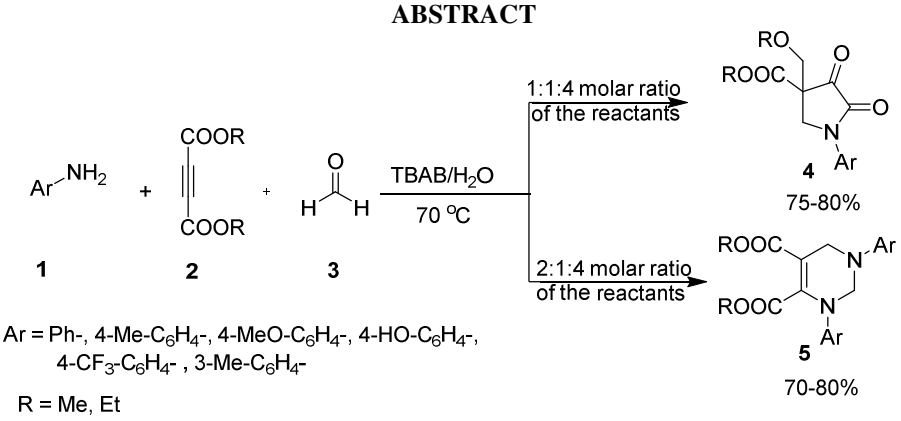
RJC

RASĀYAN ***J. Chem.***
Vol. 10 | No. 1 |6 - 12 | January - March | 2017
ISSN: 0974-1496 | e-ISSN: 0976-0083 | CODEN: RJCABP
http://www.rasayanjournal.com
http://www.rasayanjournal.co.in

SYNTHESIS OF PYRROLIDINES AND TETRAHYDROPYRIMIDINES *VIA* ONE-POT AND THREE COMPONENT CASCADE COUPLING STRATEGY IN WATER

Balaswamy Puligilla, Battu Satyanarayana* and Seema Aravind*
Department of Chemistry, Osmania University, Hyderabad, Telangana State, India-500007.
*E-mail: satyambchem@yahoo.co.in; aravind.iict@gmail.com

ABSTRACT



A simple and efficient method for the preparation of highly functionalized pyrrolidines and tetrahydropyrimidine derivatives have been accomplished in a one-pot and three component cascade reaction protocol. The reaction is mediated by inexpensive, easily accessible *tetra-n*-butylammoniumbromide, which can retain its reactivity and be recyclable and, also water as a green solvent system. Importantly, by changing the molar ratio of the three starting materials, provided biologically significant pyrrolidines (primary amine: acetylene dicarboxylate: formaldehyde in 1:1:4 molar ratio), and tetrahydropyrimidines (primary amine: acetylene decarboxylate: formaldehyde in 2:1:4 molar ratio) in a good to moderate yields.

Keywords: Multi-component reactions (MCRs), TBAB, Pyrrolidines, Pyrimidines, Water.

INTRODUCTION

The past decades have witnessed substantial progress in multicomponent reactions as a beneficial approach in the synthesis of structurally complex molecules from simple starting materials.[1-6] The highly atom- and step-economic transformations in multicomponent reactions have fascinated increasing attention in exploiting simple starting materials.

In particular, three-component coupling reactions have proven remarkably successful in generating molecular complexities in a single step operation. The polysubstituted pyrrolidines and tetrahydro pyrimidines ring systems are an important core structure in many of biologically active natural products and drug candidates. These poly substituted heterocyclic compounds (pyrrolidines and tetrahydro pyrimidines) and their derivatives are considered as important bioactive building blocks in a heterocyclic chemistry,[7-11] which have potential biological activities such as anti-cancer,[12-17] anti-histaminic, anti-bacterial,[18] anti-fungal,[19] anti-inflammatory,[20] anti-viral,[21] HIV protease inhibitors,[22] mycobacterium tuberculosis inhibitors, and muscarinic receptor agonists for the treatment of Alzheimer's disease.[23-26] Literature survey reveals that there are very few synthetic methods for construction of these heterocycles in a multicomponent protocol. Thus, considerable efforts have been made to develop reliable synthetic procedures for construction of these heterocycles are highly desirable. However, many of these classical

http://dx.doi.org/10.7324/RJC.2017.1011545

protocols often involve the use of costly reagents, high temperatures, extended reaction times and harsh reaction conditions, and they also produce mixtures of products.[27-31] These challenges can mainly be overcome by the employment of one-pot multicomponent reactions (MCRs), which would give high yields of product in shorter reaction time. In continuation of our research on the development of novel synthetic methodologies and screening of the analogues,[32-34] we have discovered efficient method for the synthesis of fully substituted pyrrolidines and tetrahydro pyrimidines derivatives.

