EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

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Authors: Sandip Bibishan Bharate; Rohit Sharma; Ram A Vishwakarma

To be cited as: Eur. J. Org. Chem. 10.1002/ejoc.201601024

Link to VoR: http://dx.doi.org/10.1002/ejoc.201601024

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Bimetallic Cu-Mn catalyzed synthesis of 2-arylquinazolin-4(*3H*)-ones: Aqueous ammonia as a source of ring nitrogen

Rohit Sharma,[a] Ram A. Vishwakarma,*[a] Sandip B. Bharate*[a]

Abstract: A new method for synthesis of 2-arylquinazolin-4(*3H*)-ones comprising a 3-component coupling of 2-bromobenzamide, aryl aldehydes and aqueous ammonia has been reported. The protocol involves Cu-Mn spinel oxide as a heterogeneous catalyst and does not require any ligand or external oxidant. Key features of the reaction include recyclable catalyst, ligand-free conditions and wide substrate scope. Reaction involves replacement of bromine with NH_2 from aqueous ammonia, which is then followed by imine formation, intramolecular ring cyclization (C-N bond formation) and aromatization.

Introduction

The cross-coupling reaction between aryl halide and amines has gained a lot of attention for construction of aromatic C-N bond.[1] Furthermore, the use of heterogeneous catalysts[2] in organic synthesis has proved to be highly beneficial from economical point of view. Amongst various heterogeneous catalysts, several bimetallic catalysts have displayed promising catalytic efficiency for wide range of chemical transformations - e.g. Ru-Ce for dihydroxylation of glycals,[3] Ni-Pd for cross-coupling of two different aryl electrophiles,[4] bimetallic Pd and Cu-Mn for Huisgen [3+2]-cycloaddition,[5] for synthesis of imidazo[1,2-a]pyridines,[6] regioselective halogenations of phenols,[7] and for coupling of aryl boronic acids with amines.[8]

Quinazolin-4(*3H*)-one scaffold has gained tremendous importance in synthetic organic chemistry in past few decades because of their diverse range of pharmacological activities such as anticancer,[9] antifungal,[10] anti-diabetic,[11] anti-inflammatory,[12] antimicrobial,[13] hypolipidemic,[14] and many other properties.[2c, 15] Furthermore, it has wide occurrence among natural products.[2c, 15b, 16] Examples of quinazolin-4(*3H*)-one natural products are shown in Figure 1.

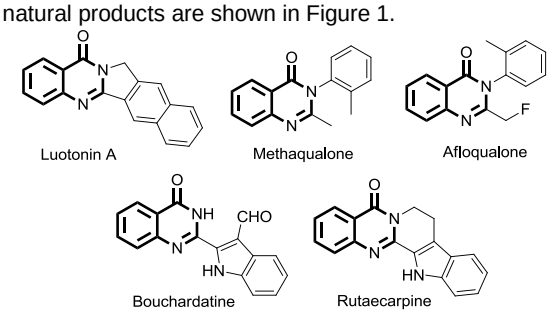

Figure 1. Examples of biologically active quinazolin-4(*3H*)-ones.

[a] Rohit Sharma, Ram A. Vishwakarma, Sandip B. Bharate
Medicinal Chemistry Division
Academy of Scientific & Innovative Research (AcSIR),
CSIR-Indian Institute of Integrative Medicine,
Canal Road, Jammu - 180001, India
E-mail: sbharate@iiim.ac.in; sandipbharate@gmail.com
www.iiim.res.in

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There are numerous reports on the synthesis of quinazolin-4-(*3H*)-ones.[15b, 16f, 17] Amongst these reports, most common approach is the condensation of 2-aminobenzamide or *O*-nitrobenzamides with aldehydes,[18],[15b] aryl acid chlorides,[19] benzyl bromides,[20] benzylamines,[21] and alcohols.[15b, 22] Another common approach is the Ullmann-type coupling of 2-bromobenzamide with benzyl amine.[23] Many of these Ullmann coupling protocols requires copper catalyst, ligand and high heating.[1c, 24] Guo *et al* reported synthesis of this scaffold by 3-component coupling of 2-bromobenzamide, aryl aldehydes and aqueous ammonia using CuBr catalyst and L-proline ligand.[25] Herein, we report ligand-free synthesis of 2-arylquinazolin-4(3*H*)-ones *via* condensation of 2-bromobenzamides, aryl aldehydes and ammonia[25] using heterogeneous bimetallic Cu-Mn catalyst. The "*aqueous ammonia*" acts as a source for ring "*nitrogen*", for construction of 2-arylquinazolin-4(*3H*)-ones (Figure 2).

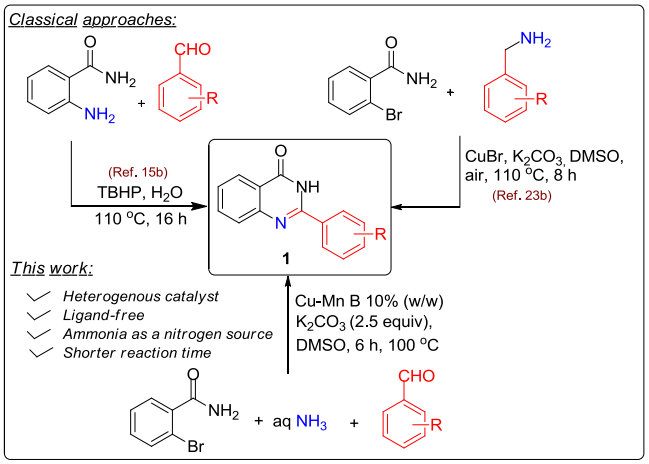
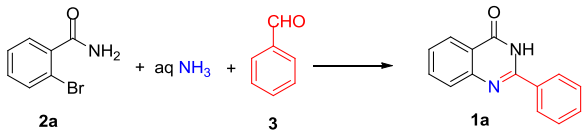


Figure 2. Approaches for synthesis of 2-aryl quinazolin-4(3H)-ones

Results and Discussion

In order to establish a protocol for synthesis 2-aryl quinazolin-4(*3H*)-ones, a model reaction between 2-bromobenzamide (**2a**), benzaldehyde (**3a**) and aqueous ammonia in presence of various copper catalysts and a base (Table 1) was investigated. Initially, CuI and CuBr catalysts were used in the presence of potassium carbonate base and DMSO as a solvent. The desired product **1a** was obtained, however only in 30-40% yield. Further, we investigated the catalytic activity of heterogeneous Cu-Mn bimetallic catalysts available in our laboratory. Three types of Cu-Mn catalysts, varying in copper and manganese content[6] i.e. Cu-Mn A (2: 0.25), Cu-Mn B (1: 0.25) and Cu-Mn C (3: 0.25) were studied. Initially, we used catalyst loading of 10% w/w for these catalysts (entries 5-7). Amongst these three catalysts, Cu-Mn B gave desired product **1a** in 85% yield (entry 4). However, in case of catalysts Cu-Mn A and Cu-Mn C, the higher product yield was obtained

