Heterocyclic Letters
Vol. 10| No.3|471-477 |May-July|2020
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

ONE-POT SYNTHESIS OF QUINAZOLINONE DERIVATIVES FROM BENZYL ALCOHOL: A MULTI-COMPONENT REACTION

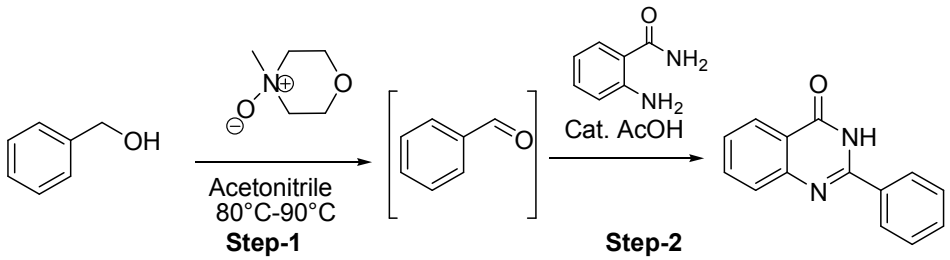
Praveen Kumar Setikam[a], Narayana Murthy Valavala[b], Raghunath Akula[b] and Srinivas rao Golagani[a]

[a]*Department of Chemistry, GIS, GITAM University, Vishakapatnam- 530045 Andhra Pradesh, India*
[b]*Custom Pharma Services, Technology Development Center, Dr. Reddy's Laboratories, Miyapur, Hyderabad-500049 Telangana, India*
Email: setikampraveenkumar@gmail.com

Abstract
An efficient one-pot approach to substituted quinazolines was developed. The reaction enables great flexibility of the substitution patterns and is applicable to give a substituted products in an easy way. This method is an alternative approach for the green synthesis of quinazoline derivatives in the chemical and pharmaceutical industries. All the compounds synthesized were characterized by spectral analysis.

Introduction

Development of shorter routes to the known and bioactive natural products via newly established methodologies is of high demand in modern organic synthesis. Indeed, these strategies allow quicker and economical access to these compounds for medicinal and other uses.



Functional group conversion plays a vital role in synthetic chemistry. Oxidation of alcohol is an important functional group conversion in industrial manufacturing and lab synthesis[i]. There are many of oxidating reagents are well known for conversion of alcolol to aldehyde functional group conversion in milligram scale to bulk scale like MnO_2, $KMnO_4$, Br_2, CrO_3, Dess–Martin periodinane etc[ii]. However all the reagents are having their own limitations like high cost, tedious workup, environmental issues etc. To overcome these drawbacks we

developed a new methodology for functional group conversion by using simple, efficient and commercially available N-methyl morpholone N-oxide.

In environmentally benign synthetic methods, one pot synthesis occupies the major part. In this synthesis more than two compounds are reacted based on their feasibility and give the desired product with good yield. One pot synthesis helps us to minimize the waste producing in reaction and work up.

Quinazolin-4(1H)-ones derivatives plays remarkable role in medicinal chemistry. They are existing in various natural products and synthetic drugs[iii]. They exhibit significant biological activity such as anti-cancer[iv], hypolipidemic[v], antiulcer[vi], anti-convulsant[vii], anti-inflammatory[viii] activity etc.

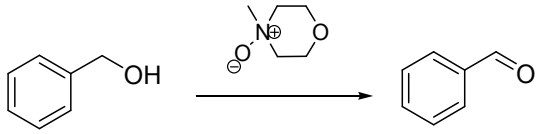
Experimental Section

Thin layer chromatography was run on silicagel-G and visualization were done using UV light or iodine. ^{1}H NMR spectra were recorded with a Varian Mercury plus 400 MHz instrumentrespectively in DMSO-d_6 solvent using trimethylsilane as internal standard. Jeol-JMS D-300 spectrometer was used to record mass spectra.

Results & discussion

Here we reported the one pot synthesis of Quinazolin-4(1H)-ones derivatives from alcohols. We developed a novel condition for oxidation of alcohols to aldehydes by using commercially available, cheaper N-methyl morpholone N-oxide in acetonitrile and its synthetic application for the synthesis of Quinazolin-4(1H)-ones derivatives in a new synthetic route.