EXPERIMENTAL

General

Glassware was dried in an oven (120 °C), and cooled before use. Unless otherwise noted, materials obtained commercially were used without purification. Reactions were monitored by TLC on silica gel plates using UV-light and *β*-naphthol for visualization. Column chromatography was performed on silica gel (60-120 mesh) using *n*-hexane and ethyl acetate as eluent. Evaporation of solvents was conducted under reduced pressure at 50 °C. NMR spectra were reported on a Bruker Avance 200 NMR spectrometer at 200 MHz (^{1}H) and 50 MHz (^{13}C). Deuterated chloroform was used as the solvent and spectra were calibrated against the residual solvent peak (7.24 ppm for ^{1}H and 77.0 ppm for ^{13}C). Chemical shifts (δ) and coupling constants (J) are given in ppm (parts per million) and Hz (Hertz), respectively. See supporting information for spectral copies of all the synthesized compounds.

General experimental procedure for the synthesis of polysubstituted pyrrolidine derivatives (4a-e)

Amine **1** (93 mg, 1 mmol) was added 10 mL of water in a 50 mL flask at rt followed by acetylenedicarboxylate **2** (1 mmol), formaldehyde **3** (4 mmol). The reaction mixture was stirred for 2 h at 70 ºC. After completion of the reaction, it was cooled and extracted with ethyl acetate (3 × 15 mL), organic layers were combined and washed with water (20 mL), brine (20 mL), and dried with anhyd Na_2SO_4. The solvent evaporated under reduced pressure, the crude product was purified by column chromatography using silica gel (eluent: EtOAc: *n*-hexane: 2:8 v/v) to afford the polysubstituted pyrrolidines (**4**) derivative as pure product. The TBAB contained aqueous phase was reused three times for same type of reactions and we observed that its catalytic activity was slightly decreased after 3 times.

Ethyl 3-(ethoxymethyl)1-phenyl-4, 5-dioxopyrrolidine-3-carboxylate (4a)

Yellow solid; mp 84-85 ºC. yield: 80%; FT-IR KBr (cm^{-1}): 1780, 1735, 1596, 1486; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.87 (2H, d, J = 8.0 Hz), 7.45 (1H, d, J = 8.0 Hz), 7.30 (1H, d, J = 12.0 Hz), 4.26 (3H, d, J = 12.0 Hz), 3.96 (2H, q, J = 7 .0 Hz), 3.60 (2H, q, J = 7 .0 Hz), 1.28 (3H, t, J = 7.0 Hz), 1.08 (3H, t, J = 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 194, 168, 156, 128, 126, 125, 119, 98, 76, 72, 68, 66, 54, 49, 17, 16; ESI-MS: *m/z* 306 [M+H]$^+$.

Ethyl-3-(ethoxymethyl), 1-(3-methylphenyl) 4, 5-dioxopyrrolidine-3-carboxylate (4b)

Yellow solid; mp 95-96 ºC; yield: 76%. FT-IR KBr (cm^{-1}): 1775, 1715, 1520, 1255; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.85 (s, 1H), 7.80 (1H, d, J = 8.0 Hz), 7.45 (1H, t, J = 8.0 Hz), 7.20 (1H, d, J = 8.0 Hz), 4.50 (1H, d, J = 12.0 Hz), 4.30 (m, 3H), 3.98 (2H, q, J = 7.0 Hz), 3.50 (2H, q, J = 7.0 Hz), 2.46 (s, 3H), 1.30 (3H, t, J = 7.0 Hz), 1.10 (3H, t, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 194, 168, 157, 140, 131, 130, 121, 118, 78, 73, 61, 56, 54, 50, 24; ESI-MS: *m/z* 320 [M+H]$^+$.

