Sulphonic acid functionalized Wang resin (Wang-OSO_3H) as polymeric acidic catalyst for the eco-friendly synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones

A.V. Dhanunjaya Rao, B.P. Vykunteswararao, T. Bhaskarkumar, Nivrutti R. Jogdand, Dipak Kalita, Jaydeep kumar D. Lilakar, Vidavalur Siddaiah, Paul Douglas Sanasi, Akula Raghunadh

PII: S0040-4039(15)00976-4
DOI: http://dx.doi.org/10.1016/j.tetlet.2015.06.004
Reference: TETL 46396

To appear in: *Tetrahedron Letters*

Received Date: 21 April 2015
Revised Date: 2 June 2015
Accepted Date: 3 June 2015

Please cite this article as: Dhanunjaya Rao, A.V., Vykunteswararao, B.P., Bhaskarkumar, T., Jogdand, N.R., Kalita, D., Lilakar, J.k.D., Siddaiah, V., Douglas Sanasi, P., Raghunadh, A., Sulphonic acid functionalized Wang resin (Wang-OSO_3H) as polymeric acidic catalyst for the eco-friendly synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones, *Tetrahedron Letters* (2015), doi: http://dx.doi.org/10.1016/j.tetlet.2015.06.004

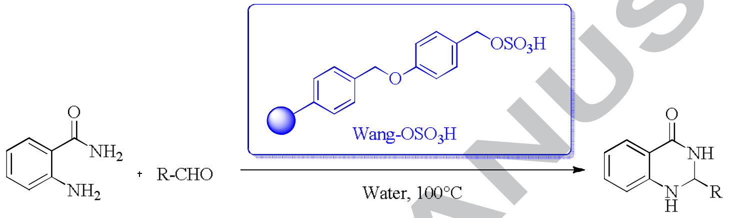
Tetrahedron Letters

Graphical Abstract:

Leave this area blank for abstract info.

Sulphonic acid functionalized Wang resin (Wang-OSO$_3$H) as polymeric acidic catalyst for the eco-friendly synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones

A.V.Dhanunjaya Rao[a, b],B.P.Vykunteswararao[a], T.Bhaskarkumar[a], Nivrutti R. Jogdand[a],Dipak Kalita[a,],Jaydeep kumar D. Lilakar[c], Vidavalur Siddaiah[b], Paul Douglas Sanasi, [d]Akula Raghunadh,[a]*



R = aryl, alkyl, cinnamyl, furanyl, quinolinyl, pyridinyl, indolyl

Tetrahedron Letters
journal homepage: www.elsevier.com

Sulphonic acid functionalized Wang resin (Wang-OSO_3H) as polymeric acidic catalyst for the eco-friendly synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones

A.V.Dhanunjaya Rao [a, b],B.P.Vykunteswararao [a], T.Bhaskarkumar [a], Nivrutti R. Jogdand [a],Dipak Kalita [a,],Jaydeep kumar D. Lilakar [c], Vidavalur Siddaiah [b], Paul Douglas Sanasi [d], Akula Raghunadh,[a]*

[a]Technology Development Centre, Custom Pharmaceutical Services, Dr. Reddy's Laboratories Ltd, Hyderabad 500049, India;
[b] Department of Organic Chemistry, Foods, Drugs and Water, Andhra University, Visakhapatnam, 530003, India.
[c] Research & Development, Bachupally, Dr. Reddy's Laboratories Ltd, Hyderabad, 500049, India;
[d] Department Of Engineering Chemistry, College Of Engineering, Andhra University, Visakhapatnam, 530003, India,
**E-mail:* raghunadha@drreddys.com

ABSTRACT

Article history:
Received
Received in revised form
Accepted
Available online

In memory of Dr. K. Anji Reddy, the founder of Dr. Reddy's Laboratories Ltd.
DRL Communication no.: IPDO IPM-00443

Keywords: Wang resin, 2,3-dihydroquinazolin-4(1*H*)-ones, 2-Aminobenzamide,aldehyde,water, green chemistry.

An efficient and green approach has been developed for the synthesis of 2-substituted 2,3-dihydroquinazolin-4(1*H*)-ones directly from corresponding substituted aromatic and aliphatic aldehyde and anthranilamide using recyclable polymer supported sulphonic acid catalyst under aqueous conditions. Environmental acceptability, operational simplicity, low cost, excellent functional group compatibility and high yields are the important features of this protocol.