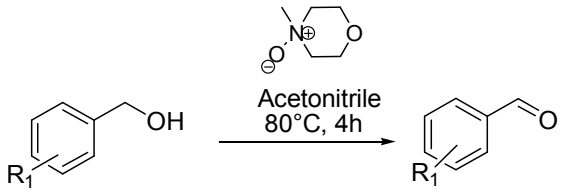
Our synthetic efforts commenced with substituted benzyl alcohol, this benzylalcohols are subjected to oxidation in the presence of N-methyl morpholone N-oxide in acetonitrile solvent at 80 °C gives corresponding aldehyde with quantitative yield. We screened the reaction conditions by using variable different molar ratio of catalyst.



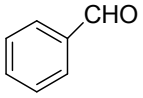
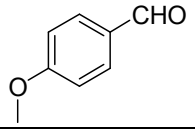
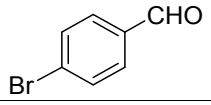
Scheme 1

S. No	Molar ratio of catalyst	Temperature	Time intervals	Yield
1.	1.0 eq.	80°C	6.0 hr	90%
2	1.2 eq.	80°C	4.5 hr	95%
3	1.5 eq.	80°C	4.0 hr	96%
4	2.0 eq.	80°C	4 .0 hr	96%

In above conditions N-methyl morpholone N-oxide in acetonitrile solvent at for four to five hours gives the quantitative yield. Advantages of this conditions are non-formation of smelly bi-products during work up, stable catalyst, removal of the catalyst by simple filtration and not observed the over oxidation product during the reaction.



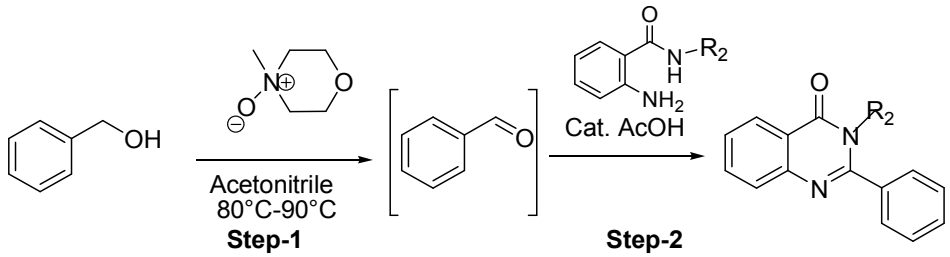
Scheme 2

S. No	R_1 (Starting material)	Product	Reaction time	Yield
1.	-H		4 hr	95%
2.	-OMe (Para)		4.5 hr	94%
3.	-Br (Para)		5.0 hr	94%

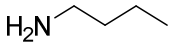
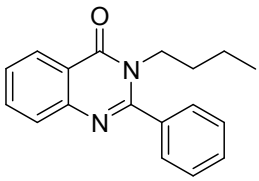
After completion of the oxidation of benzyl alcohol, crude aldehyde in reaction mixture was converted to corresponding quinazolin-4(1H)-ones derivatives without isolating the aldehyde by treating with 2-aminobenzamide. Acetic acid cartelized condensation followed by cyclisation of aldehyde with 2-aminobenzamide at 80 ℃ gives quinazoline derivatives with quantitative yield.

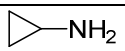
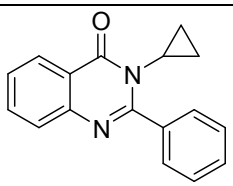
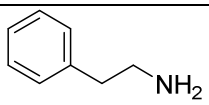
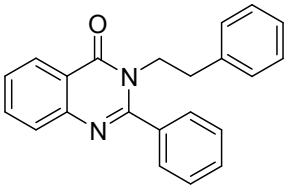
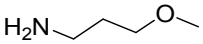
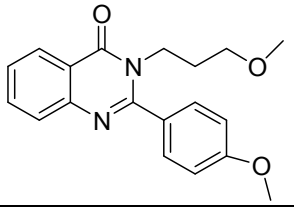
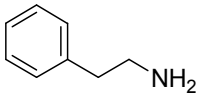
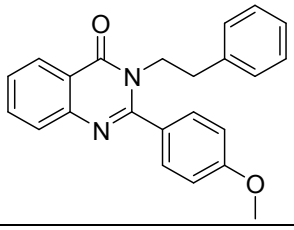
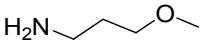
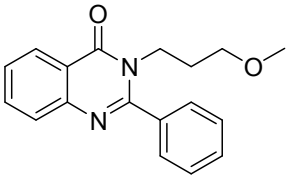
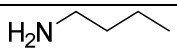
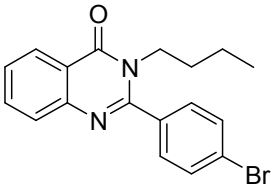
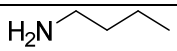
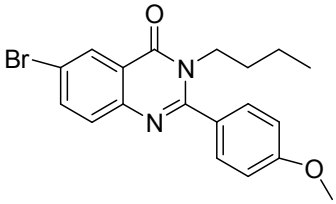
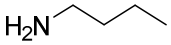
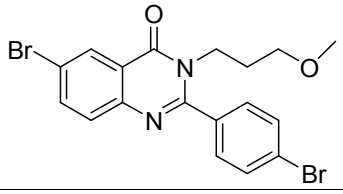
Product was isolated by removal of solvent under reduced pressure and then crude material was purified by trituration with ethanol.