Methyl 3-(methoxymethyl)-1-(*p*-tolyl)-4, 5-dioxopyrrolidine-3-carboxylate (4c)

White solid; mp 81-82 ºC; yield: 80%. FT-IR KBr (cm^{-1}): 1780, 1712, 1519, 1263; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.76 (s, 1H), 7.65 (1H, d, J = 8.0 Hz), 7.30 (1H, t, J = 78.0 Hz), 7.10 (1H, d, J = 8.0 Hz), 4.56 (1H, d, J = 12.0 Hz), 4.27 (1H, d, J = 12.0 Hz), 3.98 (1H, d, J = 10.0 Hz), 3.86 (1H, d, J = 10.0 Hz), 3.78 (s, 3H), 3.4 (s, 3H), 2.46 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 194, 167, 156, 138, 136, 128, 77, 71, 68, 66, 63, 56, 49, 24, 19, 18; ESI-MS: *m/z* 292 [M+H]$^+$.

Methyl 3-(methoxymethyl) 1-(4-hydroxyphenyl)-4, 5-dioxopyrrolidine-3-carboxylate (4d)
Yellow oil; yield: 75%; FT-IR KBr (cm^{-1}): 1378, 1776, 1696, 1520, 1460; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.68 (2H, d, J = 8.0 HZ), 6.90 (2H, d, J = 8.0 Hz), 4.50 (1H, d, J = 12.0 Hz), 4.26 (1H, d, J = 12.0 Hz), 4.0 (1H, d, J = 1.0 Hz), 3.94 (1H, d, J = 1.0 Hz), 3.86 (s, 3H), 3.36 (s, 3H), 2.86 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 194, 166, 157, 130, 122, 115, 78, 72, 60, 56, 54, 51; ESI-MS: *m/z* 294 $[M+H]^+$.

Methyl 3-(methoxymethyl) 1-(4-triflouromethylphenyl)-4, 5-dioxopyrrolidine-3-carboxylate (4e)
Yellow solid; mp 102-104 ºC; yield: 78%; FT-IR KBr (cm^{-1}): 1780, 1740, 1615, 1462; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.06 (2H, d, J = 8.0 Hz), 7.74 (2H, d, J = 8.0 Hz), 4.56 (1H, d, J = 8.0 Hz), 4.26 (1H, d, J = 8.0 Hz), 3.98 (1H, d, J = 12.0 Hz), 3.90 (1H, d, J = 8.0 Hz), 3.80 (s, 3H), 3.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 193, 166, 142, 127, 125, 119, 77, 74, 60, 56, 54, 48; ESI-MS: *m/z* 346 $[M+H]^+$.

General procedure for the synthesis of polysubstituted 1, 2, 3, 6-tetra-hydro-pyrimidine derivatives (5a-e)
TBAB (1.0 mmol) was added in 20 mL of water and warmed to 70 ºC to get clear mixture. Amine **1** (2.0 mmol), and dimethyl/diethyl-acetalynedicarboxylate (1.0 mmol) **2** were added to above reaction mixture and stirred for another 10 minutes, then formaldehyde **3** (4.0 mmol) was added and reaction mixture was heated to reflux for 2 h. After completion, indicated by TLC. Reaction mixture was cooled and extracted with ethyl acetate (3 × 15 mL), then EtOAc was washed with 20 mL water, 20 mL brine, and dried over anhyd. Na_2SO_4. Evaporated under vacuum, purification of the crude residue was done by chromatography using silica gel (eluent: EtOAc: *n*-hexane: 2:8 v/v) to afford tetrahydro pyrimidine (**5**) derivative in good yields.

Dimethyl-1, 3-diphenyl- 1, 2, 3, 6- tetrahydropyrimidine-4, 5-dicarboxylate (5a)
Yellow solid; mp 84-86 ºC. yield: 80%; FT-IR KBr (cm^{-1}): 1749, 1717, 1618, 1336; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.61 (2H, d, J = 8.1 Hz), 7.45 (2H, d, J = 8.0 Hz), 7.25 (2H, d, J = 8.0 Hz), 7.12 (2H, d, J = 8.0 Hz), 6.84 (2H, d, J = 8.0 Hz), 4.97 (s, 2H), 4.34 (s, 2H), 3.79 (s, 3H), 3.65 (s, 3H); ESI-MS: *m/z* 353 $[M+H]^+$.