Dihydroquinazolin-4(1*H*)-one skeletons constitute a class of synthetic compounds that have pharmaceutical activities and clinical applications. In particular a core structure of dihydroquinazolin-4(1*H*)-one scaffold is present in a number of compounds that demonstrated anticancer, antidiuretic, and anticonvulsant activities.[1] Some representative examples of drug molecules having quinazolinone skeleton are given in **Figure 1.** They are also useful as antihistamine, antidepressant, and vasodilating agents. Among the several methods for the preparation of 2,3-dihydroquinazolin-4(1*H*)-ones, the most direct procedure involves the condensation of aryl, alkyl and hetero aryl aldehydes with anthranilamide in the presence of *p*-toluene sulphonic acid.[2] In the past decade, a variety of synthetic methods have been employed for the preparation of functionalized 2,3-dihydroquinazolin-4(1H)-ones and the level of interest in the current domain is clearly shown by the number of publications.

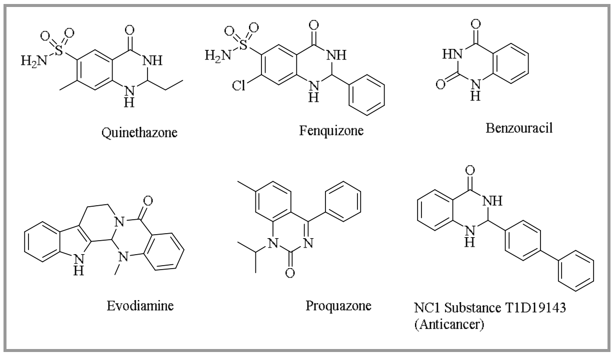


Figure 1. Examples of marketed drugs with quinazolinone skeleton

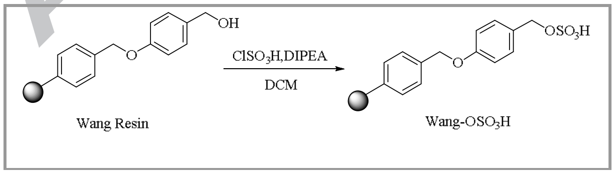
Recently, a number of classical methods for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones have been reported in the literature involving the condensation of 2-aminobenzamide with aldehydes in the presence of various catalysts like ammonium chloride,[3] fumaric acid,[4] silica-$HClO_4$,[5] iodine,[10] gallium trifluoromethanesulfonate,[11] ionic liquids,[12] bronsted acids,[13] phosphoric acid,[14] copper chloride,[15] tetrabutylammoniumbromide,[16] and $TiCl_4$/Zn.[17] However, the above mentioned methods have been associated with different drawbacks such as the use of hazardous organic solvents, low yields, strongly acidic conditions, expensive moisture sensitive catalysts, or tedious work-up conditions.

In spite of the efficiency of homogeneous acidic catalysts, their use is associated with generation of unwanted waste and with the corrosion of process equipment. In contrast, the use of heterogeneous acid catalysis often benefits from a substantial process improvement [18] including greater catalyst stability, recovery and regeneration, and enhanced process selectivity.

The researchers continue for finding a better catalyst for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones derivatives in terms of operational simplicity, economic viability, and greater selectivity.

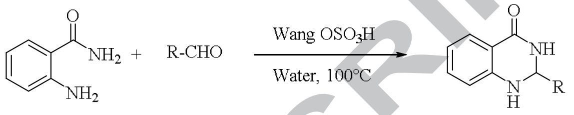
The objective of the present study was the development of a novel heterogeneous catalyst for efficient preparation of 2-substituted 2,3-dihydroquinazolin-4(1*H*)-ones. Sulfonic acid functionalized resin (Wang-SO_3H) is an efficient heterogeneous solid acid catalyst which can easily be handled and removed from the reaction mixture by simple filtration functionalized resin (Wang-SO_3H) is an efficient heterogeneous solid acid catalyst which can easily be handled and removed from the reaction mixture by simple filtration.

Wang resin[22] is most often used for the attachment of organic and inorganic acids. In particular, treatment of Wang resin with chlorosulfonic acid in the presence of N,N-diisopropylethylamine (DIPEA) results in the formation of a monosulfate ester (Wang-OSO_3H, Scheme 1).



