IJST EXPLORE International Journal of Science and Technology
CENTRE OF PROFESSIONAL RESEARCH PUBLICATIONS
ISSN 2049-7318

International Journal of Science and Technology Volume 4 No. 8, August, 2015

One-pot Synthesis of Benzothiazines via Cu(I) Catalyzed Intramolecular Cyclisation from Dithioesters

Nagarakere. C. Sandhya, C. S. Pavan Kumar and Sannaiah.Ananda
Department of Studies in Chemistry, Manasagangothri, Mysore, University of Mysore, Mysore-570006-India

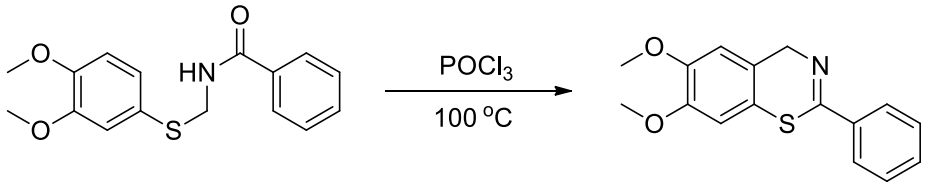
ABSTRACT

An efficient synthesis of benzothiazines from (*o*-halophenyl)methylamine has been achieved. This novel one-pot procedure involves CuI catalyzed C-S bond formation using dithioesters followed by a heterocyclization reaction. This efficient protocol has the advantages of one-pot synthesis, short reaction time, good yields (60-78%) and operational simplicity.

Key words*: S-Arylation, Benzothiazines, (O-Halophenyl) Methylamine, Heterocyclic Compounds and Dithioesters*

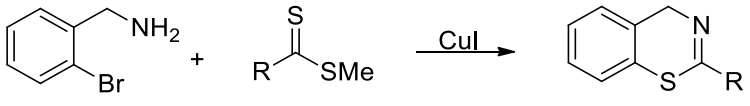
1. INTRODUCTION

Nitrogen- and sulfur-containing heterocylces are ubiquitous structures in huge number of biologically active natural products and small-bioactive molecules.[1] Benzothiazines has attracted significant interest due to their interesting pharmacological properties.[2-8] The synthetic and biological properties of the 1,3-benzothiazine nucleus is relatively un explored class of compounds from the stand point of both synthetic and biological chemistry. Sohar and co-workers reported the synthesis of 4*H*-1,3-benzothiazines from arylamide thioethers through an acid catalyzed intramolecular rearrangement with prosperous oxychloride (Scheme 1). 4*H*-1,3-benzothiazines are key intermediates for many biologically active rings like 1,5-benzothiazocines, and angularly condensed β-lactam derivatives. A series of benzothiazine derivatives like triazolobenzothiazines are known as centrally acting muscle relaxants also exhibit anitconvulsant activity and active in inhibiting various spinal polysynaptic reflexes Consequently, the development of facile and novel route for the synthesis of these sulfur-based heterocycles is of high interest.[9-11]



Scheme 1 Synthetic route benzothiazines from arylamide thioethers.

Most of the reported methods insvolve, hazardous reagents, solvents and synthetic strategy requires multistep reaction sequence. This encouraged us to consider for a direct reaction in the synthesis of functionalized benzothiazines In continuation of our work on synthesis of heterocyclic compounds,[12] herein, we report a novel method to access of benzothiazines from range of dithioesters via-S-arylation



1a **2a** **3a**

Table 1 Optimization of reaction conditions for synthesis of benzothiazines (3a)

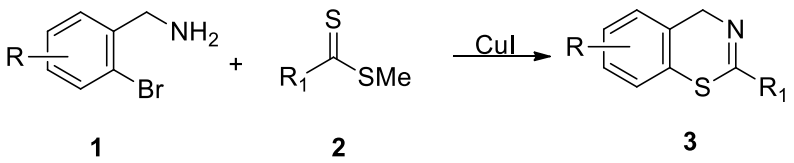
Entry	Cu catalyst	Solvent	Temp °C	Time in h	Yield (%)
1	-	THF	Reflux	24	-
2	CuI (20 mol%)	Toluene	Reflux	24	64
3	CuI (20 mol%)	CH_3CN	Reflux	24	55
4	CuI (20 mol%)	Ethylacetate	Reflux	24	20
5	CuI (20 mol%)	DMSO	Reflux	4	55
6	CuI (20 mol%)	Dioxane	Reflux	6	58
7	CuI (20 mol%)	$CHCl_3$	Reflux	6	62
8	CuI (20 mol%)	DMF	Reflux	4	70
9	CuI (50 mol%)	DMF	Reflux	4	68
10	CuI (10 mol%)	DMF	Reflux	8	57
11	-	DMF	Reflux	6	-
12	CuI (20 mol%)	DMF	100	6	74
13	CuI (20 mol%)	DMF	80	6	76
14	CuI (20 mol%)	DMF	70	6	59
15	CuBr (20 mol%)	DMF	80	6	52
16	CuOAc (20 mol%)	DMF	80	6	48