Dimethyl 1, 3-bis-(4-methoxyphenyl)-1, 2, 3, 6-tetrahydropyrimidine-4, 5-dicarboxylate (5b)
Yellow oil; yield: 75%; FT-IR KBr (cm^{-1}): 1744, 1697, 1584, 1438, 1250; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.86 (2H, d, J = 8.0 Hz), 6.75 (2H, d, J = 8.0 Hz), 6.72 (2H, d, J = 8.0 Hz), 6.70 (2H, d, J = 8.0 Hz), 4.75 (s, 2H), 4.13 (s, 2H), 3.75 (s, 6H), 3.70 (s, 3H), 3.59 (s, 3H, CH_3); ESI-MS: *m/z* 435 $[M+H]^+$.

Dimethyl 1, 3-di-*p*-tolyl-1, 2, 3, 6- tetrahydropyrimidine-4, 5-dicarboxylate (5c)
Yellow oil; yield: 75%; FT-IR KBr (cm^{-1}): 1745, 1698, 1586, 1437, 1255; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.36 (2H, d, J = 8.0 Hz), 7.23 (2H, d, J = 8.0 Hz), 6.76 (2H, d, J = 8.0 Hz), 6.66 (2H, d, J = 8.0 Hz), 4.85 (s, 2H), 4.23 (s, 2H), 3.79 (s, 3H), 3.59 (s, 3H), 2.35 (s, 3H), 2.26 (s, 3H); ESI-MS: *m/z* 381 $[M+H]^+$.

Dimethyl-1, 3-bis(4-triflouromethyl)-phenyl)-1, 2, 3, 6-tetrahydropyrimidine-4, 5-dicarboxylate (5d)
Yellow oil; yield: 70%; FT-IR KBr (cm^{-1}): 1746, 1710, 1609, 1441; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.17 (2H, d, J = 8.0 Hz), 7.40 (2H, d, J = 8.0 Hz), 7.12 (2H, d, J = 8.0 Hz), 6.86 (2H, d, J = 8.0 Hz), 4.90 (s, 2H), 4.32 (s, 2H), 3.76 (s, 3H), 3.64 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 193, 166, 156, 142, 136, 127, 124, 118, 78, 77, 76, 73, 59, 56, 54, 49; ESI-MS: *m/z* 489 $[M+H]^+$.

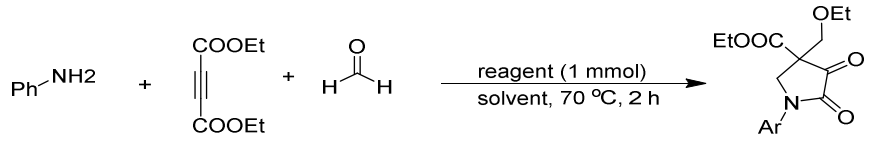
Diethyl 1, 3-bis-(4-(triflouromethyl)-phenyl)-1, 2, 3, 6–tetrahydropyrimidine 4-5- dicarboxylate (5e)
Yellow oil; yield: 70%; FT-IR KBr (cm^{-1}): 1743, 1712, 1616, 1330; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.56 (2H, d, J = 8.0 Hz), 7.43 (2H, d, J = 8.0 Hz), 7.17 (2H, d, J = 8.0 Hz), 6.77 (2H, d, J = 8.0 Hz), 4.91 (s, 2H), 4.34 (s, 2H), 4.25 (2H, q, J = 7.0 Hz), 4.10 (2H, q, J = 7.0 Hz), 1.34 (3H, t, J = 7.0 Hz), 1.08 (3H, t, J = 7.0 Hz); ^{13}CNMR ($CDCl_3$, 50 MHz): δ 196, 166, 161, 158, 146,127, 126, 120, 117, 116, 115, 114, 99, 78, 51, 47. ESI-MS: *m/z* 517 $[M+H]^+$.

RESULTS AND DISCUSSIONS

We enlighten this method to design and develop biologically significant heterocyclic compounds with the TBAB as a catalyst in aqueous medium possessing hydrophobic and hydrophilic affinity and catalyzed different chemical reactions involving reversible formation of host guest complexes between two immiscible phases. We herein, describe a novel approach for the preparation of 1,3,3-trisubstituted dioxopyrrolidine derivatives (**4**) and tetra substituted tetrahydropyrimidines (**5**) through one-pot, three-component method of aromatic amines, dialkylacetylene dicarboxylates, and formaldehyde.