Scheme 1: Preparation of Wang-OSO_3H

In this work, we report an efficient procedure for the preparation of 2,3-dihydroquinazolin-4(1H)-one derivatives through a one-step reaction between variously substituted Amberlyst-15,[6] iridium,[7] citric acid,[8] [bmim]HSO_4,[9] aromatic and aliphatic aldehydes and 2-aminobenzamide under thermal condition in the presence of Wang-OSO_3H as an efficient, green, inexpensive, reusable, and polymeric catalyst. It is pertinent to mention that this is the first report on the synthesis of 2,3-dihydroquinazolin-4(1H)-ones installing Wang-OSO_3H catalyzed protocol in aqueous media (Scheme 2).



1 2a-2v 3a-3v

Scheme 2: Wang-OSO_3H mediated synthesis of 2-substituted 2,3-dihydroquinazolin-4(1H)-ones

Table 1: Optimization of the ratio of catalyst (% w/w).

Entry	Catalyst (% w/w)	Time (hr)	Yield[b] (%)
1	No Wang-OSO_3H	3.0	70.0
2	5	1.2	74.0
3	10	0.45	86.0
4	15	0.40	84.5

Reaction and conditions: 2-Aminobenzamide (1.0 mmol), 3-hydroxybenzaldehyde (1.2 mmol) and Wang-OSO_3H in water at 100 °C. [b]Yield refers to pure products after chromatography.

We found that 2-aminobenzamide 1 readily reacts with a variety of aldehydes 2a-2v under the catalysis with Wang-OSO_3H resin to form 2-substituted 2,3-dihydroquinazolin-4(1H)-ones.

The reaction conditions were optimized with respect to the quantity of catalyst (Table 1) and the solvent (Table 2) by studying the condensation of 2-aminobenzamide (1, 1.0 mmol) with 3-hydroxybenzaldehyde (2d, 1.2 mmol). The highest isolated yields of compound 3d were obtained by carrying out the process in water at 100 °C for 0.5-1.5 hr. in the presence of 10% w/w catalyst with respect to 2-aminobenzamide.

The recovery and reuse of Wang-OSO_3H were examined in the reaction of 2-aminobenzamide with 3-hydroxybenzaldehyde. When the reaction was completed, ethyl acetate was added to the reaction mixture and the catalyst was recovered by filtration.

Table 2: Screening of solvent.

Entry	Solvent (Temp. °C)	Time (hr)	Yield^b (%)
1	DMSO (100)	1.5	75
2	DMF (100)	1.5	72
3	1,4-Dioxane (100)	4.0	78
4	Ethanol (78)	1.0	80
5	DCM (38)	1.0	81
6	Acetonitrile (80)	5.0	82
7	Methanol (64)	7.0	83
8	Toluene (110)	1.0	82
9	Water (100)	0.45	86
10	Water (100)	5.0	73$^€$
11	Water (100)	4.0	68$^¥$

Reaction and conditions: 2-Aminobenzamide (1.0 mmol), 3-hydroxybenzaldehyde (1.2 mmol) and Wang-OSO_3H (10%, w/w) in solvent at respective temperature. [b]Yield refers to pure products after chromatography. [€]Dowex50 used as catalyst. [¥]Conc. H_2SO_4 used as catalyst.

The recovered catalyst was washed, dried and reused. It was found that the catalytic activities and pH of the subsequent reaction mass of the recovered catalyst were almost the same as that of fresh catalyst over four runs (Table 3, entries 1–5).

Table 3: Recyclability of the catalyst

Entry	Cycle	Time (hr)	Yield^f (%)	pH of reaction mass
1	Fresh	0.45	86.0	2.4
2	1	0.45	85.0	2.5
3	2	0.50	85.5	2.5
4	3	0.55	84.5	2.7
5	4	0.55	84.0	2.7

Reaction and conditions: 2-Aminobenzamide (1.0 mmol), 3-hydroxybenzaldehyde (1.2 mmol) and Wang-OSO_3H (10%, w/w) in water at 100 °C. [f]Yield refers to pure products after chromatography.

Table 4: Comparison of catalytic activity of different catalysts

Entry	Catalyst	Time (hr)	Yield* (%)
1	Wang-SO_3H	0.5	88
2	Dowex 50	5	73
3	Amberlyst 15	7	71

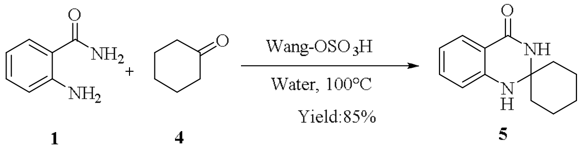
Reaction and conditions: 2-Aminobenzamide (1.0 mmol), 3-hydroxybenzaldehyde (1.2 mmol) and Catalyst (10%, w/w) in water at 100 °C. *Yield refers to pure products after chromatography.