Table 1. Catalyst and solvent optimization studies[a]



Entry	Catalyst (loading)	Base	Temp. (ºC)	Solvent	Time (h)	% Yield[b]
1.	CuI (5 mol%)	K_2CO_3	100	DMSO	6	40
2.	CuBr (5 mol%)	K_2CO_3	100	DMSO	6	30
3.	Cu $(OAc)_2$ (5 mol%)	K_2CO_3	100	DMSO	6	35
4.	Cu $(CF_3SO_3)_2$ (5 mol%)	K_2CO_3	100	DMSO	6	60
5.	Cu-Mn A (10% w/w)	K_2CO_3	100	DMSO	6	50
6. [c]	**Cu-Mn B (10% w/w)**	**K_2CO_3**	**100**	DMSO	**6**	**85**
7.	Cu-Mn C (10% w/w)	K_2CO_3	100	DMSO	6	55
8.	Cu-Mn B (5% w/w)	K_2CO_3	100	DMSO	2	70
9.	Cu-Mn A (20% w/w)	K_2CO_3	100	DMSO	6	65
10.	Cu-Mn C (20% w/w)	K_2CO_3	100	DMSO	6	50
11.	Cu-Mn B (10% w/w)	K_3PO_4	100	DMSO	6	75
12.	Cu-Mn B (10% w/w)	Cs_2CO_3	100	DMSO	6	70
13.	Cu-Mn B (10% w/w)	K_2CO_3	110	Toluene	6	60
14.	Cu-Mn B (10% w/w)	K_2CO_3	120	DMF	6	65
15.	Cu-Mn B (10% w/w)	K_2CO_3	100	1,4-dioxane	6	60

[a] Reagents and conditions: 2-bromobenzamide (1.0 equiv), aldehyde (1.8 equiv), ammonia (2.5 mL); [b] isolated yield; [c] optimized reaction conditions.

when catalyst loading was increased from 10 to 20% w/w (entries 9 and 10). The Cu-Mn B catalyst even showed good yield at 5% w/w loading of the catalyst (entry 8). Due to distinct phases of Cu and Mn present in Cu-Mn B as predicted from PXRD studies, it gave best results.[6] Amongst various bases investigated (K_2CO_3, K_3PO_4, and Cs_2CO_3), K_2CO_3 gave better results (entries 6, 11 and 12). Amongst various solvents studied (entries 6, 13-15), DMSO was found to be the best solvent for this reaction. In nutshell, the best condition identified is entry 6. In order to check whether reaction works with other amines, reaction was also carried out with methyl amine, aniline and benzylamine; however corresponding product was not formed with any of these amine substrates.

Using the optimized reaction conditions, the substrate scope of the reaction was then investigated for various substituted aldehydes (Figure 3). Reaction proceeded well with various heteroaryl and aryl aldehydes substituted with electron-withdrawing (examples **1b**, **1c**, **1e**, **1h, 1i, 1o, 1p, 1q, 1r** and **1s**) as well as electron donating groups (examples **1d**, **1f**, **1j**, **1m** and **1n**). Biphenyl aldehyde and fused aryl aldehyde also produced good yields (examples **1g** and **1l**). No specific electronic effect was seen; however the higher yields were obtained with aldehydes comprising electron-donating group in comparison to aldehydes with electron-withdrawing groups. It is noteworthy to mention that reaction worked well with *ortho*-substituted aryl aldehydes (examples **1d**, **1e**, **1h**, **1i**) as well as with phenolic OH group containing aryl aldehydes (example **1f**). Reaction also worked well with heteroaryl aldehydes such as 4-pyridine carboxyaldehyde (example **1t**) and 3-pyridine carboxaldehyde (example **1u**). Next, we explored the substrate scope of this reaction for aliphatic aldehydes (phenyl acetaldehyde, hexanal), however desired product was not formed. Next, we also attempted the reaction with N-substituted 2-bromobenzamide but desired product was not formed.

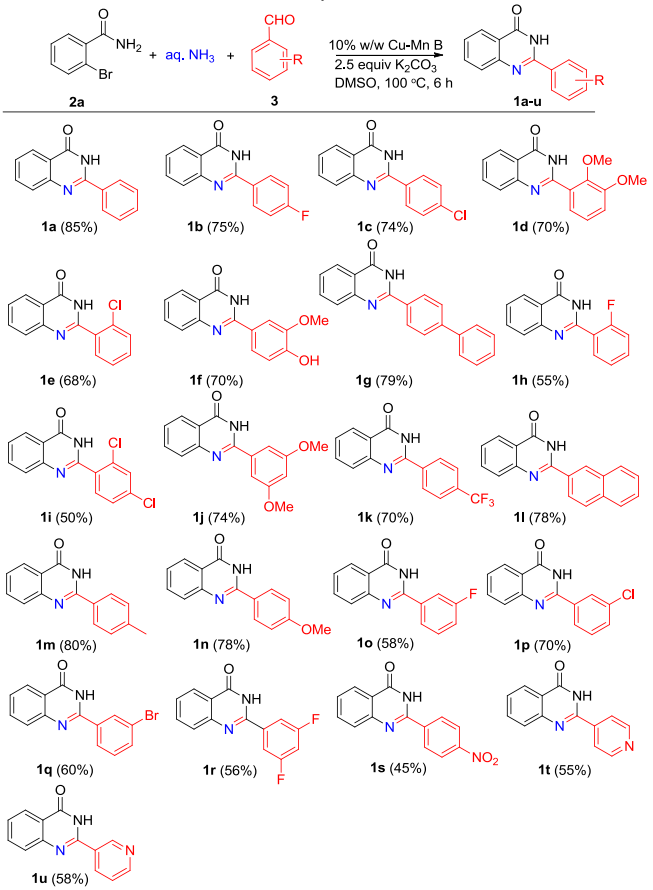


Figure 3. Substrate scope of the reaction. Reagents and

conditions: 2-bromobenzamide **2** (1.0 equiv), aldehyde **3** (1.8 equiv), aq. ammonia (2.5 ml), Cu-Mn B (10% w/w), K_2CO_3 (2.5 equiv) in DMSO (5 mL), 6 h, 50-85%.

