Accepted Manuscript

A facile and versatile protocol for the one-pot $PhI(OAc)_2$ mediated divergent synthesis of quinazolines from 2-aminobenzylamine

Moumita Saha, Prasun Mukherjee, Asish R. Das

PII: S0040-4039(17)30463-X
DOI: http://dx.doi.org/10.1016/j.tetlet.2017.04.036
Reference: TETL 48828

To appear in: *Tetrahedron Letters*

Received Date: 28 February 2017
Revised Date: 4 April 2017
Accepted Date: 8 April 2017

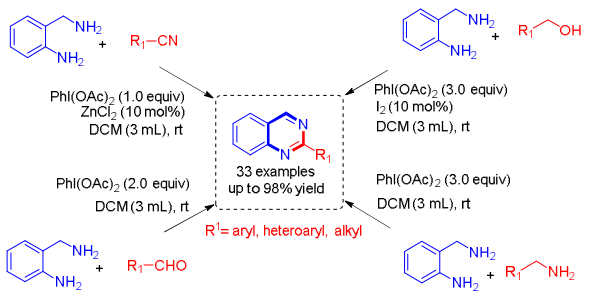
Please cite this article as: Saha, M., Mukherjee, P., Das, A.R., A facile and versatile protocol for the one-pot $PhI(OAc)_2$ mediated divergent synthesis of quinazolines from 2-aminobenzylamine, *Tetrahedron Letters* (2017), doi: http://dx.doi.org/10.1016/j.tetlet.2017.04.036

Graphical Abstract

A facile and versatile protocol for the one-pot PhI(OAc)$_2$ mediated divergent synthesis of quinazolines from 2-aminobenzylamine

Moumita Saha, Prasun Mukherjee, Asish R. Das*

Leave this area blank for abstract info.



ELSEVIER

Tetrahedron Letters
journal homepage: www.elsevier.com

A facile and versatile protocol for the one-pot $PhI(OAc)_2$ mediated divergent synthesis of quinazolines from 2-aminobenzylamine

Moumita Saha, Prasun Mukherjee, Asish R. Das*

Department of Chemistry, University of Calcutta, Kolkata-700009, India
**Corresponding author: Tel.: +913323501014, +919433120265; fax:913323519754;*
E-mail address: ardchem@caluniv.ac.in , ardas66@rediffmail.com

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
2-substituted quinazoline
iodobenzenediacetate
diverse starting materials
well tolerance of oxidant prone functional groups

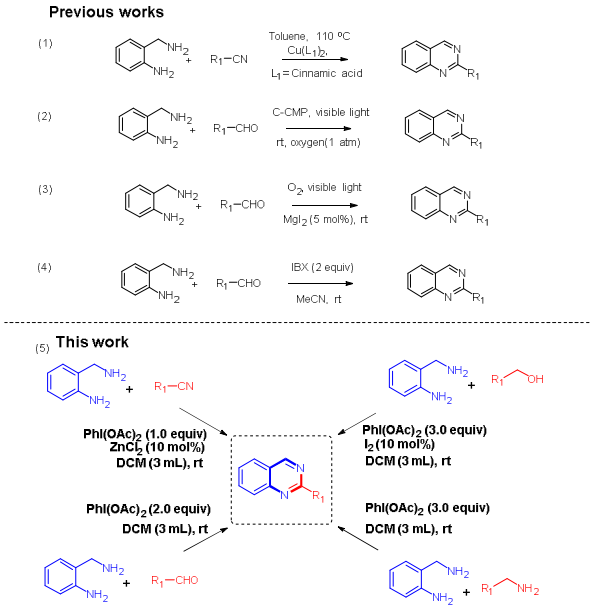
ABSTRACT

In this present work iodobenzenediacetate (PIDA) has been found to be the key reagent in absence or presence of catalytic amount of molecular iodine (I_2)/zinc chloride ($ZnCl_2$) to construct quinazoline scaffold from 2-aminobenzylamine and a variety of easily available aldehydes, aryl and aliphatic amines, aliphatic and aryl alcohols and nitriles. This protocol provides mild and robust conditions along with great versatility to synthesize 2-substituted quinazolines from diverse starting materials in good to excellent yields.The developed protocol is also well applicable to reactants containing ease to oxidation prone functional groups.

