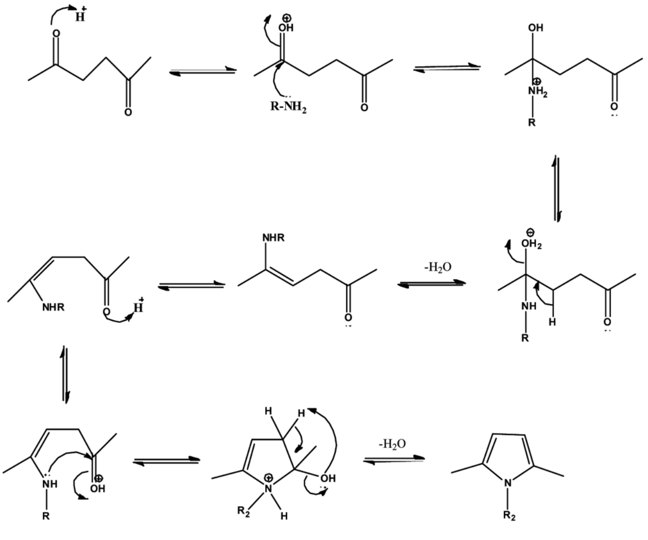
Table 3. Synthesis of 1-benzyl-2,5-dimethyl-1H-pyrrole in different solvents

Entry	Solvent	Temperature (°C)	Yield (%) for **12a**
1	Water	100	96
2	Methanol	65	95
3	Ethanol	78	94
4	Acetone	56	90
5	Chloroform	62	81
6	Ethyl acetate	77	96
7	THF	66	94
8	DCM	40	93
9	Toluene	110	91
10	Hexane	69	80
11	None	25	30

Note: Reaction conditions: Benzylamine (10 mmol), 2,5-hexzadione (10 mmol), solvent (5 mL), 15 min.

Table 4. Comparison of some other methods with the present procedure for the synthesis of 2,5-dimethyl-1-phenyl-1*H*-pyrrole

Entry	Catalyst/solvent	T (°C)	Time	Yield (%)	Ref.
1	I_2/THF	25	9 h	89	4
2	Montmorillonite,KSF/CH_2Cl_2	25	10 h	95	4
3	Fe^3-montmorillonite/CH_2Cl_2	25	3 h	96	16
4	$Sc(OTf)_3$/solvent-free	30	25 min	96	7
5	$Sc(OTf)_3$/CH2Cl_2	30	25 min	77	7
6	$Cu(OTf)_2$/solvent-free	30	25 min	78	7
7	$CuCl_2$/solvent-free	30	25 min	34	7
8	α-$Zr(KPO_4)_2$/solvent-free	60	24 h	56	8
9	α-$Zr(CH_3PO_3)1.2(O_3PC_6H_4SO_3H)$ 0.8/solvent-free	60	2 h	88	8
10	$ZnCl_4$/solvent-free	40	7 min	98	17
11	p-TSA/CH_3CN	80	1 h	83	18
12	Cationic exchange resin/H_2O	130	5 h	85	18
13	[MIMBS]3PW12O40/CH_3CN	80	2 h	93	18
14	γ-Fe_2O_3@SiO_2-Sb(III)-IL/H_2O	100	40 min	95	19
15	$NiCl_2/H_2O$	100	2 h	62	19
16	$ZnBr_2/H_2O$	100	80 min	48	19
17	[Bmim]I ionic liquid	25	3 h	96	20
18	$UO_2(NO_3)_2 \cdot 6H_2O$/MeOH/.	25	35 min	96	21
19	Microwave/I_2	60	5 min	98	22
20	$Bi(NO)_3 \cdot 5H_2O/CH_2Cl_2$	25	10 h	96	6
21	Ps/$GaCl_3$/CH_3CN	reflux	20 min	92	23
22	$BiCl_3/SiO_2$/hexane	25	12 h	98	24
23	$Bi(NO_3)_3 \cdot 5H_2O$/Microwave	90	5 min	100	25
24	Noncatalyst/H_2O	100	15min	96	Table 3



Scheme 2. Plausible mechanism for Paal–Knorr pyrrole cyclocondensation in water.

CONCLUSIONS

In summary, considering the requirement of green chemistry, water was successfully used as solvent in place of organic solvents for the Paal–Knorr reaction. *N*-Substituted 2,5-dimethyl pyrrole compounds were synthesized in the condensation reaction of hexan-2,5-dione with various aliphatic and aromatic primary amines at the boiling point of water without using any catalysts or organic solvents. The poor solubility of products in water facilitated the isolation protocol based on extraction, filtration, or crystallization. In most cases, the crude products are pure and do not need any further purifications. The pyrrole compounds were obtained in good to excellent yields (75–98%) via the properties of water and they were characterized by melting point, Fourier transform–infrared (FT-IR), ^{1}H NMR, and ^{13}CNMR techniques.

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer 55148 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 300-MHz Ultrashield spectrometer and a Bruker Avance III 400-MHz spectrometer, and shifts are given in parts per million (ppm) downfield from tetramethylsilane (TMS) as an internal standard. Melting points were determined using an Electrothermal 9100 instrument.

General Experimental Procedure (1a–23a)

A round-bottom flask equipped with a magnetic stirrer was charged with primary aliphatic, aromatic amines (10 mmol), hexa-2,5-dione (10 mmol), and distilled water (5 mL). This suspension was refluxed at 100 °C for 15 min. The reaction was monitored by thin-layer chromatography (TLC) (4:1 n-hexane/ethylacetate). After the reaction mixture was cooled to room temperature, the product was filtered and washed with water. It was recrystallized from methanol. The resulting product was identified using FT-IR and NMR spectroscopy.