Next, in order to understand the catalytic efficiency of Cu-Mn B catalyst on its repeated use, we performed recyclability studies. Under optimized reaction conditions, the product **1a** was obtained in 85, 80, 73 and 67% yields over four cycles, indicating excellent catalytic activity on repeated use. The metal content of the catalyst before and after use was also analyzed using ICP-MS studies. The catalyst recycled after 4 cycles showed similar metal (Cu and Mn) content. This clearly indicated that even after recycling catalyst for 4 times, there was no leaching of metals from the bimetallic spinel catalyst.

Towards elucidating the reaction mechanism, a control reaction of 2-bromobenzamide (**2a**) with aqueous ammonia under optimized reaction conditions was carried out, which led to the formation of anthranilamide **4a** (Figure 4) in 80% yield.

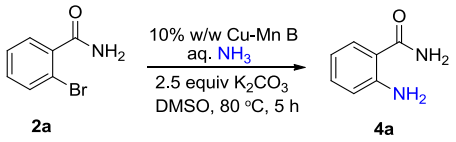


Figure 4. Reaction of 2-bromobenzamide (**2a**) with aqueous ammonia under optimized reaction conditions

On the basis of control experiment, a plausible mechanism for synthesis of **1a** has been depicted in Figure 5. First, the Cu-Mn B catalyzed amination of **2a** with aqueous ammonia through intermediates **I** and **II** leads to formation of anthranilamide **4a**. Condensation of **4a** with aryl aldehyde produces imine intermediate **III**, which on intramolecular cyclization followed by aromatization leads to the formation of quinazolinone **1a**.

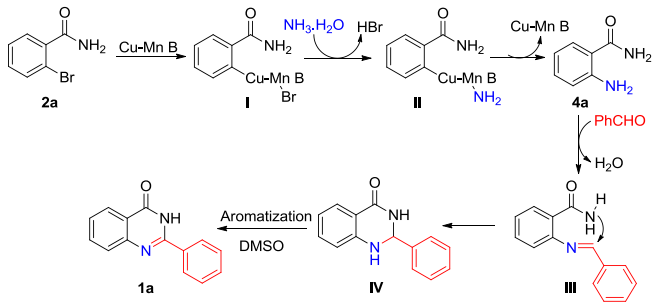


Figure 5. Proposed mechanism for synthesis of **1a**.

Conclusions

In summary, we have developed an efficient, Cu-Mn B catalysed synthesis of 2-arylquinazolin-4(*3H*)-ones using aqueous ammonia as a nitrogen source. Cu-Mn B is recyclable heterogeneous catalyst and can be used up to 4 cycles without significant loss of catalytic activity. The reaction has broad substrate scope and tolerates wide range of functional groups.

Experimental Section

General. All chemicals were obtained from Sigma-Aldrich Company and used as received. 1H, 13C and DEPT NMR spectra were recorded on Brucker-Avance DPX FT-NMR 500 and 400 MHz instruments. Chemical data for protons are reported in parts per million (ppm) downfield from tetramethylsilane and are referenced to the residual proton in the NMR solvent ($CDCl_3$, 7.26 ppm; CD_3OD, 3.31 ppm; DMSO-d_6, 2.55, 3.33ppm). The carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 125 MHz or 100 MHz: chemical data for carbons are reported in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to the carbon resonance of the solvent ($CDCl_3$, 77.16 ppm; CD_3OD, 49.0; DMSO-d_6, 39.52 ppm). ESI-MS and HRMS spectra were recorded on Agilent 1100 LC-Q-TOF and HRMS-6540-UHD machines. IR spectra were recorded on Perkin-Elmer IR spectrophotometer. Melting points were recorded on digital melting point apparatus.

General procedure for synthesis of 2-phenylquinazolin-4(*3H*)-ones 1a-u. To the solution of 2-bromobenzamide (**2a**, 1 equiv.) in 4 mL of DMSO was added aqueous ammonia (2.5 mL), aryl aldehyde (3, 1.8 equiv.), Cu-Mn B (10% w/w) and K_2CO_3 (2.5 equiv). Reaction mixture was then heated at 100 °C for 6 h. Completion of the reaction was monitored by TLC. Reaction mixture was cooled and filtered to recover catalyst and further extracted with ethyl acetate (50 ml × 3). Combined organic layer was dried over anhydrous sodium sulphate and evaporated on *vacuo* rotavapor to get crude product. Crude products were purified by silica gel (#100-200) column chromatography to get **1a-s** formed in 85-45% yield. The products were characterized by comparison of their spectral data with literature values.

*2-Phenylquinazolin-4(3H)-one (**1a**[26]).* White solid; yield 95 mg; mp 232-235 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 10.94 (bs, 1H), 8.34-8.32 (m, 1H), 8.20-8.18 (m, 2H), 7.86-7.79 (m, 2H), 7.61-7.49 (m, 4H).); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.2, 152.3, 148.7, 134.6, 132.7, 131.4, 128.6, 127.7, 127.5, 126.6, 125.8, 120.9; ESI-MS: *m/z* 223.20 $[M+H]^+$; HRMS: *m/z* 223.0867 calcd for $C_{14}H_{10}N_2O+H^+$ (223.0866); IR ($CHCl_3$): ν_{max} 2918, 2850, 2344, 1664, 1601, 1572, 1555, 1480, 1469, 1451, 1286, 1143, 1020 cm^{-1}.

*2-(4-Fluorophenyl)quinazolin-4(3H)-one (**1b**[26]).* White solid; yield 90 mg; mp 240-242 °C; ^1H NMR (400 MHz, $CDCl_3$ + CD_3OD) δ 8.29 (d, *J* = 7.6 Hz, 1H), 8.13-8.09 (m, 2H), 7.82 (d, 3.6Hz, 2H), 7.53-7.50 (m,1H), 7.27-7.23 (m, 1H);); ^{13}C NMR (125 MHz, DMSO-d_6): δ 165 (d, $^1J_{CF}$ = 249 Hz), 163, 162.3, 151.5, 134.6, 130.4, 130.3, 129.2, 127.4, 126.6, 125.8, 120.8, 115.7 (d, $^2J_{CF}$ = 21.9 Hz); ESI-MS: *m/z* 241.20 $[M+H]^+$; HRMS: *m/z* 241.0802 calcd for $C_{14}H_{10}FN_2O+H^+$ (241.0772); IR ($CHCl_3$): ν_{max} 3584, 3392, 2920, 2851, 1680, 1609, 1484, 1447, 1346, 1288, 1236, 1148, 1020 cm^{-1}.