Initially, aniline (**1**), dimethylacetylene decarboxylate (**2**) and formaldehyde (**3**) were chosen as model substrates for the optimization of reaction conditions (Table-1). To our delight, cascade reactions did not take place in water at 50 ºC for 12 h (entry 1, table 1), but the product can be isolated with a TBAB catalyst and the expected product was formed in a 45% yield when TBAI was used as the catalyst and found no improvement in the yield was observed (entry 2–3, Table-1). With 1 equivalent of TBAB in water at 70 ºC for 2 h gave 80% yield of corresponding pyrrolidines derivative. Furthermore, the extensive range of solvents such as DMF, THF, 1,4-dioxane, ethanol and solvent free conditions were screened, and water was found to be superior to the others (entries 4–9). It is noteworthy to mention that changing the molar ratios of the staring materials gave the five and six membered heterocycles as a major product in a good to moderate yields along with other heterocyclic compound (**4** or **5**) as a minor product.

Table-1: Optimization of multicomponent reaction for the synthesis of 4[a]



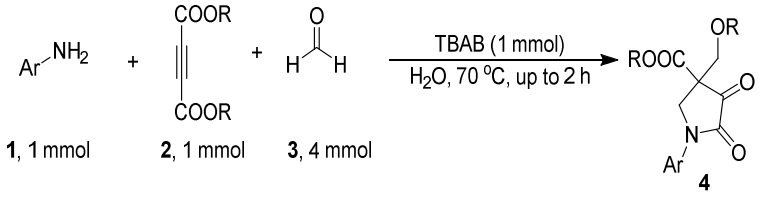
1, 1 mmol **2**, 1 mmol **3**, 4 mmol **4a**

entry	solvent	reagent (mole %)	time (h)	yield (%)[b] 4
1	water	--	2.0	0
2	water	TBAB (10)	2.0	45
3	water	TBAI (10)	2.0	30
4	water	TBAB (100)	2.0	80
5	THF	TBAB (100)	2.0	50
6	DMF	TBAB (100)	2.0	60
7	1,4-dioxane	TBAB (100)	2.0	45
8	ethanol	TBAB (100)	2.0	55
9	solvent free	TBAB (100)	2.0	complex mixture

[a]Reaction conditions: DEAD (1.0 mmol), amine (1.0 mmol), TBAB (1.0 mmol), formaldehyde (4.0 mmol), water, 70 ºC, [b]Isolated yield of **4a**.

With the optimal reaction conditions established, we have investigated the scope of anilines (**1**), dimethyl, diethylacetylene dicarboxylates (**2**) and formaldehyde (**3**) using TBAB mediated conditions, with 1:1:4 molar ratios of reactants afforded the desired pyrrolidine products as a major compound, respectively in good yields (Table-2). The 4,5-dioxopyrrolide scaffolds (**4**) were formed in excellent yields in 2 h at 70 ºC in water as a green solvent. The present reaction conditions are mild, various functionalities remain intact in the products, and water as a solvent makes the present protocol efficient.

Table-2: Synthesis of polysubstituted pyrrolidines[a]



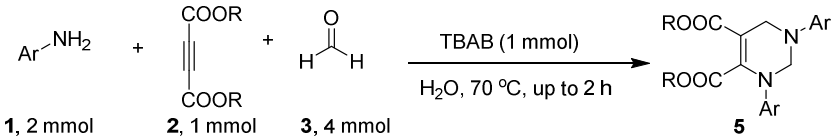
1, 1 mmol **2**, 1 mmol **3**, 4 mmol **4**

Ar = C_6H_5-, 4-Me-C_6H_4-, 4-MeO-C_6H_4-, 4-HO-C_6H_5-, 4-CF_3-C_6H_4-
R = -CH_3, -C_2H_5

entry	Ar	R	product	temp (°C)	time (h)	yield (%)[b]
1	C_6H_5	Et	**4a**	70	2	80
2	3-Me-C_6H_4	Et	**4b**	70	2	76
3	4-MeO-C_6H_4	Me	**4c**	70	1.5	80
4	4-HO-C_6H_4	Me	**4d**	70	2	75
5	4-F_3C-C_6H_4	Me	**4e**	70	2	78

[a]Reaction conditions: DMAD/DEAD (1.0 mmol), amine (1.0 mmol), TBAB (1.0 mmol), formaldehyde (4.0 mmol), aqueous solvent, temperature 70 °C, [b]Isolated yield of **4**; we have also isolated the compounds (**5a-e**) in this reactions up to 12% yield.