The experimental details captured in the table (Table 4, entries 1–3) clearly indicate that the yields obtained in the optimized reaction conditions using Dowex 50 and Amberlyst 15 are low compared to Wang-OSO_3H. The highest isolated yields of compound were obtained by carrying out the process in water at 100 °C for 0.5 hr. in presence of 10% w/w wang-SO_3H catalyst with respect to 2-aminobenzamide. The reaction time is also comparatively very less.

Spiroheterocycles have remained relatively less investigated class of compounds until recent past. The development of newer methods for their synthesis however has gained enormous attention especially in the area of organic as well as medicinal chemistry. The condensation of 2-aminobenzamide (1, 1.0 mmol) with cyclohexnone (4, 1.2 mmol) to furnish spiro 2,3-dihydroquinazolin-4(1*H*)-ones (5) in 85% yield were obtained by carrying out the process in water at 100 °C for 0.5-1.0 hr in the presence of 10% w/w catalyst with respect to 2-aminobenzamide.

The scope and the utility of the suggested synthetic protocol was demonstrated by reacting compound 2 (2a-2v, Table 5) with a wide variety of aliphatic, aromatic, heteroaromatic, and α,β-unsaturated aldehydes to result in the target 2,3-dihydroquinazolin-4(1H)-ones (3a-3v, Table 5) in invariably high yields (78-88%).

In conclusion, we have reported a highly efficient and ecofriendly method for the synthesis of novel 2-substituted 2,3-dihydroquinazolin-4(1*H*)-ones products with good yield using Wang–OSO_3H as an inexpensive, biodegradable and recyclable catalyst. Prominent advantages of this method are broad scope, operational simplicity, practicability, economic viability, good yield of the products in shorter reaction time, easy work-up, and reusability of the catalyst.



Scheme 3: Wang-OSO_3H mediated synthesis of spiro 2,3-dihydroquinazolin-4(1*H*)-ones (**5**)

Table 5: Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones catalyzed by Wang-OSO_3H

Entry	Aldehyde (2)	Product (3)	Time (hr)	Yield^{i} (%)	M.P (°C)
1	2,4-Dimethylbenzaldehyde, **2a**	**3a**	0.50	87	161-163
2	4-Methoxybenzaldehyde**, 2b**	**3b**	0.45	88	198-201
3	4-Hydroxybenzaldehyde**, 2c**	**3c**	0.45	86	209-210
4	3-Hydroxybenzaldehyde**, 2d**	**3d**	0.50	88	215-217
5	3,4,5-Trimethoxybenzaldehyde**, 2e**	**3e**	0.55	81	186-187
6	4-Chlorobenzaldehyde**, 2f**	**3f**	0.40	84	193-194
7	2-Chlorobenzaldehyde**, 2g**	**3g**	0.45	83	206-208
8	4-Bromo-2,6-difluorobenzaldehyde**, 2h**	**3h**	0.45	83	205-206
9	4-Nitrobenzaldehyde**, 2i**	**3i**	0.50	85	202-203
10	Hexanal, **2j**	**3j**	1.00	80	160-162
11	Pivalaldehyde**, 2k**	**3k**	0.50	81	188-190
12	Cinnamaldehyde**, 2l**	**3l**	0.50	81	155-157
13	Furan-2-carbaldehyde**, 2m**	**3m**	0.45	80	163-164
14	Isonicotinaldehyd**e, 2n**	**3n**	0.45	78	264-266
15	5-Fluoro-1*H*-indole-3-carbaldehyde**, 2o**	**3o**	0.45	84	Pasty solid
16	2-Chloro-8-methylquinoline-3-carbaldehyde**, 2p**	**3p**	1.05	86	269-271
17	2-Chloro-7-methylquinoline-3-carbaldehyde**, 2q**	**3q**	1.00	84	270-272
18	2-Chloro-6-methylquinoline-3-carbaldehyde**, 2r**	**3r**	1.00	85	267-268
19	2-Chloro-6-ethoxyquinoline-3-carbaldehyde**, 2s**	**3s**	0.55	82	274-275
20	2-Chloro-7-methoxyquinoline-3-carbaldehyde**, 2t**	**3t**	0.50	80	278-279
21	2-Chloro-6-methoxyquinoline-3-carbaldehyde, **2u**	**3u**	0.55	83	275-277
22	2-Chloro-6-fluoroquinoline-3-carbaldehyde**, 2v**	**3v**	1.10	82	264-265

Reaction and conditions: 2-Aminobenzamide 1 (1.0 mmol), aldehyde 2 (1.2 mmol) and Wang-OSO_3H (10%, w/w) in water at100 °C. All products were characterized by ^{1}H NMR, IR and Mass spectroscopy. ^{i}Yield refers to pure products after chromatography.