*2-(4-Chlorophenyl)quinazolin-4(3H)-one (**1c**[27]).* White solid; yield 95 mg; mp 239-240 °C; ^1HNMR (400 MHz, DMSO-d_6) δ 12.64 (bs, 1H)8.22-8.16 (m, 3H), 7.88 (t, *J* = 6.4, 12 Hz, 1H), 7.77 (d, *J* = 6.4 Hz, 1H), 7.65 (d, *J* = 6.4 Hz, 2H), 7.56 (t, *J* = 6, 12 Hz, 1H);); ESI-MS: *m/z* 257.20 $[M+H]^+$; HRMS: *m/z* 257.0492 calcd for $C_{14}H_{10}ClN_2O+H^+$ (257.0476); IR ($CHCl_3$): ν_{max} 3584,

3397, 2919, 2850, 2091, 1672, 1600, 1555, 1468, 1442, 1344, 1279, 1148, 1119, 1094, 1011 cm^{-1}.

2-(2,3-Dimethoxyphenyl)quinazolin-4(3H)-one (***1d***[28]). White solid; yield 100 mg; mp 270-272 °C; ^{1}HNMR (400 MHz, DMSO-d_6) δ 12.23 (bs, 1H), 8.17-8.16 (m, 1H), 7.85-7.83 (m, 1H), 7.72 (d, *J* = 6.4 Hz, 1H), 7.57-7.55 (m, 1H), 7.27-7.21(m, 3H) 3.89 (s, 3H), 3.77 (s, 3H) ; ^{13}C NMR (125 MHz, DMSO-d_6) δ 161, 153, 152, 149, 147, 135, 128, 127, 126, 125, 122, 121, 116, 61, 56; ESI-MS: *m/z* 283.08 $[M+H]^+$; HRMS: *m/z* 283.1074 calcd for $C_{16}H_{15}N_2O_3+H^+$ (283.1077) ; IR ($CHCl_3$): ν_{max} 3291, 3018, 2922, 2848, 1747, 1679, 1604, 1563, 1573, 1474, 1434, 1310, 1297, 1166, 1134, 1112, 1085, 1057 cm^{-1}.

2-(2-Chlorophenyl)quinazolin-4(3H)-one (***1e***[27]). White solid; yield 88 mg; mp 239-240 °C; ^{1}HNMR (400 MHz, $CDCl_3$ + CD_3OD) δ 8.31 (d, *J* = 7.6 Hz, 1H), 7.84-7.82 (m, 2H), 7.72-7.69 (m, 1H), 7.57-7.45 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$ + CD_3OD) δ 162, 151, 149, 135, 133, 132, 131, 130, 128, 127, 127, 121); ESI-MS: *m/z* 257.20 $[M+H]^+$; HRMS: *m/z* 257.0474 calcd for $C_{14}H_{10}ClN_2O+H^+$ (257.0476); IR ($CHCl_3$): ν_{max} 3584, 3388, 2918, 2346, 1671, 1604, 1565, 1471, 1447, 1303, 1145, 1052 cm^{-1}

2-(4-Hydroxy-3-methoxyphenyl)quinazolin-4(3H)-one (***1f***[29]). White solid; yield 92 mg; mp 286-288 °C; ^{1}HNMR (400 MHz, DMSO-d_6) δ 12.56 (bs, 1H), 8.24-8.16 (m, 2H), 7.87 (t, J = 6.8, 14 Hz, 1H), 7.79 (t, 6.8, 14 Hz, 1H), 7.61-7.47 (m, 3H), 3.43 (s, 3H); ESI-MS: *m/z* 269.10 $[M+H]^+$; IR ($CHCl_3$): ν_{max} 3386, 3009, 2918, 2147, 1617, 1509, 1471, 1435, 1405, 1316, 1141, 1020 cm^{-1}.

2-([1,1'-Biphenyl]-4-yl)quinazolin-4(3H)-one (1g[30]). White solid; yield 118 mg; mp 247-249 °C; ^{1}HNMR (400 MHz, $CDCl_3$) δ 9.80 (bs,1H), 8.34 (d, *J* = 7.6 Hz, 1H), 8.16 (d, *J* = 8 Hz, 1H), 7.91-7.79 (m, 4H), 7.68-7.61 (m, 3H), 7.52-7.41 (m, 4H); ESI-MS: *m/z* 299.50 $[M+H]^+$; IR ($CHCl_3$): ν_{max} 3389, 2959, 2921, 2853, 2226, 2147, 1970, 1672, 1667, 1614, 1563, 1517, 1487, 1471, 1435, 1405, 1315, 1290, 1141, 1119, 1023 cm^{-1}.

2-(2-Fluorophenyl)quinazolin-4(3H)-one (***1h***[31]). White solid; yield 67 mg; mp 239-240 °C; ^{1}HNMR (400 MHz, DMSO-d_6) δ 12.58 (s, 1H), 8.19-8.17 (m, 1H), 7.89-7.86 (m, 1H), 7.82-7.80 (m, 1H), 7.78-7.73 (m, 1H), 7.65-7.56 (m, 2H), 7.43-7.36 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.9, 161.3 (d, $^1J_{CF}$ = 248 Hz), 150.4, 135.1, 133.3, 131.5, 127.9, 127.5, 126.3, 125.1 (d, $^2J_{CF}$ = 3.4 Hz), 122.8, 116.7 (d, $^2J_{CF}$ = 21.3 Hz); ESI-MS: *m/z* 240.70 $[M+H]^+$; HRMS: *m/z* 241.0776 calcd for $C_{14}H_{10}FN_2O+H^+$ (241.0772); IR ($CHCl_3$): ν_{max} 3194, 3065, 1692, 1602, 1578, 1469, 1308, 1255, 1218, 1148, 1120, 1020 cm^{-1}.

2-(2,4-Dichlorophenyl)quinazolin-4(3H)-one (***1i***[32]). White solid; yield 70 mg; mp 280-283 °C; ^{1}HNMR (400 MHz, DMSO-d_6) δ 12.68 (s, 1H), 8.20 (d, *J* = 7.6 Hz, 1H), 7.89-7.83 (m, 2H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.62-7.57 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161, 151, 148, 135, 134, 132, 132, 132, 129, 127, 127, 126, 121; ESI-MS: *m/z* 291.01 $[M+H]^+$; HRMS: *m/z* 291.0095 calcd for $C_{14}H_9Cl_2N_2O+H^+$ (291.0086); IR ($CHCl_3$): ν_{max} 3585, 3362, 2920, 1678, 1304, 1552, 1472, 1374, 1300, 1255, 1219, 1114, 1019 cm^{-1}.