Conditions: **1a** (1.0 mmol), **1b** (1.0 mmol) in DMF, CuI (20 mol%), Yields are isolated yields of chromatographically purified compounds.

We set out to identify the possible mild conditions under which, the reaction of (2-bromorophenyl)methanamine **1a** and phenyl dithioester **2a** would proceed with synthetically useful rate. The reaction requirements including catalysts, were screened and the results are listed in Table 1. Initially, the reaction was conducted with (2-bromorophenyl)methanamine **1a** and phenyl dithioester **2a** was examined in THF in the absence of CuI, at reflux, the intermediate product *N*-(2-bromobenzyl)benzothiaomide was isolated in 75% yield. Encouraged by this initial result the reaction was screened with various solvents like toluene, THF, DMF, CH_3CN, ethyl acetate, DMSO, dioxane, $CHCl_3$ were screened and DMF was found to be the better choice. We also studied the effect of temperature it was found that optimum temperature is 80 °C. We evaluated the effect of catalyst on the reaction rate and yield, the reaction was found to proceed efficiently in the presence of CuI (20 mol %) giving the highest yield of **3a** (76%). An increase in the loading to 50 mol% failed to offer any significant advantages over the 20 mol% catalyst loading (Table 1, entry 9). A reduction in the loading of CuI showed negative effect on the yield of **3a** (Table 1, entry 10), whereas the yield was drastically decreased in the absence of CuI, (Table 1, entry 11). Other copper salts were also tested but CuI remained as the best one (Table 1, entries 15-16). In another set of experiments, effect of additive was tested. No significant improvement was observed in the presence of additives like proline, pivalic acid, picolic acid. Copper-catalyzed nitrogen free intramolecular C-S bond formation was shown to proceed efficiently without any bases and additives. With the optimized reaction conditions established, the substrate scope was examined, and results are summarized in (Table 2). Different dithioesters with electron-donating and electron-withdrawing groups on the benzene ring reacted smoothly with (2-bromorophenyl)methanamine **1a** to give the corresponding benzothiazines in moderate to good yields at 80 °C (Table 2). This reaction was not limited to aromatic dithioesters, but heterocyclic dithioester also underwent the reaction equally under mild conditions.

Dithioesters with –Me, methoxy functionalities obtained with good yields **3(b-c).** Dithioesters bearing halogens such as –F, –Cl, –Br were employed and the desired products were obtained in moderate to good yields **3(f–h).** Heterocyclic dithioester also underwent the reactions to offer the corresponding products with comparable yield **3(i-j)** Reactions of (2-bromorophenyl)methanamine with a range of dithioesters derived from differently substituted dithioesters were evaluated under the optimized conditions (Scheme 2). In all cases, products were obtained in good yields at 80 °C temperature or slightly at elevated temperatures products **3(a−j).** Importantly, other amine (-bromo-5-fluorophenyl)methanamine also underwent the title reaction under equally mild conditions. To prove the particularly of the present method in the synthesis of polycyclic amines, a gram scale synthesis of **3a** was performed.

