Asian Journal of Chemistry; Vol. 25, No. 9 (2013), 4935-4938

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2013.14146

Synthesis of N-Arylisatins Using Different Heterogeneous Catalyst Under Microwave Irradiations

RAVINDER SINGH* and RAMESH KUMAR

Department of Chemistry, Pt. N.R.S. Government College, Rohtak-124 001, India

*Corresponding author: E-mail: gahlawat.ravinder@gmail.com

(*Received*: 4 June 2012; *Accepted*: 11 March 2013) AJC-13107

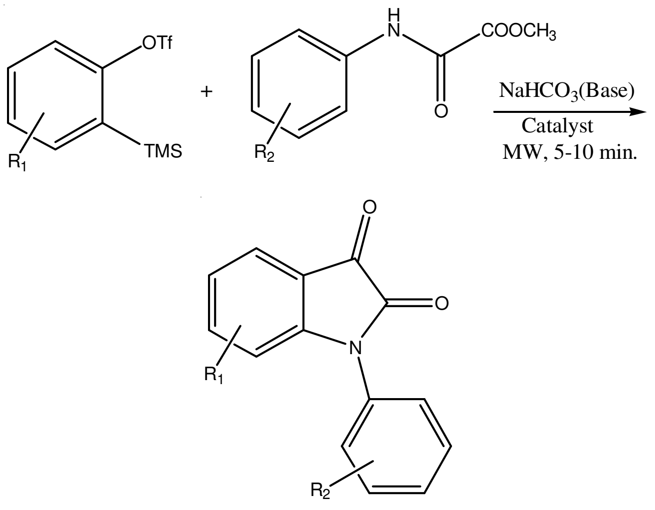
N-Arylisatins having both biological and medical properties are synthesized by the reaction of methyl-2-oxo-2-(arylamino)acetates and arynes using $NaHCO_3$ in presence of different heterogeneous catalyst under microwave irradiations in high yield in shorter reaction time.

Key Words: Synthesis, N-Arylisatin, Microwave irradiation.

INTRODUCTION

Isatins have both biological and medical properties including antifungal, antiviral, anti HIV, anti AIDS, antiprotozoal, anticancer and antileukema[1-7]. In recent years, isatins have been synthesized by different methods but they require tedious work up and long reaction time[8-17]. Microwave assisted organic synthesis is currently gaining ground in synthetic organic chemistry largely due to the dramatic reduction in time (from days or hours to minutes or seconds)[18,19].

Here, we report a microwave assisted synthesis of N-arylisatin by reaction of arynes with methyl-2-oxo-2-(arylamino)acetate in excellent yield in shorter reaction time (**Scheme-I**).



Scheme-I

We started our work by reacting methyl-2-oxo(phenylamino)acetate with 2-(trimethylsilyl) phenyltrifluoromethanesulphonate in presence of NaX zeolite catalyst under microwave irradiation at 560 W for 4 to 10 min. The corresponding N-phenylisatin is obtained in 65-94 % yield.