2-(3,5-Dimethoxyphenyl)quinazolin-4(3H)-one (***1j***[33]). White solid; yield 100 mg; mp 280-282 °C; ^{1}HNMR (400 MHz, DMSO-d_6) δ 12.5 (s, 1H), 8.17 (d, *J* = 7.6 Hz, 1H), 7.87 (t, *J* = 1.2, 8 Hz, 1H), 7.77 (d, *J* = 8 Hz, 1H), 7.55 (t, *J* = 7.2, 14.4 Hz, 1H), 7.40-7.39 (m, 2H), 6,71 (s, 1H), 3.5 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163, 161, 152, 149, 135, 135, 128, 127, 126, 121, 106, 104, 57; ESI-MS: *m/z* 283.08 $[M+H]^+$; HRMS: *m/z* 283.1084 calcd for $C_{16}H_{15}N_2O_3+H^+$ (283.1077); IR ($CHCl_3$): ν_{max} 3685, 3367, 2821, 1730, 1680, 1649, 1613, 1585, 1460, 1419, 1335, 1261, 1185, 1062, 1019 cm^{-1}.

2-(4-(Trifluoromethyl)phenyl)quinazolin-4(3H)-one (***1k***[34]). White solid; yield 103 mg; mp 240-242 °C; ^{1}HNMR (400 MHz, DMSO-d_6) δ 12.8 (s, 1H), 8.39 (d, *J* = 8 Hz, 2H), 8.20 (d, *J* = 7.6 Hz, 1H), 7.95 (d, *J* = 8.4 Hz, 2H), 7.88-7.86(m, 1H), 7.80 (d, *J* = 8 Hz, 1H), 7.59 (t, *J* = 7.6, 14.8 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 162.1, 151.2, 148.4, 136.6, 134.7, 131.2 (d, $^1J_{CF}$ = 31 Hz), 128.7, 127.6, 127.1, 125.9, 125.5 (dd, $^2J_{CF}$ = 3.3, 7.1 Hz), 125, 124.9, 122.9, 121.2; ESI-MS: *m/z* 291.08 $[M+H]^+$; HRMS: *m/z* 291.0738 calcd for $C_{15}H_{10}F_3N_2O+H^+$ (291.0740); IR ($CHCl_3$): ν_{max} 3334, 2919, 2850, 1739, 1667, 1602, 1489, 1449, 1471, 1341, 1328, 1290, 1114, 1084, 1067, 1019 cm^{-1}.

2-(Naphthalen-2-yl)quinazolin-4(3H)-one (***1l***[35]). White solid; yield 106 mg; mp 239-240 °C; ^{1}HNMR (400 MHz, DMSO-d_6) δ 12.70 (s,1H), 8.83 (s, 1H), 8.32 (d, *J* = 6.8 Hz, 1H), 8.20 (d, *J* = 6.4 Hz, 1H), 8.09-8.02 (m, 3H), 7.89-7.80 (m, 2H), 7.68-7.62 (m, 2H), 7.57 (t, *J* = 6, 12 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163, 153, 149, 135, 134, 132, 130, 129, 128, 128, 128, 128, 128, 127, 127, 126, 125, 122; ESI-MS: *m/z* 273.13 $[M+H]^+$; HRMS: *m/z* 273.1025 calcd for $C_{18}H_{13}N_2O+H^+$ (273.1022); IR ($CHCl_3$): ν_{max} 3744, 3335, 2921, 1672, 1610, 1570, 1510, 1470, 1449, 1348, 1306, 1248, 1151 cm^{-1}.

2-(p-Tolyl)quinazolin-4(3H)-one (***1m***[26]). White solid; yield 95 mg; mp 232-233 °C; ^{1}HNMR (400 MHz, DMSO-d_6) δ 12.42 (bs, 1H), 8.16-8.10 (m, 3H), 7.86-7.73 (m, 2H), 7.54 (t, *J* = 7.6, 15.2Hz, 1H), 7.38 (d, *J* = 8 Hz, 2H), 2.40 (s, 3H);); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.3, 152.2, 148.8, 141.4, 134.5, 129.9, 129.8, 129.2, 127.7, 126.4, 125.8, 120.8; ESI-MS: *m/z* 237.30 $[M+H]^+$; HRMS: *m/z* 237.1015 calcd for $C_{15}H_{13}N_2O+H^+$ (237.1022); IR ($CHCl_3$): ν_{max} 3585, 3385, 3134, 3061, 2917, 2850, 1672, 1601, 1557, 1526, 1486, 1469, 1444, 1344, 1241, 1193, 1076, 1020 cm^{-1};

2-(4-Methoxyphenyl)quinazolin-4(3H)-one (***1n***[26]). White solid; yield 102 mg; mp 241-243 °C; ^{1}HNMR (400 MHz, DMSO-d_6) δ 12.56 (s,1H), 8.18 (d, *J* = 8 Hz, 1H), 7.87-7.76(m, 4H), 7.56 (t, 7.2, 14.8 Hz, 1H), 7.47 (t, *J* = 8, 16 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160, 157, 150, 146, 133, 132, 127, 125, 124, 123, 119, 118, 115, 110, 53;); ESI-MS: *m/z* 253.20 $[M+H]^+$; HRMS: *m/z* 253.0977 calcd for $C_{15}H_{13}N_2O_2+H^+$ (253.0972);IR ($CHCl_3$): ν_{max} 3585, 33922, 3122, 3035, 2917, 1672, 1610, 1587, 1505, 1471, 1444, 1309, 1284, 1266, 1221, 1147, 1094, 1045 cm^{-1}); ESI-MS: *m/z* 253.20 $[M+H]^+$

2-(3-Fluorophenyl)quinazolin-4(3H)-one (1o[36]). White solid; yield 70 mg; mp 232-234 °C; ^{1}HNMR (400 MHz, DMSO-d_6) δ 12.64 (s, 1H), 8.18 (d, *J* = 7.6 Hz, 1H), 8.08-8.07 (m, 2H), 7.89 (t, *J* = 7.2, 14.8 Hz, 1H), 7.79 (d, *J* = 8 Hz, 1H), 7.65-7.44 (m, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 163.3, 162.2 (d, $^1J_{CF}$ = 131 Hz), 151.1, 148.4, 135, 134.7, 130.8, 127, 126.9, 125.9, 123.9, 123.8, 121.1, 118.3 (d, $^2J_{CF}$ = 21 Hz), 114.6 (d, $^2J_{CF}$ = 24 Hz); ESI-MS: *m/z* 240.70 $[M+H]^+$; HRMS: *m/z* 241.0790 calcd for $C_{14}H_{10}FN_2O+H^+$ (241.0772); IR ($CHCl_3$): ν_{max} 3585, 2920, 2066, 1678, 1605, 1576, 1471, 1454, 1343, 1317, 1343, 1298, 1275, 1143, 1021 cm^{-1}.