1. Introduction

Hypervalent iodine reagents have gained significant consideration over the past decades as eco-friendly and robust oxidants for numerous valuable organic transformations.[1] In particular, several protocols have been developed where these reagents have been successfully employed instead of using expensive metal catalysts and strong oxidizing agents.[2] The ability to provide a metal free reaction condition has made hypervalent iodine reagents important in medicinal field to construct biologically relevant heterocycles. Among them iodobenzene diacetate (PIDA) has employed in numerous organic transformations as the key oxidant due to its ready availability and less toxicity.[3] In our previous work, we have established the synthesis of 2-substituted benzimidazoles through ring distortion strategy by reacting 2-aminobenzylamine with aldehydes and arylamines employing PIDA and molecular iodine reagent combination to generate the key reagent IOAc in-situ.[4]Interestingly, during the study of optimization of reaction conditions, 2-phenylquinazoline was obtained in a considerable amount when PIDA and molecular iodine was taken in 1.5:0.5 ratio along with the ring distorted product 2-phenylbenzimidazole.

Quinazoline is the key structural motif of several biologically significant natural products.[5]Besides, they are well known for their broad spectrum of bioactivity, such as, sedative, anticonvulsant, antitussive, hypotensive, antidiabetic, anticancer, antiviral, antitubercularproperties.[6] In addition, there are several quinazoline derivatives marketed as potent drugs.[7]Consequently, several protocols have been developed over the past decades to access these particular heterocycles.[8] However, the established protocols to synthesize quinazoline derivatives require either very strong, hazardous oxidizing agent or expensive transition metal catalysts along with long reaction time and elevated temperature. Recently, Li et al, have established the synthesis of quinazolines from 2-aminobenzylamine and nitrile derivatives in presence of copper cinnamate as catalyst in toluene at 110 °C (Scheme 1, entry 1).[9d]



Scheme 1.Synthesis of 2-substitutedquinazolines

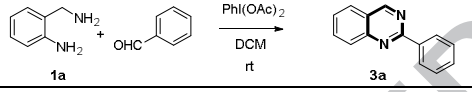
Su and co-workers have employed carbazolic conjugated microporous polymers as visible-light photocatalyst to synthesize quinazoline scaffolds from tetrahydroquinazolines (Scheme 1, entry 2).[9a] Yamaguchi's group has reported magnesium iodide-catalyzed synthesis of quinazolines from aldehydes and 2-aminobenzylamine under visible light and oxygen atmosphere (scheme 1, entry 3).[9b] In addition, Sen et al, have reported IBX promoted synthesis of quinazolines from aldehydes and 2-aminobenzylamine (scheme 1, entry 3).[9a] However, no protocol has been developed so far which can afford quinazolines from the reaction of 2-aminobenzylamine with either aldehydes, aryl amines, aryl alcohols or aromatic nitriles by employing a common oxidant as the key reagent. Thus the synthesis of quinazolines is still seeking a mild, competent and versatile methodology with a broad range of substrate scope.

Following our latest efforts in hypervalent iodine mediated formation of carbon-carbon and carbon-heteroatom bond to synthesize bioactive heterocycles,[10] herein we wish to report a hypervalent iodine promoted mild and robust synthesis of quinazoline derivatives by reacting 2-aminobenzylamine with aldehydes, arylamines, arylalcohols and aromatic nitriles, using DCM as solvent at room temperature (Scheme 1, entry 5).