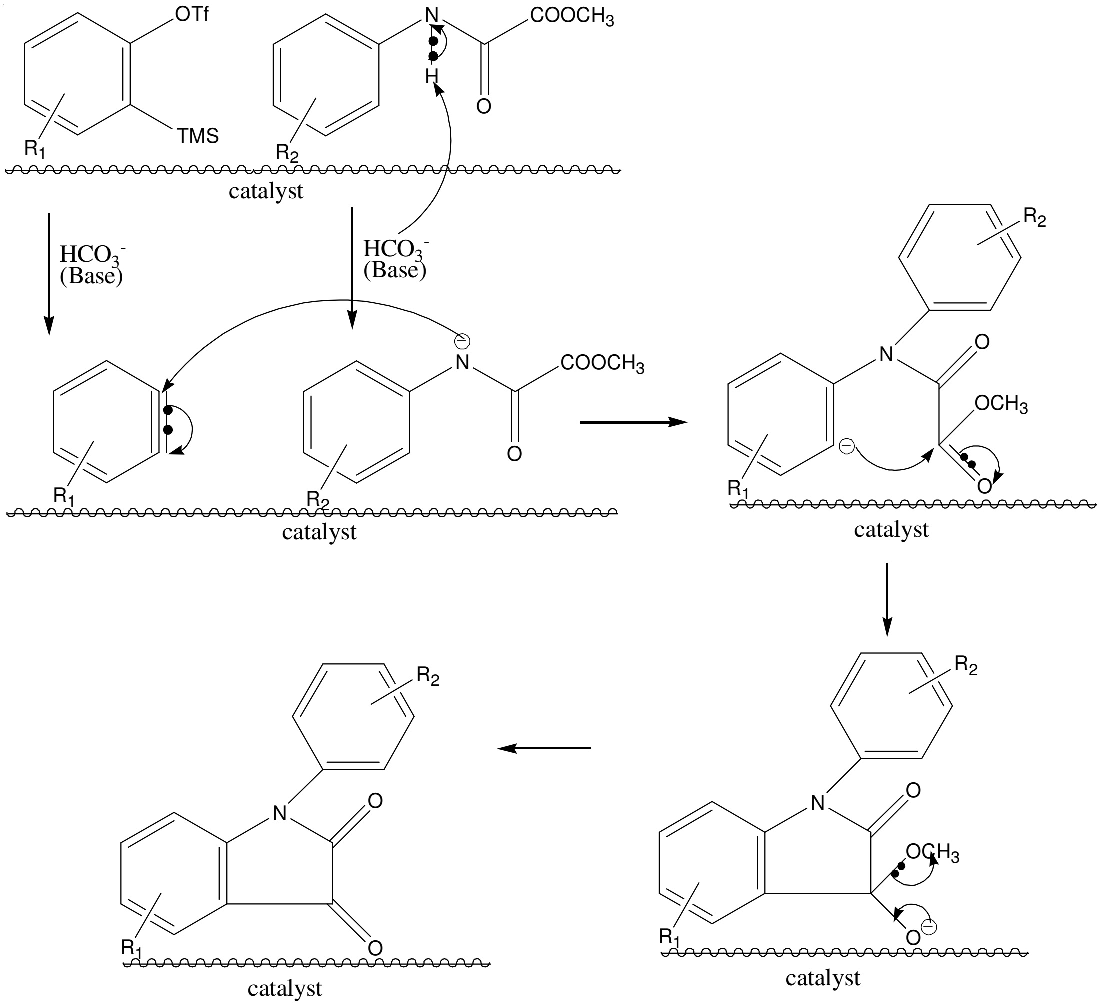
Mechanistically, it is believed that in first step, the nucleophilic attack by nitrogen on the benzyne occurs, resulting in the formation of an aryl carbanion. The aryl carbanion attacks the distant ester carbonyl and displaces a methoxy group which eventually lead to the desired isatin (**Scheme-II**).

We further explored our work by reacting different methyl-2-oxo(arylamino)acetate with 2-(trimethylsilyl)phenyltrifluoromethanesulphonate using NaX, NaY and NaZ zeolite catalyst under microwave ireradiation at 560 W power. The results are shown in Table-1. Here electron-rich substituent seems to promote this reaction to a small extent, whereas electron deficient group lower the yield of the reaction in same way as in ordinary conditions.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz, respectively. Thin layer chromatography was performed using commercially prepared 60-mesh silica gel plates and visualization was effected with short wavelength UV light (254 nm).

Typical procedure for synthesis of the isatin derivatives (1-17): To a dry s dram vial containing a solution of the amide (0.5 mmol) and the aryl amino precursor (1.0 mmol) in MeCN (5.0 mL, anhydrous) was added $NaHCO_3$ (1.0 mmol) and CsF (3.0 mmol). The vial was sealed and allowed to stir for 24 h. The reaction mixture was then filtered through a lug of silica gel using ethyl acetate, concentrated *in vacuo* and purified by



Scheme-II: Possible mechanism for **Scheme-I**

flash chromatography using gradient solvent combinations of ethyl acetate/hexanes or dichloromethane/hexanes.

1-Phenylindoline-2,3-dione (1): The product was isolated as an orange solid. ^{1}H NMR (300 MHz,$CDCl_3$) δ 7.70 (ddd, *J* = 0.6, 1.3, 7.5Hz,1H), 7.60-7.41 (m, 6H), 7.18 (td,*J* = 0.8, 7.6 Hz, 1H), 6.91 (d, *J* = 8.1 Hz, 1H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.1, 157.5, 151.9, 138.5, 133.4, 130.2, 129.0, 126.2, 125.8, 124.5, 117.5; HRMS (EI) calcd. (%) for $[M + H]^+$ ($M=C_{14}H_9NO_2$) 224.0706, found (%) 224.0707.