2-(3-Chlorophenyl)quinazolin-4(3H)-one (***1p***[37]). White solid; yield 90 mg; mp 232-234 °C; ^{1}HNMR (400 MHz, DMSO-d_6) δ 12.64 (bs, 1H), 8.25-8.16 (m, 3H), 7.86-7.84(m, 2H), 7.68-7.55 (m, 3H); ESI-MS: *m/z* 257.10 $[M+H]^+$; HRMS: *m/z* 257.0474 calcd for $C_{14}H_{10}ClN_2O+H^+$ (257.0476); IR ($CHCl_3$): ν_{max} 3123, 3027, 2915, 1739, 1680, 1610, 1566, 1505, 1472, 1450, 1410, 1346, 1272, 1153, 1091 cm^{-1}.

2-(3-Bromophenyl)quinazolin-4(3H)-one (***1q***[22d]). White solid; yield 90 mg; m.p 220-230; ^{1}HNMR (400 MHz, DMSO-d_6) δ 12.61 (bs, 1H), 8.39 - 8.38 (m, 1H), 8.21 – 8.16 (m, 2H), 7.87 – 7.77 (m, 3H), 7.57 – 7.51 (m, 2H);); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162, 150.9, 145, 134.9, 134.6, 133.9, 130.7, 130.3, 126.8, 126.7, 125.8, 121.8, 121; IR ($CHCl_3$): ν_{max} 3583, 3387, 3060, 2917, 2343, 1739, 1680, 1606, 1559, 1504, 1470, 1309, 1269, 1152, 1069, 1021 cm^{-1}. ESI-MS: *m/z* 303.50 $[M+H]^+$

2-(3,5-Difluorophenyl)quinazolin-4(3H)-one (***1r***[38]). White solid; yield 75 mg; m.p 255-260; ^{1}HNMR (400 MHz, DMSO-d_6) δ 12.63 (bs, 1H), 8.17 - 8.16 (m, 1H), 7.94 – 7.85 (m, 3H), 7.78 – 7.76 (m, 1H), 7.58 – 7.53 (m, 2H);); ^{13}C NMR (125 MHz, DMSO-d_6): δ 163.7, 162.5 (d, $^1J_{CF}$ = 250 Hz), 161.7 (d, $^1J_{CF}$ = 248 Hz), 148.6, 135.2, 128.2, 127.7, 126.4, 121.7, 111.6 (d, $^2J_{CF}$ = 22 Hz); IR ($CHCl_3$): ν_{max} 3585, 3354, 3043, 2919, 2851, 1745, 1682, 1610, 1595, 1509, 1472, 1432, 1316, 1258, 1126, 1020 cm^{-1}. ESI-MS: *m/z* 259.30 $[M+H]^+$; HRMS: *m/z* 259.0682 calcd for $C_{14}H_9F_2N_2O+H^+$ (259.0677);

2-(4-Nitrophenyl)quinazolin-4(3H)-one (***1s***[15c]). White solid; yield 60 mg; m.p 198-202; ^{1}HNMR (400 MHz, DMSO-d_6) δ 12.83 (bs, 1H), 8.45 – 8.39 (m, 4H), 8.21 – 8.18 (m, 1H), 7.91 – 7.80 (m, 2H), 7.61 – 7.57 (m, 1H); IR ($CHCl_3$): ν_{max} 3585, 3300, 3178, 3025, 2921, 2852, 1751, 1681, 1589, 1468, 1450, 1349, 1304, 1291, 1150, 1107, 1014 cm^{-1}. ESI-MS: *m/z* 268.40 $[M+H]^+$

2-(pyridin-4-yl)quinazolin-4(3H)-one (***1t***[39]). White solid; m.p 280-283; ^{1}HNMR (400 MHz, DMSO-d_6) δ 12.76 (bs, 1H), 8.80 (d, *J* = 6Hz, 2H), 8.20 (d, *J* = 8Hz, 1H), 8.12 (d, *J* = 6Hz, 2H), 7.91 – 7.87 (m, 1H), 7.81 (d, *J* = 7.6Hz, 1H), 7.61 – 7.57 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 162, 150.6, 150.2, 139.9, 134.7, 127.7, 127.4, 125.9, 121.6, 121.4; IR ($CHCl_3$): ν_{max} 3401, 2921, 2256, 2129, 1679, 1607, 1552, 1505, 1487, 1469, 1449, 1410, 1303, 1225, 1151, 1048 cm^{-1}. ESI-MS: *m/z* 224.01 $[M+H]^+$; HRMS: *m/z* 224.0796 calcd for $C_{13}H_9N_3O+H^+$ (224.0818).

2-(Pyridin-3-yl)quinazolin-4(3H)-one (**1u**[2c]). White solid; m.p. 272-275 °C; ^{1}H NMR (400 MHz, CD_3OD): δ 9.26 (d, *J* = 1.9 Hz, 1H), 8.74 (d, *J* = 3.7 Hz, 1H), 8.51 – 8.47 (m, 1H), 8.30 (d, *J* = 8.1 Hz, 1H), 7.86-7.83 (m, 2H), 7.60-7.54 (m, 2H); IR ($CHCl_3$): ν_{max} 3585, 2921, 1673, 1467, 1169 cm-1; ESI-MS: *m/z* 224.07 $[M+H]^+$; HRMS: *m/z* 224.0790 calcd for $C_{13}H_9N_3O+H^+$ (224.0824).

Recyclability of the catalyst. The recyclability of Cu-Mn B catalyst was checked using a model reaction between 2-bromobenzamide (**2a**, 1 equiv.), benzaldehyde (**3a**, 1.8 equiv.) and aqueous ammonia (2.5 ml) under optimized reaction conditions. After completion of the reaction, it was filtered to recover catalyst. Water was added to the filtrate and then product was extracted with EtOAc. The recovered catalyst was dried in oven and was reused for next cycle. The catalyst was recycled 4 times and the amount of catalyst recovered and percentage yield of the **1a** was determined.

Acknowledgements

RS is thankful to DST for the award of research fellowship. SBB thanks DST-SERB for financial support under Fast-Track Scheme (grant no. SR/FT/CS-168/2011). Authors are thankful to Ms. Parveen Sharma for technical support.