Scheme 2: Substrate scope for the [3 + 2]-cycloaddition with benzylamines



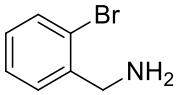
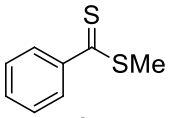
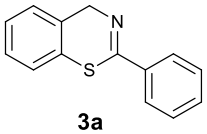
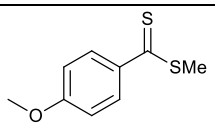
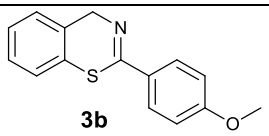
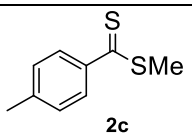
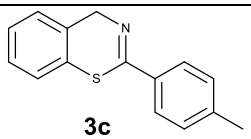
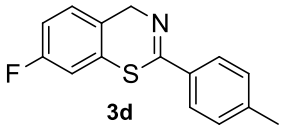
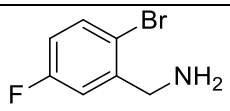
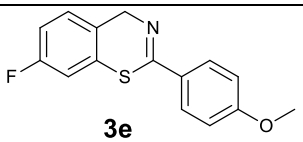
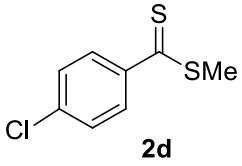
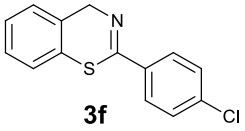
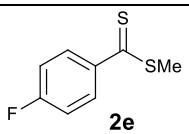
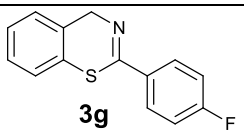
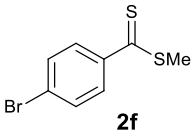
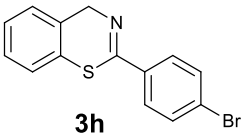
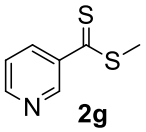
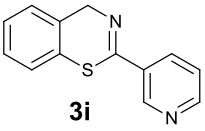
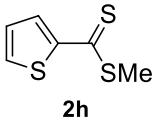
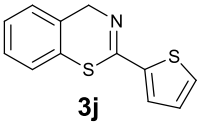
1 **2** **3**

2. CONCLUSION

In summary, we are successful in developing a new efficient method to produce substituted benzothiazine derivative via copper (I)-catalyzed intramolecular C-S bond formation. This approach is valuable alternative to widely used arylaminde

thioethers reactions. This method is complimentary to existing methods for the benzothiazines.

Table: 2 Synthesis of 4H [e] 1,3 benzothiazines from dithioesters.

Entry	Substrate	Dithioester	Product	Time in (h)	Yield in(%)
1	 **1a**	 **2a**	 **3a**	24	66
2	**1a**	 **2b**	 **3b**	24	61
3	**1a**	 **2c**	 **3c**	24	57
4	**1a**	**2b**	 **3d**	24	62
5	 **1b**	**2b**	 **3e**	24	61
6	**1a**	 **2d**	 **3f**	24	64
7	**1a**	 **2e**	 **3g**	24	60
8	**1a**	 **2f**	 **3h**	24	60
9	**1a**	 **2g**	 **3i**	24	65
10	**1a**	 **2h**	 **3j**	24	64

Characterisation data

2-Phenyl-4H-benzo[e][1,3]thiazine (3a)
Yield: 66%. White solid; ^{1}H NMR (400 MHz, $CDCl_3$ δ ppm): **δ** 4.83 (s, 2H, CH_2) 7.33-7.31 (1H, m), 7.36-7.34 (2H, m), 7.41-7.38 (1H, m), 7.47-7.45 (2H, m), 7.52-7.50 (1H, m), 8.07-8.05 (2H, m) ; ^{13}C NMR (100 MHz,$CDCl_3$ δ ppm): **δ** 29.6, 55.3, 126.5, 127.5, 127.7, 127.8, 128.1, 128.7, 129.8, 130.7, 132.0, 135.4 ; ESIMS [M + H]$^+$ m/z 226.01 Anal.Cald for $C_{14}H_{11}NS$ C, 74.63; H, 4.92; N, 6.22; S, 14.23. Found: C, 74.65; H, 4.90; N, 6.23; S, 14.21.

2-(4-methoxyphenyl)-4H-benzo[e][1,3]thiazine (3b)

Yield: 61% Pale Yellow solid;. ^{1}H NMR (400 MHz, $CDCl_3$ δ ppm): **δ** 3.83 (3H, s), 4.74 (2H, s), 6.93-6.90 (2H, m), 7.31-7.26 (3H, m), 7.38-7.36 (1H, m), 7.97-7.95 (2H, m) ; ^{13}C NMR (100 MHz,$CDCl_3$): **δ** 55.3, 56.5, 113.7, 126.6, 126.8, 127.3, 127.4, 129.4, 131.1, 131.7, 161.2, 162.0.; ESIMS [M + H]$^+$ m/z 256.04 Anal.Cald for $C_{15}H_{13}NOS$ C, 70.56; H, 5.13; N; 5.49; O, 6.27; S, 12.56. Found: C, 70.52; H, 5.10; N, 5.46; O, 6.28; S, 12.58.