1-*p*-Tolylindoline-2,3-dione (2): The product was isolated as a red-orange solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.5 Hz,1 H), 7.66 (t, *J* = 7.3 Hz, 1H), 7.49 (d, *J* =

TABLE-1
REACTION OF VARIOUS METHYL-2-OXO-2(ARYLAMINO)ACETATES WITH 2-(TRIMETHYLALLYL)PHENYL TRIFLUOROMETHANESULFONATE

S. No.	Substrate (R_2)	Time (min)	Yield (%)			m.p. (ºC)
			Using NaX catalyst	Using NaY catalyst	Using NaZ catalyst	
1	H	7	89	91	85	136-139
2	4-Me	6	85	95	83	137-139
3	4-Oph	5	86	95	84	145-148
4	4-F	6	92	97	91	235-237
5	4-Cl	7	72	81	68	194-197
6	4-Br	7	75	83	72	178-180
7	4-I	7	79	87	74	198-201
8	2-I	7	88	94	85	173-176
9	4-CN	4	78	86	75	282-284
10	4-CO_2Et	10	80	88	78	127-129
11	4-CF_3	8	65	71	61	177-181
12	3-CF_3	9	68	75	64	124-127
13	2-t-Bu	8	90	94	84	109-113
14	2-Ph	8	84	89	81	157-162
15	2,5-$(OMe)_2$	5	82	91	78	114-117
16	2,4,6-Me_3	5	74	82	71	164-168
17	2,3-$(CH)_4$	5	94	98	90	130-133

8.2 Hz, 2H), 7.42 (d, *J* = 8.3H z, 2H), 7.30 (d, *J* = 7.5 Hz, 1H) 7.00 (d, *J* = 8.1 Hz, 1H) 2.56 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.2, 157.6, 152.0, 139.1, 138.5, 130.7, 130.3, 126.0, 125.6, 124.3, 117.6, 111.4, 21.4; HRMS(EI) calcd. (%) for $C_{18}H_{11}NO_2$ 237.0790, found (%) 237.0791.

1-(4-Phenoxyphenyl)indoline-2,3-dione (3): The product was isolated as a yellow-orange solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.4 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.40-7.34 (m, 4H), 7.18-7.11 (m, 4H), 7.07 (d, *J* = 8.2 Hz, 2H), 6.88 (d, *J* = 7.97 Hz, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.0, 157.9, 157.6, 156.2, 151.8, 138.5, 130.1, 127.7, 127.4, 125.6, 124.4, 124.3, 119.8, 119.5, 117.5, 111.3, HRMS (EI) calcd for $C_{20}H_{13}NO_3$ 315.0895, found (%) 315.0899.

1-(4-Fluorophenyl)indoline-2,3-dione (4): The product was isolated as a bright orange solid. ^{1}H NMR (400 MHz,$CDCl_3$) δ 7.72(d, *J* = 7.5 Hz, 1H), 7.57 (t, *J* = 7.8 Hz, 1H), 7.44-7.40 (m, 2H), 7.29-7.24 (m, 2H), 7.20 (t, *J* = 7.6 Hz, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), ^{13}C NMR (100 MHz, $CDCl_3$ extra peaks due to C-F coupling) δ 182.8, 163.7, 161.2, 157.6, 151.7, 138.6, 129.0, 128.9, 128.3, 128.2, 125.9, 124.7, 117.7, 117.4, 117.2, 111.3, HRMS(EI) calcd. (%) for $C_{14}H_8FNO_2$ 241.0539, found. (%) 241.0539.

1-(4-Chlorophenyl)indoline-2,3-dione (5): The product was isolated as an orange solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71(d, *J* = 7.5 Hz, 1H), 7.59-7.53 (m, 3H), 7.39 (d, *J* = 8.6 Hz, 2H), 7.20 (t, *J* = 7.6 Hz, 1H), 6.90 (d, *J* = 6.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 128.6, 157.4, 151.3, 138.6, 134.7, 131.5, 134.4, 137.5, 126.0, 124.7, 117.7, 111.3 HRMS(EI) calcd. (%) for $C_{14}H_8NO_2Cl$ 257.0244, found (%) 257.0248.