Table-3: Synthesis of polysubstituted tetrahydro pyrimidines [a]



1, 2 mmol **2**, 1 mmol **3**, 4 mmol **5**

Ar = C_6H_5-, 4-Me-C_6H_4-, 4-MeO-C_6H_4-, 4-HO-C_6H_5-, 4-CF_3-C_6H_4-
R = -CH_3, -C_2H_5

entry	Ar	R	product	temp (°C)	time (h)	yield (%)[b]
1	C_6H_5	Me	**5a**	70	2	80
2	3-MeO-C_6H_4	Me	**5b**	70	2	75
3	4-Me-C_6H_4	Me	**5c**	70	1.5	75
4	4-CF_3-C_6H_4	Me	**5d**	70	2	70
5	4-CF_3-C_6H_4	Et	**5e**	70	2	70

[a]Reaction conditions: DMAD/DEAD (1.0 mmol), amine (2.0 mmol), TBAB (1.0 mmol), Formaldehyde (4.0 mmol), aqueous solvent, temperature 60-70 °C, [b]Isolated yield of **5**; we have also isolated the compounds (**4a-e**) in this reactions up to 14% yield.

When the reaction was carried out with 2:1:4 molar ratios of reactants aniline (**1a**), dimethyl acetylenedicarboxylate (**2**) and formaldehyde (**3**) resulted 1,3,4,5-tetrasubstituted 1,2,3,6-

tetrahydopyrimidine (**5a**) derivative (Table-3) under similar conditions as applied for the preparation of pyrrolidines. From these results, we also examined various anilines (**1**), both dimethyl and diethyl acetylenedicarboxylates (**2**) and formaldehyde (**3**) under similar reaction conditions gave moderate to good yields of products as shown in table 3. On the basis of the above screening, we studied and pleased to find that, the present protocol continued efficiently, and the corresponding products were furnished in good yields. The electronic effects of the aromatic amines had shown a slight influence in the product formation was observed.

CONCLUSION

In conclusion, we have described the synthesis of substituted pyrrolidines and pyrimidines under TBAB mediated one-pot, multi-component domino cyclization reaction. With the use of water as a green solvent and inexpensive TBAB, under mild reaction condition the present protocol is convenient, cost-effective and environmentally benign. This phase transfer catalyst mediated green reactions may have widespread applications in pharmaceutical, organic and medicinal chemistry and further applications of this protocol to make medicinally important heterocycles are underway in our laboratory.

ACKNOWLEDGEMENT

The authors thankful to Department of Chemistry, Osmania University, Hyderabad, 500007, India for constant encouragement, generously supported and facilitations provided in this research work as well as financial support.