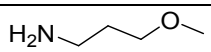
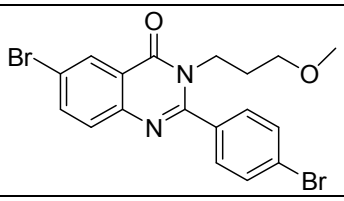
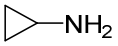
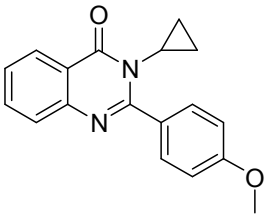
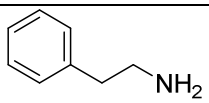
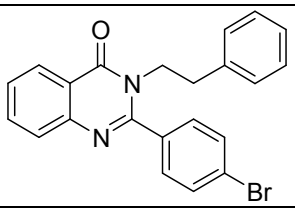
We successfully completed the quinazolin-4(1H)-ones derivatives from corresponding alcohols in one pot synthesis.



Scheme 3

S. No	NH_2-R_2	Product	Reaction time	Yield
1.			~8-10 hr	80%

2.			~8-10 hr	70%
3.			~10-12 hrs	85%
4.			~8-10 hr	75%
5.			~10-12 hrs	79%
6.			~8-10 hr	76%
7.			~8-10 hr	85%
8.			~8-10 hr	82%
9.			~8-10 hr	85%

10.			~8-10 hr	80%
11.			~8-10 hr	78%
12.			~10-12 hrs	85%

Final reaction tried with different solvents:

Solvent	Temperature	Time	yield
Toluene	110	22 hr	53
1,4-Dioxane	105	24 hr	60
CHCl3	60	24 hr	--
2-Me THF	85	16 hr	30
Acetonitrile	80-82	8 hr	85

Reaction conditions: Isatoicanhydride (1 mmol), amine (1 mmol), aldehyde (1mmol), Acetic acid (0.1 mol %), Acetonitrile (10 mL).

3-butyl-2-phenylquinazolin-4(3H)-one:
^{1}H NMR (400 MHz, DMSO-d6): 8.10-8.05 (d, 2H), 7.81-7.60 (t, 2 H), 7.45-7.39 (m, 5H), 3.21-3.16 (t, 2 H), 1.71-1.60 (t, 2 H), 1.41-1.39 (t, 2H), 1.01-0.91(t, 3H); Mass *m/z* 279 [M+H]
3-cyclopropyl-2-phenylquinazolin-4(3H)-one:
^{1}H NMR (400 MHz, DMSO-d6): 8.05-8.00 (d, 2H), 7.77-7.70 (t, 2 H), 7.49-7.38 (m, 5H), 2.35-2.27 (t, 1H), 0.62-0.58(t, 4H). Mass *m/z* 263 [M+H]
3-phenethyl-2-phenylquinazolin-4(3H)-one:
^{1}H NMR (400 MHz, DMSO-d6): 8.17-8.11 (d, 2H), 7.95-7.92 (t, 2 H), 7.79-7.71 (d, 2H), 7.69-7.61 (d, 3H), 7.55-7.42 (d, 2H). 7.42-7.38 (d, 3H), 3.81-3.78 (t, 2 H), 3.51-3.48 (t, 2H), Mass *m/z* 327 [M+H]
2-(4-methoxyphenyl)-3-(3-methoxypropyl)quinazolin-4(3H)-one:
^{1}H NMR (400 MHz, DMSO-d6): 8.11-8.05 (d, 2H), 7.98-7.91 (t, 3 H), 7.79-7.71 (d, 2H), 7.58-7.55 (d, 2H), 3.89-3.82 (q, 2 H), 3.72 (s, 3 H), 3.53 (s. 3H) 3.18-3.12 (t, 2H), 1.87-1.82 (t, 2H). Mass *m/z* 325 [M+H]
2-(4-methoxyphenyl)-3-phenethylquinazolin-4(3H)-one:
^{1}H NMR (400 MHz, DMSO-d6): 8.18-8.10 (d, 2H), 7.95-7.91 (t, 2 H), 7.79-7.71 (d, 2H), 7.70-7.61 (d, 3H), 7.45-7.42 (d, 2H). 7.28-7.21 (d, 2H), 3.82-3.78 (t, 2 H), 3.62 (s, 3 H), 3.48-3.42 (t, 2H), Mass *m/z* 357 [M+H]