1-(4-Bromophenyl)indoline-2,3-dione (6): The product was isolated as a light orange solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.66 (m, 3H) 7.56 (t, *J* = 7.8 Hz, 1H), 7.32 (d, *J* = 8.5 Hz, 2H), 7.20 (t, *J* = 7.5 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.5, 157.2, 151.1, 138.6, 133.3, 132.0, 127.7, 125.9, 124.7, 122.6, 117.6, 111.3, HRMS (EI) calcd. (%) for $C_{14}H_8NO_2Br$ 300.9738, found (%) 300.9742.

1-(4-Iodophenyl)indoline-2,3-dione (7): The product was isolated as an orange solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.5 Hz, 2H), 7.69 (d, *J* = 7.51 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 7.21-7.17 (m, 3H), 6.90 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.5, 157.2, 151.1, 139.3, 138.6, 132.7, 127.8, 126.0, 124.8, 117.6, 11.3, 94.1; HRMS (EI) calcd. (%) for $C_{14}H_8NO_2I$ 348.9600, found (%) 348.9601.

1-(2-Iodophenyl)indoline-2,3-dione (8): The product was isolated as a ruby red solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01(d, *J* = 7.9 Hz, 1H), 7.70 (d, *J* = 7.4 Hz, 1H), 7.53-7.51 (m, 2H), 7.36 (d, *J* = 7.6 Hz, iH), 7.26-7.15 (m, 2H), 6.49 (d,*J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz,$CDCl_3$) δ 182.6, 157.0, 151.3, 140.8, 138.7, 136.2, 131.5, 130.2, 129.7, 125.8, 124.5, 117.2, 111.8, 98.1; HRMS(EI) calcd. (%) for $[M + Na]^+$ ($M=C_{14}H_8INO_2$) 371.9492, found (%) 371.9497.

4-(2,3-Dioxoindolin-1-yl)benzonitrile (9): The product was isolated as a light orange solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.3 Hz, 2H), 7.714-7.705 (m, 3H), 7.64 (t, *J* = 7.8Hz, 1H), 7.23 (t, *J* = 7.51 Hz, 1H), 6.99 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.9, 157.2, 150.0, 137.9, 137.6, 133.8, 127.0, 124.9, 124.1, 118.4, 117.9, 110.9, 110.5, HRMS(EI) calcd. (%) for $[M + H]^+$ ($M=C_{15}H_8N_2O_2$) 249.0659, found (%) 249.0656.

Ethyl-4-(2,3-dioxoindolin-1-yl)benzoate (10): The product was isolated as a light orange solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.6 Hz, 2H), 7.70 (d, *J* = 7.5 Hz, 1H), 7.59-7.52 (m, 3H), 7.20 (t, *J* = 7.51 Hz, 1H), 6.97 (d, *J* = 8.1 Hz, 1H), 4.40 (d, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.3, 165.6, 157.1, 150.9, 138.6, 136.9, 131.3, 130.6, 126.0, 125.5, 124.8, 117.7, 111.4, 61.5, 14.5; HRMS(EI) calcd. (%) for $C_{17}H_{13}NO_4$ 295.0839, found (%) 295.0845.

1-[4-(Trifluoromethyl)phenyl]indolin-2,3-dione (11): The product was isolated as a bright orange solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.4 Hz, 2H), 7.73 (d, *J* = 6.9 Hz, 1H), 7.62-7.59 (m, 3H), 7.23 (t, *J* = 7.5 Hz, 1H), 6.98 (d, *J* = 8.1Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, extra peaks due to C-F coupling) δ 182.2, 157.2, 150.8, 138.7, 136.2, 131.0, 130.6, 128.9, 127.33, 127.29, 127.26, 127.22, 126.3, 126.1, 125.1, 125.0, 122.4, 117.7, 111.3, HRMS(EI) calcd. (%) for $C_{15}H_8F_3NO_2$ 291.0507, found (%) 291.0509.