2,5-Dimethyl-1-propyl-1H-pyrrole (1a) (1a, C9H15N)

Yellow oil; yield 1.32 g (96 %); υ_{max} (KBr) 3100, 2965, 2932, 2875, 1519, 1348; δ_H (300 MHz, $CDCl_3$; Me_4Si) 5.85 (s, 2H), 3.77 (t, *J* = 7.8 Hz, 2H), 2.31 (s, 6H), 1.78–1.68 (m, 2H), 1.03 (t, *J* = 7.5 Hz, 3H); δ_C (75 MHz, $CDCl_3$; Me_4Si) 127.44, 105.00, 45.30, 24.30, 12.57, 11.44. Found: C, 78.47; H, 11.09; N, 10.44. Calcd. for $C_9H_{15}N$: C, 78.77; H, 11.02; N, 10.21%.

FUNDING

The authors are thankful to the Scientific and Technical Research Council of Turkey (Grant TUBITAK-211T146) for the financial support.

SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

REFERENCES

1. (a) Horvath, I. T. *Green Chem*. **2008**, *10*, 1024; (b) Lancester, M. *Green Chemistry: An Introductory Text;* Royal Society of Chemistry: Cambridge, 2002; (c) Matlack, A. S. *Introduction to Green Chemistry*; Marcel Dekker: New York, 2001; (d) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University, New York, 1988.
2. (a) Breslow, R.; Maitra, U. *Tetrahedron Lett.* **1984,** *25*, 1239–1240; (b) Breslow, R.; Maitra, U.; Rideout, D. *Tetrahedron Lett.* **1983**, *24*, 1901–1904; (c) Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816–7817.
3. (a) Muldoon, S. J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3275–3279; (b) Jung, Y. S.; Marcus, R. A. *J. Am. Chem. Soc.* **2007**, *129*, 5492–5502.
4. Banik, B. K.; Samajdar, S.; Banik, I. *J. Org. Chem.* **2004**, *69*, 213–216.
5. Rao, H. S. P.; Jothilingam, S.; Scheeren, H. W. *Tetrahedron* **2004**, *60*, 1625–1630.
6. Banik, K. B.; Banik, I.; Dasgupta, K. S. *Tetrahedron Lett.* **2005**, *46*, 2643–2645.
7. Chen, J.; Wu, H.; Zhang, X.; Su, W. *Tetrahedron Lett.* **2006**, *47*, 5383–5387.
8. Curini, M.; Montanari, F.; Margarita, R. *Tetrahedron Lett.* **2003**, *44*, 3923–3925.
9. Dieter, R. K.; Yu, H. *Organic Lett.* **2000**, *2*, 2283–2286.
10. Arcadi, A.; Rossi, E. *Tetrahedron* **1998**, *5*, 15253–15272.
11. Lee, C. F.; Yang, L. M.; Hwu, T. Y.; Feng, A. S.; Thseng, J. C.; Luh, T. Y. *J. Am. Chem. Soc.* **2000**, *122*, 4992–4993.
12. Bharadwaj, A. R.; Scheidt, K. A. *Organic Lett*. **2004**, *6*, 2397–2399.
13. Katritzky, A.; Jiang, J.; Steel, P. J. *J. Org. Chem.* **1994**, *59*, 4551–4555.
14. (a) Doğan, A.; Giray, E. S. Proceedings of 12th European Meeting on Supercritical Fluids, Austria, 2010; (b) şirin, Ö.; Giray, E. S. Proceedings of 12th European Meeting on Supercritical Fluids, Austria, 2010; (c) Koldaş, S.; Giray, E. S. Proceedings of 12th European Meeting on Supercritical Fluids, Austria, 2010; (d) Şimşek, İ.; Giray, E. S. Proceedings of 9th International Symposium on Super critical Fluids, France, 2009; (e) Alpman, S. F.; Koldaş, S.; Giray, E. S. Proceedings of 9th International Symposium on Supercritical Fluids, France, 2009.
15. (a) Sreekumar, R.; Padmakumar, R. *Synth. Commun.* **1998**, *28*(9), 1661; (b) Texier-Boullent, F.; Klein, B.; Hamlein, J. *Synthesis* **1986**, 409.
16. Song, G.; Wang, B.; Wang, G.; Kang, Y.; Yang, T.; Yang, L. *Synth. Commun.* **2005**, *35*(8), 1051–1057.
17. Zhang, Z.; Li, J.; Li, T. *Ultrason. Sonochem.* **2008**, *15*, 673–676.
18. Gao, L.; Bing, L.; Zhang, Z.; Deng, K. *J. Organomet. Chem.* **2013**, 735, 26–31.
19. Ma, F. P.; Li, B. L.; Mo, L. B.; Liu, N.; Kang, H. J.; Liu, Y. N.; Zhang, Z. H. *Appl. Catal. A* **2013**, 457, 34–41.
20. Wang, B.; Gu, Y.; Suo, J. *Tetrahedron Lett.* **2004**, *45*, 3417–3419.
21. Sivakumar, A.; Satyanarayana, V. S. V. *Ultrason. Sonochem.* **2011**, *18*, 917–922.
22. Bandyopadhyay, D.; Mukherjee, S.; Banik, B. *Molecules* **2010**, *15*, 2520–2525.
23. Rahmatpour, A. *J. Organomet. Chem.* **2012**, *712*, 15–19.
24. Aghapoor, K.; Ebadi-Nia, L.; Mohsenzadeh, F.; Morad, M. M.; Balavar, Y.; Darabi, H. R. *J. Organomet. Chem.* **2012**, *708–709*, 25–30.
25. Rivera, S.; Bandyopadhyay, D.; Banik, B. *Tetrahedron Lett.* **2009**, *50*, 5445–5448.