2-(p-tolyl)-4H-benzo[e][1,3]thiazine (3c)

Yield: 57%. Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$ δ ppm): **δ** 2.26 (3H, s), 4.65 (2H, s), 7.11 (2H d, *J* = 8Hz,), 7.25-7.15 (4H, m), 7.81 (2H, d, *J* = 8.4Hz) ; ^{13}C NMR (100 MHz,$CDCl_3$ δ ppm): **δ** 56.4, 126.8, 127.50, 127.53, 127.8, 129.26, 129.28, 130.9, 131.4, 134.0, 141.6, 161.8.; ESIMS [M + H]$^+$m/z 240.11 Anal.Cald for $C_{15}H_{13}NS$ C, 75.28; H, 5.47; N, 5.85; S,13.40. Found: C, 75.20; H, 5.44; N, 5.83; S, 13.41.

7-fluoro-2-(p-tolyl)-4H-benzo[e][1,3]thiazine (3d)

Yield: 62% Brown Oily Compound; ^{1}H NMR (400 MHz, $CDCl_3$ δ ppm): **δ** 2.29 (3H, s), 4.61 (2H, s), 7.04-7.00 (2H, m), 7.11 (d, 2H, *J*=8.4Hz,), 7.31-7.27 (1H, m), 7.93 (1H, s) ; ^{13}C NMR (100 MHz,$CDCl_3$ δ ppm): **δ** 21.4, 28.9, 38.7, 113.8, 114.6, 114.8, 127.7, 128.0, 129.4, 132.4, 142.2, 160.6, 163.1.; ESIMS [M + H]$^+$ m/z ; 258.12 Anal.Cald for $C_{15}H_{12}FNS$ C, 70.01; H, 4.70; F, 7.38; N, 5.44; S, 12.46. Found: C, 70.03; H, 4.68; F, 7.39; N, 5.46; S, 12.45.

7-fluoro-2-(4-methoxyphenyl)-4H-benzo[e][1,3]thiazine (3e)

Yield: 61% Pale Yellow solid;. ^{1}H NMR (400MHz, $CDCl_3$ δ ppm): **δ** 3.79 (3H, s), 4.68 (2H, s), 6.89-6.87(2H, m), 6.96 (d, 1H, *J*=2Hz), 7.07, 7.07 (dd, 1H, *J*=11.2, 5.6Hz), 7.24-7.19(1H, m), 7.96-7.94 (2H, m).; ^{13}C NMR (100MHz, $CDCl_3$ δ ppm): **δ** 55.4, 113.7, 114.8, 115.0, 126.9, 127.0, 128.1, 128.2, 130.0, 132.0, 160.7, 163.0, 163.1.; ESIMS [M + H]$^+$ m/z ; 274.09 Anal.Cald for $C_{15}H_{12}FNOS$ C, 65.91; H, 4.43; F, 6.95; N, 5.12; O, 5.85; S, 11.73. Found: C, 65.89; H, 4.45; F, 6.92; N, 5.14; O, 5.84; S, 11.75.

2-(4-chlorophenyl)-4H-benzo[e][1,3]thiazine (3f)

Yield: 64% Pale Yellow solid;. ^{1}H NMR (400 MHz, $CDCl_3$ δ ppm): **δ** 2.27 (3H, s), 4.67 (2H, s), 7.13 (d, 2H, *J*=8.4Hz), 7.27-7.17 (4H, m), 7.82 (d, 2H, *J*=8Hz,).; ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): **δ** 21.4, 56.3, 126.8, 127.53, 127.54, 127.7, 127.8, 129.2, 130.8, 131.4, 133.9, 141.7, 162.1.; ESIMS [M + H]$^+$ m/z ; 260.13 Anal.Cald for $C_{14}H_{10}ClNS$ C, 64.73; H, 3.88; Cl; 13.65; N, 5.39; S, 12.34. Found: C, 64.71; H, 3.89; N, 5.37, S, 12.36.