REFFERENCES

1. P. G. Rambhau and P. R. Ambarsing, *Drug invent. Today*, **5**, 148 (2013).
2. N. Naresh, R. Kant and T. Narender, *J. Org. Chem.*, **79**, 3821 (2014).
3. S. Bommagani, N. R. Penthala, S. Parkin and P. A. Crooks, *ActaCryst.* E, **71**, 1536 (2015).
4. M. D. Reddy, F. R. Fronczek and E. B. Watkins, *Org. Lett.*, **18**, 5620 (2016).
5. M. D. Reddy and E. B. Watkins, *J. Org. Chem.* **80**, 11447 (2015).
6. K. N. Puri, G. V. Korpe, *Rasayan J. Chem.* **9**, 401 (2016)
7. N. Srivastav, T. Manning, Y. Kunimoto and R. Kumar, *Bioorg. Med. Chem.* **15**, 2045 (2007).
8. C. R. Reddy, P. Sujatha and M. D. Reddy, *Org. Lett*. **17**, 896 (2015)
9. S. M. Sondhi, R. Shuklab and R. Raghubir, *Bioorg. Med. Chem.,* **15**, 3334 (2007).
10. C. R. Reddy, M. D. Reddy and U. Dilipkumar, *Eur. J. Org. Chem.*, 6310 (2014)
11. G. Raju, R. Srinivas, M. D. Reddy, C. R. Reddy and N. Nagesh, *Nucleos Nucleot Nucl.* **33**, 489 (2014).
12. T. Janecki, E. Blaszczyk, E. Studzian, A. Janecka, U. Krajewska and M. Rozalski, *J. Med. Chem.* **48**, 3516 (2005).
13. N. R. Penthala, V. Janganati, S. Bommagani and P. A. Crooks, *Med. Chem. Comm.* **5**, 886 (2014).
14. P. Suman, T. R. Murthy, K. Rajkumar, D. Srikanth, C. Dayakar, C. Kishor, A. Addlagatta, S. V. Kalivendi and B. C. Raju, *Eur. J. Med. Chem.*, **90**, 603 (2015).
15. P. Suman, C. Dayakar, K. Rajkumar, B. Yashwanth, P. Yogeeswari, D. Sriram, J. V. Rao and B. C. Raju, *Bioorg. Med. Chem. Lett.* **25**, 2390 (2015).
16. B. C. Raju, R. N. Rao, P. Suman, P. Yogeeswari, D. Sriram, T. B. Shaik and K. S. Vardhan, *Bioorg. Med. Chem. Lett.* **21**, 2855 (2011).
17. K. Rajkumar, P. Suman and B. C. Raju, *RSC Adv.* **5**, 73850 (2015).
18. C. Y. Hong, Y. K. Kim, J. H. Chang, S. H. Kim, H. Choi, D. H. Nam, Y. Z. Kim and J. H. Kwak, *J. Med. Chem.* **40**, 3584 (1997).
19. A. A. Raj, R. Raghunathan, M. Kumari and N. Raman, *Bioorg. Med. Chem*. **11**, 407 (2003).
20. G. Naresh, N. Jaiswal, P. Sukanya, A. K. Srivastava, A. K. Tamrakar and T. Narender, *Bioorg. Med. Chem. Lett.*, **22**, 5648 (2012).
21. R. Pattarini, R. J. Smeyne, J. I. Morgan, *Neuroscience* **145**, 654 (2007).
22. P. G. Dunbar, G. J. Durant, T. Rho, B. Ojo, J. J. Huzl, D. A. Smith, M. A El-Assadi, S. Sbeih, D. O. Ngur, S. Periyasamy, W. Hoss and W. S. Messer, *J. Med. Chem.* **37**, 2774 (1994).
23. C. R. Reddy, G. Krishna and M. D. Reddy, *Org. Biomol. Chem*. **12**, 1664 (2014).

24. C. R. Reddy and M. D. Reddy, *J. Org. Chem*. **79**, 106 (2014).
25. K. P. Pande, *Rasayan J. Chem.* **8**, 152 (2015).
26. K. N. Puri and G. V. Korpe, *Rasayan J. Chem.* **9**, 52 (2016).
27. C. Hulme, J. Zhu and H. Eds. Bienayme, In Multicomponent Reactions: Wiley-VCH: Weinheim, 311 (2005).
28. M. Zhang, H. F. J. Jiang, H. L. Liu and Q. H. Zhu, *Org. Lett.* **9**, 4111 (2007).
29. D. Biswanath, D. B. Shinde, B. S. Kanth and G. Satyalakshmi, *Synthesis* **16**, 2823 (2010)
30. N. Lingaiah, H. V. Reddy, C. Venkatanarsihmaji, B. Rajashaker and R. A. Reddy, *Syn. Comm.* **42**, 2131 (2012).
31. N. Nagesh, G. Raju, R. Srinivas, P. Ramesh, M. D. Reddy and C. R. Reddy, *Biochim. Biophys. Acta*, **1850**, 129 (2015).
32. S. Rajaram, U. Ramulu, S. Aravind and K. S. Babu, *Helv. Chim. Acta*, **98**, 650 (2015).
33. S. Aravind, N. Reddy, *Helv. Chim. Acta*, **98**, 557 (2015).
34. R. Venkateshwarlu, B. Chinnababu, R. Udugu, K. P. Reddy, M. D. Reddy, P. Sowjanya, P. V. Rao and S. Aravind, *MedChemComm,* ASAP, DOI: 10.1039/C6MD00606J (2016).

[RJC-1545/2016]