Keywords: 2-aryl quinazolin-4(3*H*)-ones • Cu-Mn catalyst • aqueous ammonia • heterogeneous catalyst • Ligand-free

[1] a) B. Li, S. Guo, J. Zhang, X. Zhang and X. Fan, *J. Org. Chem.* **2015**, *80*, 5444-5456; b) X. Fan, B. Li, S. Guo, Y. Wang and X. Zhang, *Chem. Asian J.* **2014**, *9*, 739-743; c) K. Okano, H. Tokuyama and T. Fukuyama, *Chem. Commun.* **2014**, *50*, 13650-13663; d) D. Wang, Q. Cai and K. Ding, *Adv. Synth. Catal.* **2009**, *351*, 1722-1726; e) N. Xia and M. Taillefer, *Angew. Chem. Int. Ed.* **2009**, *48*, 337-339.

[2] a) M. Muruganandham, R. P. Suri, M. Sillanpa, J. J. Wu, B. Ahmmad, S. Balachandran and M. Swaminathan, *J. Nanosci. Nanotechnol.* **2014**, *14*, 1898-1910; b) A. H. Chughtai, N. Ahmad, H. A. Younus, A. Laypkov and F. Verpoort, *Chem. Soc. Rev.* **2015**, *44*, 6804-6849; c) X. Chen, T. Chen, Y. Zhou, D. Han, L.-B. Han and S.-F. Yin, *Org. Biomol. Chem.* **2014**, *12*, 3802-3807.

[3] P. Tiwari and A. K. Misra, *J. Org. Chem.* **2006**, *71*, 2911-2913.

[4] L. K. G. Ackerman, M. M. Lovell and D. J. Weix, *Nature* **2015**, *524*, 454-457.

[5] S. K. Yousuf, D. Mukherjee, B. Singh, S. Maity and S. C. Taneja, *Green Chem.* **2010**, *12*, 1568-1572.

[6] J. B. Bharate, S. K. Guru, S. K. Jain, S. Meena, P. P. Singh, S. Bhushan, B. Singh, S. B. Bharate and R. A. Vishwakarma, *RSC Adv.* **2013**, *3*, 20869-20876.

[7] P. P. Singh, T. Thatikonda, K. A. Kumar, S. D. Sawant, B. Singh, A. K. Sharma, P. R. Sharma, D. Singh and R. A. Vishwakarma, *J. Org. Chem.* **2012**, *77*, 5823-5828.

[8] S. D. Sawant, M. Srinivas, K. A. A. Kumar, G. L. Reddy, P. P. Singh, B. Singh, A. K. Sharma, P. R. Sharma and R. A. Vishwakarma, *Tetrahedron Lett.* **2013**, *54*, 5351-5354.

[9] a) Y. Takase, T. Saeki, N. Watanabe, H. Adachi, S. Souda and I. Saito, *J. Med. Chem.* **1994**, *37*, 2106-2111; b) P. M. Chandrika, T. Yakaiah, A. R. R. Rao, B. Narsaiah, N. C. Reddy, V. Sridhar and J. V. Rao, *Eur. J. Med. Chem.* **2008**, *43*, 846-852; c) S.-L. Cao, Y.-P. Feng, Y.-Y. Jiang, S.-Y. Liu, G.-Y. Ding and R.-T. Li, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1915-1917.

[10] a) J. H. Chan, J. S. Hong, L. F. Kuyper, D. P. Baccanari, S. S. Joyner, R. L. Tansik, C. M. Boytos and S. K. Rudolph, *J. Med. Chem.* **1995**, *38*, 3608-3616; b) N. J. Liverton, D. J. Armstrong, D. A. Claremon, D. C. Remy, J. J. Baldvin, R. J. Lynch, G. Zhang and R. J. Gould, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 483-486.

[11] a) M. S. Malamas and J. Millen, *J. Med. Chem.* **1991**, *34*, 1492-1503; b) S. E. de Laszlo, C. S. Quagliato, W. J. Greenlee, A. A. Patchett, R. S. L. Chang, V. J. Lotti, T. B. Chen, S. A. Scheck and K. A. Faust, *J. Med. Chem.* **1993**, *36*, 3207-3210.

[12] a) K.-i. Ozaki, Y. Yamada, T. Oine, T. r. Ishizuka and Y. Iwasawa, *J. Med. Chem.* **1985**, *28*, 568-576; b) J. A. Lowe, R. L. Archer, D. S. Chapin, J. B. Cheng, D. Helweg, J. L. Johnson, B. K. Koe, L. A. Lebel and P. F. Moore, *J. Med. Chem.* **1991**, *34*, 624-628.

[13] A. Nanda, S. Ganguli and R. Chakraborty, *Molecules* **2007**, *12*, 2413.