1-[3-(Trifluoromethyl)phenyl]indolin-2,3-dione (12): The product was isolated as a yellow orange solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74-7.65 (m, 5H), 7.60 (td, *J* = 1.2, 8.0 Hz, 1H), 7.23 (t, *J* = 7.6 Hz, 1H), 6.92 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, extra peaks due to C-F coupling) δ 182.3, 157.3, 150.9, 138.7, 133.7, 130.9, 129.6, 126.1, 125.74, 125.70, 125.0, 123.04, 123.00, 117.7, 111.2; HRMS(EI) calcd. (%) for $C_{15}H_8F_3NO_2$ 291.0507, found (%) 291.0507.

1-(2-*tert*-Butylphenyl)indolin-2,3-dione (13): The product was isolated as a light orange solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (t, *J* = 7.9 Hz, 2H), 7.51 (td, *J* = 1.1, 7.8 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 1H), 7.34 (td, *J* = 1.3,7.5 Hz, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.05 (dd, *J* = 1.4, 7.8 Hz, 1H), 6.42 (d, *J* = 8.0 Hz, 1H), 1.32(s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, δ 183.4, 159.2, 154.1, 149.6, 138.7, 131.7, 130.5, 130.2, 129.4, 128.4, 125.4, 124.2, 11.8, 112.7, 35.8, 31.9; HRMS(EI) calcd. (%) for $C_{18}H_{17}NO_2$ 279.1259, found (%) 279.1259.

1-((1,1/-Biphenyl)-2-Yl]indoline-2,3-dione (14): The product was isolated as a red solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56-7.53 (m, 4H), 7.40-7.36 (m, 2H), 7.26-7.23 (m, 5H), 7.03 (t, *J* = 7.3 Hz, 1H), 6.48 (d, *J* = 7.5 Hz, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.8, 158.0, 152.2, 141.1, 138.3, 138.2, 131.7, 130.6, 130.1, 129.3, 128.74, 128.69, 128.2, 128.1, 125.4, 124.1, 117.2, 111.6, HRMS(EI) calcd. (%) for $C_{30}H_{11}NO_2$ 299.0946, found (%) 299.0946.

1-(2,4-Dimethoxyphenyl)indoline-2,3-dione (15): The product was isolated as a orange solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 7, 7.5 Hz, 1H), 7.49 (t, *J* = 1.4, 7.9 Hz, 1H), 7.11 (td, *J* = 0.73, 7.5 Hz, iH), 7.02-6.96 (m, 2H), 6.86 (d, *J* = 2.6Hz, 1H), 6.59 (d, *J* = 8.0 Hz, 1H), 3.77 (s, 3H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.1, 157.7, 154.0, 152.2, 149.3, 138.4, 125.3, 124.0, 121.6, 117.6, 116.0, 114.7, 113.7, 111.8, 56.4, 56.0; HRMS(EI) calcd. (%) for $C_{16}H_{13}NO_4$ 283.0845, found (%) 283.0839.

1-Mesitylindoline-2,3-dione (16): The product was isolated as a yellow orange solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.2 Hz, 1H), 7.51 (t, *J* = 7.7 Hz, 1H), 7.16 (t, *J* = 7.5 Hz, iH), 7.03 (s, 2H), 6.4 (d, *J* = 7.8 Hz, 1H), 2.35 (s, 3H), 2.14 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.2, 157.5, 151.7, 139.8, 138.8, 136.3, 129.9, 128.0, 125.8, 124.3, 117.7, 111.2, 21.3, 18.1; HRMS(EI) calcd. (%) for $C_{17}H_{15}NO_2$ 265.1100 found (%) 265.1103.

1-(Naphthalen-1-yl)indoline-2,3-dione (17): The product was isolated as an orange solid. ^{1}H NMR(400 MHz, CDCl$_3$) δ 8.02 (d, J = 8.2 Hz, 1H), 7.98 (d, J = 8.2 Hz, 1H), 7.75 (d, J = 7.3 Hz, iH), 7.70 (t, J = 8.4 Hz, 1H), 7.64-7.49 (3, 4H), 7.45 (td, J = 1.1, 7.9 Hz, 1H), 7.17 (t, J = 7.5 Hz, 1H), 6.44 (d, J = 8.0 Hz, 1H), 6H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 183.1, 158.2, 152.8, 138.8, 135.0, 130.4, 129.5, 129.0, 127.6, 127.1, 126.0,. 125.7, 124.4, 122.6, 117.6, 112.0; HRMS(EI) calcd. (%) for $C_{18}H_{11}NO_2$ 273.0790 found (%) 273.0786.