Acknowledgments:

The authors would like to thank Dr. Vilas Dahanukar, Dr. Upadhya Timmana, Dr. Rama Mohan, Dr. Rashid Abdul Rehman Khan and the analytical group of CPS-DRL for spectral data. Mr A.V.Dhanunjaya Rao thanks the CPS-DRL, Hyderabad, India for encouragement.

References:

1. (a) Yale H. L.; Kalkstin M. *J. Med. Chem.* **1967**, *10*, 334; (b) Peet N. P.; Sunder S.; Cregge R. J. *J. Org. Chem.* **1976**, *41*, 2733; (c) Ozaki K.; Yamada Y.; Oine T., Ishizuka T.; Iwasawa Y. *J. Med. Chem.* **1985**, *28*, 568; (d) Jiang J. B.; Hesson D. P.; Dusak B. A.; Dexter D. L.; Kang G. J.; Hamel E. *J. Med. Chem.* **1990**, *33*, 1721; (e) Wolfe J. F.; Rathman T. L.; Sleevi M. C.; Campbell J. A.; Greenwood T. D. *J. Med. Chem.* **1990**, *33*, 161; (f) Bridges A. J.; Zhou H.; Cody D. R.; Rewcastle G. W.; McMichael A.; Showalter H. D.; Fry D. W.; Kraker A. J.; Deny W. A. *J. Med. Chem.* **1996**, *39*, 267. (g) Osborne D.; Stevenson P. J. *Tetrahedron Lett.* **2002**, *43*, 5469; (h) Shi, D. Q.; Rong L. C.; Wang J. X.; Zhuang Q.Y.; Wang X. S.; Hu, H.W. *Tetrahedron Lett.*. **2003**, *44*, 3199; (J) D. Rambabu, S. Kiran Kumar, B. Yogi Sreenivas, Sandhya Sandra, Ajit Kandale, Parimal Misra, M.V. Basaveswara Rao, Manojit Pal *Tetrahedron Lett.* **2013**, *vol. 54, 6,* 495 – 501.
2. (a) Sharma, S.D.; Kaur, V. *Synthesis*, **1989**, 677; (b) Moore, J. A.; Sutherland, G. J.; Sowerby, R.; Kelly, E. G.; Palermo, S.; Webster, W. *J. Org.Chem.* **1969**, *34*, 887.