[14] Y. Kurogi, Y. Inoue, K. Tsutsumi, S. Nakamura, K. Nagao, H. Yoshitsugu and Y. Tsuda, *J. Med. Chem.* **1996**, *39*, 1433-1437.
[15] a) Y. Kabri, A. Gellis and P. Vanelle, *Green Chem.* **2009**, *11*, 201-208; b) M. Sharif, J. Opalach, P. Langer, M. Beller and X.-F. Wu, *RSC Adv.* **2014**, *4*, 8-17; c) N. Kausar, I. Roy, D. Chattopadhyay and A. R. Das, *RSC Adv* **2016**, *6*, 22320-22330; d) X.-F. Wu, L. He, H. Neumann and M. Beller, *Chem. Eur. J.* **2013**, *19*, 12635-12638.
[16] a) H. Chai, J. Li, L. Yang, H. Lu, Z. Qi and D. Shi, *RSC Adv.* **2014**, *4*, 44811-44814; b) I. Khan, A. Ibrar, N. Abbas and A. Saeed, *Eur. J. Med. Chem.* **2014**, *76*, 193-244; c) D. Martine and B. Isabelle, *Curr. Med. Chem.* **2013**, *20*, 794-814; d) J. P. Michael, *Nat. Prod. Rep.* **2008**, *25*, 166-187; e) D. A. Horton, G. T. Bourne and M. L. Smythe, *Chem. Rev.* **2003**, *103*, 893-930; f) L. He, H. Li, J. Chen and X.-F. Wu, *RSC Adv.* **2014**, *4*, 12065-12077.
[17] a) J. Chen, K. Natte, A. Spannenberg, H. Neumann, P. Langer, M. Beller and X.-F. Wu, *Angew. Chem. Int. Ed.* **2014**, *53*, 7579-7583; b) K. Natte, H. Neumann and X.-F. Wu, *Catal. Sci. Tech.* **2015**, *5*, 4474-4480; c) X.-X. Qi, Z.-Z. Song, J.-L. Gong, Z.-Y. Fang and X.-F. Wu, *Chin. Chem. Lett.* **2016**, *27*, 21-24; d) H. Li, L. He, H. Neumann, M. Beller and X.-F. Wu, *Green Chem.* **2014**, *16*, 1336-1343; e) L. He, M. Sharif, H. Neumann, M. Beller and X.-F. Wu, *Green Chem.* **2014**, *16*, 3763-3767; f) C. Shen, N. Y. T. Man, S. Stewart and X.-F. Wu, *Org. Biomol. Chem.* **2015**, *13*, 4422-4425; g) X.-F. Wu, S. Oschatz, M. Sharif, M. Beller and P. Langer, *Tetrahedron* **2014**, *70*, 23-29; h) X.-F. Wu, S. Oschatz, A. Block, A. Spannenberg and P. Langer, *Org. Biomol. Chem.* **2014**, *12*, 1865-1870.
[18] B. Han, X.-L. Yang, C. Wang, Y.-W. Bai, T.-C. Pan, X. Chen and W. Yu, *J. Org. Chem.* **2012**, *77*, 1136-1142.
[19] a) S. B. Mhaske and N. P. Argade, *J. Org. Chem.* **2004**, *69*, 4563-4566; b) A. Witt and J. Bergman, *Tetrahedron* **2000**, *56*, 7245-7253.
[20] H. Wei, T. Li, Y. Zhou, L. Zhou and Q. Zeng, *Synthesis* **2013**, *45*, 3349-3354.
[21] T. B. Nguyen, J. L. Bescont, L. Ermolenko and A. Al-Mourabit, *Org. Lett.* **2013**, *15*, 6218-6221.
[22] a) J. Fang and J. Zhou, *Org. Biomol. Chem.* **2012**, *10*, 2389-2391; b) D. Zhao, Y.-R. Zhou, Q. Shen and J.-X. Li, *RSC Adv.* **2014**, *4*, 6486-6489; c) W. Ge, X. Zhu and Y. Wei, *RSC Adv* **2013**, *3*, 10817-10822; d) J. Zhou and J. Fang, *J. Org. Chem.* **2011**, *76*, 7730-7736; e) H. Hikawa, Y. Ino, H. Suzuki and Y. Yokoyama, *J. Org. Chem.* **2012**, *77*, 7046-7051.
[23] a) R. Sharma, R. A. Vishwakarma and S. B. Bharate, *Adv. Synth. Catal.* **2016**, 10.1002/adsc.201600549; b) W. Xu, Y. Jin, H. Liu, Y. Jiang, Fu and Hua, *Org. Lett.* **2011**, *13*, 1274-1277.
[24] a) S. Guo, L. Tao, W. Zhang, X. Zhang and X. Fan, *J. Org. Chem.* **2015**, *80*, 10955-10964; b) I. P. Beletskaya and A. V. Cheprakov, *Organometallics* **2014**, *31*, 7753-7808; c) X. Fan, B. Li, S. Guo, Y. Wang and X. Zhang, *Chem. Asian. J.* **2013**, *9*, 739-743.
[25] S. Guo, Y. Li, L. Tao, W. Zhang and X. Fan, *RSC Adv.* **2014**, *4*, 59289-59296.
[26] S. Mohammed, R. A. Vishwakarma and S. B. Bharate, *J. Org. Chem.* **2015**, *80*, 6915-6921.
[27] M. Arfan, R. Khan, M. A. Khan, S. Anjum, M. I. Choudhary and M. Ahmad, *J. Enzyme Inhib. Med. Chem.* **2010**, *25*, 451-458.
[28] A. H. Romero, J. Salazar and S. E. Lopez, *Synthesis* **2013**, *45*, 2043-2050.
[29] J. Zhang, D. Ren, Y. Ma, W. Wang and H. Wu, *Tetrahedron* **2014**, *70*, 5274-5282.
[30] X. Jiang, T. Tang, J.-M. Wang, Z. Chen, Y.-M. Zhu and S.-J. Ji, *J. Org. Chem.* **2014**, *79*, 5082-5087.
[31] Z. Zhang, M. Wang, C. Zhang, Z. Zhang, J. Lu and F. Wang, *Chem. Commun.* **2015**, *51*, 9205-9207.
[32] Y. Feng, Y. Li, G. Cheng, L. Wang and X. Cui, *J. Org. Chem.* **2015**, *80*, 7099-7107.
[33] X.-S. Wang, K. Yang, M.-M. Zhang and C.-S. Yao, *Synth. Commun.* **2010**, *40*, 2633-2646.
[34] M. Sharif, J. Opalach, P. Langer, M. Beller and X.-F. Wu, *RSC Adv* **2014**, *4*, 8-17.
[35] X. Chen, T. Chen, F. Ji, Y. Zhou and S.-F. Yin, *Catal. Sci. Tech.* **2015**, *5*, 2197-2202.
[36] H. Chai, J. Li, L. Yang, H. Lu, Z. Qi and D. Shi, *RSC Adv* **2014**, *4*, 44811-44814.
[37] R. Subramaniam, G. Rao and M. Abraham, *Der. Pharmacia. Lett.* **2014**, *6*, 56-60.
[38] X. Jiang, T. Tang, J.-M. Wang, Z. Chen, Y.-M. Zhu and S.-J. Ji, *J. Org. Chem.* **2014**, *79*, 5082-5087.
[39] X. Zhang, D. Ye, H. Sun, D. Guo, J. Wang, H. Huang, X. Zhang, H. Jiang and H. Liu, *Green Chem.* **2009**, *11*, 1881-1888.

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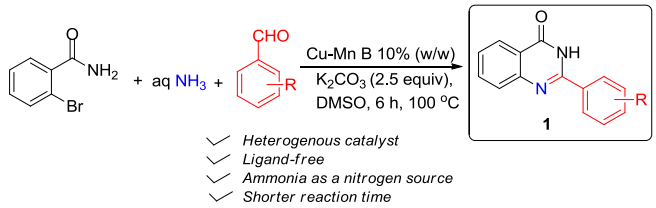

A Cu-Mn catalyzed synthesis of 2-arylquinazolin-4(*3H*)-ones comprising a 3-component coupling of 2-bromobenzamide, aryl aldehydes and aqueous ammonia has been reported.

C-N Bond formation*

Rohit Sharma, Ram A. Vishwakarma, Sandip B. Bharate**

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Bimetallic Cu-Mn catalyzed synthesis of 2-arylquinazolin-4(3H)-ones: Aqueous ammonia as a source of ring nitrogen