REFERENCES

1. (a) S.N. Pandeya, S. Samitha, M. Jyoti and S.K. Sridhar, *Acta Pharm*., **55**, 27 (2005); (b) K.L. Vine, L. Matesh, J.M. Locke, M. Ranson, D. Kropeta, *Med Chem*., **9**, 397 (2009); (c) S.J. Shultleworth, D. Nasturica, C. Gervais, M.A. Siddiqui, R.F. Rando and N. Lee, *Bioorg. Med. Chem. Lett*., **10**, 250 (2000).
2. M.R. Islam, M.J. Abedin, M.M. Hossain and H.J. Doddeck, *Bangladesh Chem. Soc*., **11**, 71 (1998).
3. K.J. Kilpin, W. Henderson and B.K. Nicholson, *Polyhedron*, **26**, 2004 (2007).
4. M.R. Islam, J. Abedin and K. Khayer, *Indian J. Chem*., **40B**, 240 (2001).
5. R.S. Varma and I.A. Khan, *Polish J. Pharmacol. Pharm*., **29**, 549 (1977).
6. C. Li, Y. Go, Z. Mao, K. Koyano, Y. Kai, N. Kanesha, Q. Zhu, Z. Zho and S. Wu, *Bull. Chem. Soc. (Japan)*, **69**, 1621 (1996).
7. T.A. Mcnell, *Antimicrob. Agents Chemother*., **4**, 105 (1973).
8. (a) R. Romagnoli, P.G. Baraldi, C. Cruz-Lopez, D. Preti, J. Bermejo and F. Estavez, *Chem. Med. Chem*., **4**, 1668 (2009); (b) M.G. Bursavich, A.M. Gilbert, S. Lombardi, K.E. Georgiadis, E. Reifenberg, C.R. Flannery and E.A. Morris, *Bioorg. Med. Chem. Lett*., **17**, 5630 (2007); (c) M.J. Konkel, M. Packiarajan, H. Chem, U.P. Topiwala, H. Jimenez, I.J. Talisman, H. Coate and M.W. Walker, *Bioorg. Med. Chem. Lett.*, **16**, 3950 (2006); (d) P.Y.S. Lam, G. Vinoent, C.G. Clark, S. Dcudon and P.K. Jadhav, *Tetrahedron Lett*., **42**, 3415 (2001).
9. (a) A.V. Shindikar, F. Khan and C.L. Viswanathan, *Eur. J. Med. Chem*., **41**, 786 (2006); (b) P. Moser, A. Sallmann and I.J. Wieserberg, *Med. Chem*., **33**, 2358 (1990); (c) R. Sarges, H.R. Howard, H.K. Koe and A. Weissman, *J. Med. Chem*., **32**, 437 (1989).
10. N. Peet, *J. Heterocycl. Chem*., **17**, 1514 (1990).
11. (a) Y. Chem and R.C. Larock, in ed.: J. Ackerman, In Modern Arylation Methods, Wiley/VCH New York (2009); (b) R. Sanz, *Org. Prep. Proced. Int*., **40**, 215 (2008).
12. (a) Z. Lin and R.C. Larock, *J. Org. Chem*., **71**, 3198 (2006); (b) Z. Lin and R.C. Larock, *Org. Lett*., **5**, 4673 (2003); (c) Z. Lin and R.C. Larock, *Org. Lett*., **6**, 99 (2004).
13. Z. Liu and R.C. Larock, *J. Am. Chem. Soc*., **127**, 13112 (2005).
14. D.G. Pintori and M.F. Greaney, *Org. Lett*., **12**, 168 (2010).
15. H. Yoshida, E. Shirakawa, Y. Honda and T. Hiyama, *Angew. Chem. Int. Ed*., **41**, 3246 (2002).
16. J. Zhao and R.C. Larock, *J. Org. Chem*., **72**, 583 (2007).
17. D.C. Rogness and R.C. Larock, *Tetrahedron Lett*., **50**, 4003 (2009).
18. Z. Lin and R.C. Larock, *J. Org. Chem*., **71**, 3198 (2006).
19. S. Peddibhotla, *Curr. Bioact. Compd*., **5**, 20 (2009).