2-(4-fluorophenyl)-4H-benzo[e][1,3]thiazine (3g)

Yield: 60% Pale Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$ δ ppm): **δ** 4.71 (2H, s), 7.13 (d, 2H, *J*=8.4Hz), 7.17-7.27 (4H, m) 7.82 (d, 2H, *J*=8Hz); ^{13}C NMR (100 MHz, $CDCl_3$ δ ppm): **δ** 56.3, 116.5, 127.53, 127.54, 127.81, 129.6, 130.8, 131.4, 132.0, 141.7, 162.1, 165.5 ; ESIMS [M + H]$^+$ m/z ; 244.21. Anal.Cald for $C_{14}H_{10}FNS$ C, 69.11; H, 4.14; F, 7.81; N, 5.76; S, 13.18. Found: C, 69.10; H, 4.15; F, 7.83; N, 5.75; S, 13.17.s

2-(4-bromophenyl)-4H-benzo[e][1,3]thiazine (3h)

Yield 60%. White solid; ^{1}H NMR (400 MHz, $CDCl_3$ δ ppm): **δ** 4.80 (2H, s), 7.13(d, 2H *J*= 8.4Hz), 7.17-7.27(4H, m), 7.72 (d, 2H, *J*= 8Hz,).; ^{13}C NMR (100 MHz, $CDCl_3$ δ ppm): **δ** 56.3, 125.4, 126.5, 126.8, 127.5, 127.8, 129.2, 130.8, 131.4, 133.9, 135.7, 162.1.; ESIMS [M + H]$^+$ m/z; 305.19 Anal.Cald for $C_{14}H_{10}BrNS$ C, 55.28, H, 3.31; Br, 26.27, N, 4.60; S, 10.54. Found: C, 55.26; H, 3.32; Br, 26.28; N, 4.59; S, 10.55.

2- (Pyridin-3-yl)-4H-benzo[e][1,3]thiazine (3i)

Yield. 65% Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$ δ ppm): **δ** 4.83 (2H, s), 7.33-7.31(1H, m), 7.36-7.34 (2H, m), 7.41-7.38 (1H, m), 7.47-7.45 (2H, m), 7.52-7.50 (1H, m), 8.07-8.05(1H, m).; ^{13}C NMR (100 MHz,$CDCl_3$ δ ppm): **δ** 55.3, 126.5, 127.5, 127.7, 127.8, 128.1, 128.7, 129.8, 130.7, 132.0, 135.4, 151.5, 151.9; ESIMS [M + H]$^+$ m/z; 227.30 Anal.Cald for $C_{13}H_{10}N_2S$ C, 69.00, H, 4.45, N, 12.38, S, 14.17. Found: C, 69.09, H, 4.42, N, 12.39, S, 14.18.

2-(thiophene-2-yl)-4H-benzo[e][1,3]thiazine (3j)

Yield 64% White solid ;^{1}H NMR (400 MHz, $CDCl_3$ δ ppm): **δ** 4.61 (2H, s), 6.96(t, 1H, *J*= 3.6Hz,), 7.15-7.18 (3H, m),7.23-7.25 (1H, m) 7.32 (d, 1H, *J*= 4.8Hz), 7.58-7.59(1H, m).; ^{13}C NMR (100 MHz, $CDCl_3$ δ ppm): **δ** 56.0, 126.6, 127.0, 127.6, 129.42, 129.40, 130.01, 130.07, 130.3, 131.8, 141.6, 155.6.; ESIMS [M + H]$^+$ m/z; 232.32 Anal.Cald for $C_{12}H_9NS_2$ C, 62.30; H, 3.92; N, 6.05; S, 27.72. Found: C, 62.29; H, 3.93; N, 6.04; S, 27.70

Acknowledgement

We thank for the NMR facility, IOE, University of Mysore, Manasagangotri, Mysuru-570006 for spectral studies.

REFERENCES

[1] (a) Llauger, L.; He, H. Z.; Kim, J.; Aguirre, J.; Rosen, Z.; Peters, U.; Davies, P.; Chiosis, G. *J. Med. Chem.* (2005), 48, 2892–2905; (b) Kiihler, T. C.; Fryklund, J.; Bergman, N.; Weilitz, J.; Lee, A.; Larssonl, H. *J. Med. Chem.* (1995), 38, 4906–4916; (c) Madsen, P.; Knudsen, L. B.; Wiberg, F. C.; Carr, R. D. *J. Med.*

Chem. (1998), 41, 5150–5157; (d) Pietrancosta, N.; Moumen, A.; Dono, R.; Lingor, P.; Planchamp, V.; Lamballe, F.; Bahr, M.; Kraus, J.-L.; Maina, F. *J. Med. Chem.* (2006), 49, 3645; (e) Mavrova, A. T.; Vuchev, D.; Anichina, K.; Vassilev, N. *Eur. J. Med. Chem*. (2010), 45, 5856.

[2] Nomura, Y.; Goto, Y. WO 26,959, (1995); *Chem. Abstr. (*1996), *124*, 146182m.