3-(3-methoxypropyl)-2-phenylquinazolin-4(3H)-one:
^{1}H NMR (400 MHz, DMSO-d6): 8.10-8.08 (d, 2H), 7.95-7.91 (t, 2 H), 7.71-7.62 (m, 5H), 3.91-3.84 (q, 2 H), 3.58 (s, 3 H), 3.12-3.09 (t, 2H), 1.82-1.78 (q, 2H), Mass *m/z* 295 [M+H]
2-(4-bromophenyl)-3-propylquinazolin-4(3H)-one:
^{1}H NMR (400 MHz, DMSO-d6): 8.08-8.06 (d, 2H), 7.78-7.71 (t, 2 H), 7.42-7.38 (d, 2H), 7.32-7.28 (d, 2 H), 3.10-3.01 (q, 2H), 1.71-1.61 (q, 2H), 0.99-0.91 (t, 3H), Mass *m/z* 343 [M+H]
6-bromo-3-butyl-2-phenylquinazolin-4(3H)-one:
^{1}H NMR (400 MHz, DMSO-d6): 8.18-8.09 (m, 1H), 7.88-7.82 (dd, 1 H), 7.67-7.62 (dd, 1H), 7.42-7.38 (m, 5H), 3.15-3.09 (q, 2H), 1.71-1.62 (q, 2H), 1.42-1.38 (q, 2H), 1.01- 0.95 (t, 3H), Mass *m/z* 358 [M+H]
6-bromo-3-butyl-2-(4-methoxyphenyl)quinazolin-4(3H)-one:
^{1}H NMR (400 MHz, DMSO-d6): 8.18-8.12 (d, 1H), 7.91-7.89 (dd, 1 H), 7.82-7.78 (dd, 1H), 7.51-7.42 (d, 2H), 7.40-7.30 (d, 2H), 3.7 (s, 3H), 3.15-3.05 (q, 2H), 1.72-1.64 (q, 2H), 1.42-1.38 (q, 2H), 0.95-1.01 (t, 3H), Mass *m/z* 388 [M+H]
6-bromo-2-(4-bromophenyl)-3-(3-methoxypropyl)quinazolin-4(3H)-one:
^{1}H NMR (400 MHz, DMSO-d6): 8.18-8.15 (d, 1H), 7.91-7.88 (dd, 1 H), 7.71-7.69 (dd, 1H), 7.51-7.48 (d, 2H), 7.32-7.28 (d, 2H), 3.7 (s, 3H), 3.58-3.51 (m, 2H), 3.18-3.08 (q, 2H) 1.72-1.63 (q, 2H) Mass *m/z* 453 [M+H]
3-cyclopropyl-2-(4-methoxyphenyl)quinazolin-4(3H)-one:
^{1}H NMR (400 MHz, DMSO-d6): 8.03-8.01 (d, 2H), 7.72-7.69 (t, 2 H), 7.43-7.41 (d, 2H), 7.23-7.21 (d, 2H), 4.02 (s, 3H) 3.63 (s, 1H), 2.32-2.29 (t, 1H) 0.62-0.58 (t, 4H) Mass *m/z* 293 [M+H]
2-(4-bromophenyl)-3-phenethylquinazolin-4(3H)-one:
^{1}H NMR (400 MHz, DMSO-d6): 8.12-8.09 (d, 2H), 7.95-7.92 (t, 2 H), 7.63-7.61 (d, 2H), 7.51-7.42 (d, 2H), 7.31-7.28 (d, 2H), 7.22-7.18 (d, 3H), 3.72-3.68 (t, 2H), 3.05-3.01 (t, 2H) Mass *m/z* 406 [M+H]

Conclusion

In conclusion, we have successfully developed a one-pot three-component four-center reaction strategy leading to quinazolinones which are two important pharmacological and biological scaffolds, starting from simple and readily available inputs.

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Received on June17, 2020.