3. Shaabani, A.; Maleki, A.; Mofakham, H. *Synthetic Comm.***2008**, *38*, 3751.
4. Kiaee, S.; Masoumnia, A.; Maghsoodlou, M. *Research in Pharmaceutical Sciences* **2012,** 7.
5. Bharate, S. B.; Mupparapu, N.; Manda, S.; Bharate, J. B.; Mudududdla, R.; Yadav, R. R.; Vishwakarma, R.A. *ARKIVOC,* **2012**, *8*, 308.
6. Murthy, P. V. N. S.; Rambabu, D.; Rama Krishna, G.; Malla Reddy, C.; Prasad, K. R. S.; Basaveswara Rao, M.V.; Pal, M. *Tetrahedron Lett.***2012**, *53*, 863.
7. Jianguang, Z.; Jie, F. *J. Org. Chem.* **2011** dx. doi: org/10.1021/jo201054k
8. Ghorbani-Choghamarani, A.; Taghipour, T. *Lett. Org. Chem*. **2011**, *8*, 470.
9. Darvatkar, N. B.; Bhilare, S. V.; Deorukhkar, A. R.; Raut, D. G.; Salunkhe, M. M. *Green Chem. Lett. Rev*. **2010**, *3*, 301.
10. Zeng, L.-Y.; Cai, C. *J. Heterocycl. Chem.* **2010**, *47*, 1035.
11. Chen, J.; Wu, D.; He, F.; Liu, M.; Wu, H.; Ding, J.; Su, W. *Tetrahedron Lett.*. **2008**, *49*, 3814.
12. Chen, J. X.; Su, W. K.; Wu, H. Y.; Liu, M. C.; Jin, C. *Green Chem*. **2007**, *9*, 972.
13. Rueping, M.; Antonchick, A. P.; Sugiono, E.; Grenader, K. *Angew. Chem. Int. Ed*. **2009**, *48*, 908.
14. Cheng, X.; Vellalath, S. K.; Goddard, R.; List, B. *J. Am. Chem. Soc*. **2008**, *130*, 15786.
15. Abdel-Jalil, R. J.; Voelter, W.; Saeed, M. *Tetrahedron Lett.*. **2004**, *45*, 3475.
16. Davoodnia, A.; Allameh, S.; Fakhari, A. R.; Tavakoli-Hoseini, N. *Chin. Chem. Lett*. **2010**, *21*, 550.
17. Shi, D. Q.; Rong, L. C.; Wang, J. X.; Zhuang, Q. Y.; Wang, X. S.; Hu, H. W. *Tetrahedron Lett.*. **2003**, *44*, 3199.
18. (a) Okuhara, T. *Chem. Rev*. **2002**, 102, 3641; (b) Clark, J. H.; Macquarrie, D. J. *Handbook of Green Chemistry and Technology, Blackwell*, Oxford, **2002**.
19. (a) Widdecke, H. Hogde, S. P. (Eds.), Synthesis and Separations Using Functional Polymers, Wiley, New York, **1998**, p. *149*; (b) Harland, C. E. Ion Exchange, 2nd ed., Royal Society of Chemistry, London, **1994**; (c) Corma, A. *Chem. Rev*. **1995**, *95*, 559; (d) Clark, J. H.; Macqquarrie, D. J. *Chem. Soc. Rev*. **1996**, *25*, 310; (e) Harmer, M. A.; Sun, Q. *Appl. Catal. A* . **2001**, *221*, 45; (f) Chakraborthy, A.; Sharma, M.M. *React. Funct. Polym*. **1993**, 20, 1. (g) Gogoi, P. *Synlett,* **2005**, *14*, 2263.
20. (a) Olah, G. A. Iyer, P.S.; Suryaprakash, G. K. *Synthesis,* **1986**, *513*; (b) Sandmacher, K.; Kunne, H.; Kunz, H. *Chem. Eng. Technol*. **1998**, *21*, 6; (c) Harmer, M.A. Sun, Q.; Farneth, W. E. *J. Am. Chem. Soc*. **1996**, *118*, 7708; (d) Harmer, M.A. Sun, Q.; Farneth, W. E. *Adv. Mater*. **1998**, 10, 1255; (e) Harmer, M. A.; Sun, Q.; Vega, A. J.; Farneth, W. E.; Heidekum, A.; Hoeldrich, W. F. *Green Chem*. **2000**, *2*, 7.
21. (a) Meziani, M.J.; Zajac, J.; Jones, D.J.; Partyka, S.; Roziere, J.; Auroux, A. *Langmuir* **2000**, *16*, 2262; (b) Brunel, D.; Blanc, A. C.; Galarneau, A.; Fajula, F. *Catal. Today* 2002, *73*, 139.
22. Wang, S. *J. Am. Chem. Soc*. **1973**, *95*, 1328.

23. **Preparation of Wang-OSO$_3$H**:

Wang-OSO$_3$H was prepared by adding freshly distilled ClSO$_3$H (2.0 mmol) to wang resin (1.0 mmol), DIPEA (5.0 mmol) in DCM (10 volumes) and the resulting solution was stirred at 25-35 °C for 2 hr. The reaction mass was filtered and washed with DMF (5 x 10 volumes), DCM (5 x 10 volumes) and Isopropanol (5 x 10 volumes) and the wang catalyst was dried at 130 ^{0}C for 3 hr.

24. **General procedure for the preparation of 2,3-dihydroquinazolin-4(1*H*)-ones**:

A mixture of 2-aminobenzamide **1** (1 mmol) and aldehyde 2 (2a-2v) or ketone 4 (1.2 mmol) was dissolved in 5 ml of water and Wang-OSO$_3$H (10% w/w) was added under stirring condition at 100 $^{\circ}$C. Stirring was continued in for the stipulated period of time (Table 5). The progress of the reaction was monitored with TLC. After completion of the reaction, the reaction mixture was diluted with 1:9 mixture of methanol: ethyl acetate to dissolve the precipitated product and the catalyst was removed simply by filtration. The residual catalyst was repeatedly washed with ethyl acetate (3 x 5 volumes). The combined filtrate and washings, on evaporation, gave the desired product. This was further purified by column chromatography using silica gel (60-120 mesh) with ethyl acetate and hexane (4:6) as eluent to afford the desired product 3(3a-3v) or 5.