[3] Levi, S.; Benedini, F.; Bertolini, G.; Dona, G.; Gromo, G.; Sala, A. WO 25,542, 1993; *Chem. Abstr. (*1994), *120*, 245128x..

[4] Levi, S.; Benedi, F.; Bertolini, G.; Gromo, G.; Mizrhai, J.; Sala, A. WO 04,048, 1995; *Chem. Abstr. (*1995,) *123*, 9449

[5] (a) Cecchetti, V.; Cruciani, G.; Filiponi, E.; Fravolini, A.; Tabarrini, O.; Xin, T. *Bioorg. Med. Chem. (*1997), *5*, 1339.

[6] Lopatina, K. I.; Artemenko, G. N.; Sokolova, T. V.; Salimov, R. V.; Vikhlayaev, Yu. I.; Zagorevskii, V. A. *Khim.-Farm. Zh. (*1978), *12*, 65; *Chem. Abstr.(* 1978), *89*, 109315.

[7] Palaska, E.; Erdogan, H.; Sakak, C.; Sarac, S.; Yulug, N.; *Turk.J. Med. Sci. (*1993), *18*, 209; *Chem. Abstr. (*1994), *120*, 129372y.

[8] (a) Hari, A.; Miller, B. L.*Organic Lett. (*2000), *2*, 3667. (b). Fernandes, M. A.; Reid, D. H. *Synlett. (*2003), 2231.

[9] Junnarkar, A. Y.; Singh, P. P.; Patnaik, G. K.; Shrotri, D. S. *Pharmacol. Res*. (1992), 26, 131.

[10] Grandolini, G.; Tiralti, M. C.; Rossai, C.; Ambrogi, V.;Orzalesi, G.; De Regis, M. *Farm Ed. Sci*. (1987), 42,43.

[11] Grandolini, G.; Rossi, C.; Tiralti, M. C.; Orzalesi, G.;De Regis, M. *Farm Ed. Sci*. (1985), 40, 221.

[12] (a) S. Vijay Kumar, Santosh K. Yadav, B. Raghava, B. Saraiah, H. Ila, K. S. Rangappa, and A. Hazra, *J. Org. Chem.*, (2013), 78(10), 4960; (b) A. Jenifer Vijay, K. N. Nandeesh, G. M. Raghavendra, K. S. Rangappa, K. Mantelingu, *Tett. Lett*., (2013), 54, 6533

[13] (a) K. S. Sharath Kumar, T. R. Swaroop, K. B. Harsha, K. H. Narasimhamurthy and K. S. Rangappa, *Tett. Lett. (*2012), 42(17), 5619; (b) T. R. Swaroop, R. Roopashree, H. Ila and K. S. Rangappa, *Tett. Lett.* (2013), 54(2), 147.

[14] (a) B. Raghava, G. Parameshwarappa, A. Acharya, T.R. Swaroop, K. S. Rangappa and H. Ila, *Eu. J. Org. Chem.*, (2014), 9, 1882; (b) A.C. Vinayaka, M. P. Sadashiva, X. Wu, S. S. Biryukov, J. A. Stoute, K. S. Rangappa and D. Channe Gowda *Org. Biomol. Chem*., (2014), 12, 8555. (c) G. S. Lingaraju, T. R. Swaroop, A. C. Vinayaka, K. S. Sharath Kumar, M. P. Sadashiva, K. S. Rangappa. *Synthesis.*, (2012), 44(9), 1373,
Y. R. Girish, K. S. Sharath Kumar, M. Umashankar, N. K. Lokanath, K. S. Rangappa and S. Shashikanth, *RSC Adv*., (2014), 4, 55800.

[15] S. Chandrappa, K. Vinaya, M. Umashankara and K. S. Rangappa *Tett. Lett.*, (2011), 52(42), *5474.*

[16] S. Chandrappa, C.V. Kavitha, M.S. Shahabuddin, K. Vinaya, C.S. Ananda Kumar, S.R. Ranganatha, S. C. Raghavan, and K.S. Rangappa, *Bioorganic & Medicinal Chemistry.*, (2009), 17(6), 2576

[17] D. Karthigeyan, S. Siddhanta, A. Hari Kishore, Sathya S. R. R. Perumal, H. Ågren, Surabhi Sudevan, A. V. Bhat, K. Balasubramanyam, K.S. Rangappa, T. K. Kundu, and C. Narayana, *PNAS (USA).*, (2014), 111(29), 10416.