2. Results and Discussion

Initially, to optimize the reaction conditions for the synthesis ofquinazoline scaffold **1a** (1.0 mmol) and benzaldehyde (1.0 mmol) were treated with 2.0 mmol PIDA in 3 mL of DCM at room temperature. To our satisfaction, the product **3a** was obtained in 92% yield after 0.7 h (Table 1, entry 1). The reaction was then

Table 1. Optimization of the reaction condition to synthesize quinazoline[a]



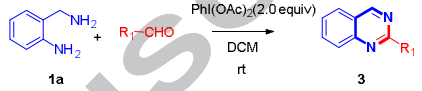
entry	PIDA (mmol)	solvent	additive (2mmol)	time (h)	yield[b] (%)
1	**2.0**	**DCM**	**-**	**0.7**	**92**
2	1.8	DCM	-	1.0	82
3	2.1	DCM	-	1.0	91
4	2.0	DCE	-	1.5	88
5	2.0	CH_3CN	-	2.0	86
6	2.0	EtOAc	-	4.0	70
7	2.0	THF	-	3.0	76
8	2.0	toluene	-	2.0	80
9	2.0	DCM	Et_3N	1.0	91
10	2.0	DCM	K_2CO_3	1.0	90
11	2.0	DCM	Cs_2CO_3	1.0	92

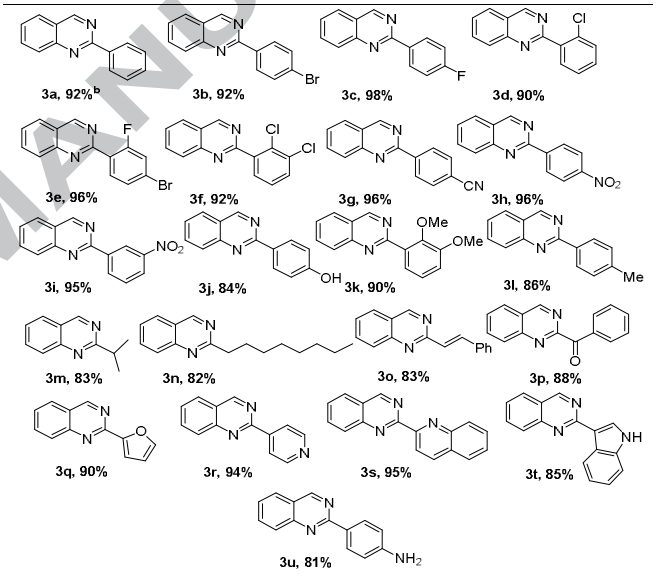
[a]In each case **1a** (1.0mmol), benzaldehyde (1.0mmol), 3 mL solvent were used. [b] yield.

carried out by using PIDAin different amounts. Significant decrease in the product yield was observed when 1.8 mmol of PIDA was employed (Table 1, entry 2). However, use of 2.1 mmol of PIDA was found to be fruitless to increase the product yield (Table 1, entry 3). Replacement of DCM with other solvents results in a decrease in product yield along with a longer reaction time (Table 1, entry 4-8). To explore the necessity of a base during the reaction; triethylamine, K_2CO_3 and Cs_2CO_3 were employed in conjunction. However, presence of a base was found to be ineffective to increase the product yield in this particular reaction (Table 1, entry 9-11).

Having the optimized reaction condition in hand, we have then investigated the scope and limitation of this protocol. Various aromatic, heteroaromatic and aliphatic aldehydes along with 2-aminobenzylamine were treated with 2.0 equiv PIDA in 3 mL DCM at rt. In all cases the reaction proceeded with equal efficiency to provide the functionalized quinazoline derivatives in good to excellent yield (Table 2, entry **3a-u**). The reaction is greatly product selective affording no side products after completion of the reaction. Importantly, in this protocol also the oxidant sensitive functional groups were able to survive during the reaction (Table 2, entry **3j**, **3k, 3o**, **3t** and **3u**).

Table 2. Substrate scope for the synthesis of quinazolines[a]

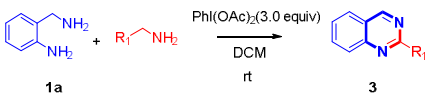


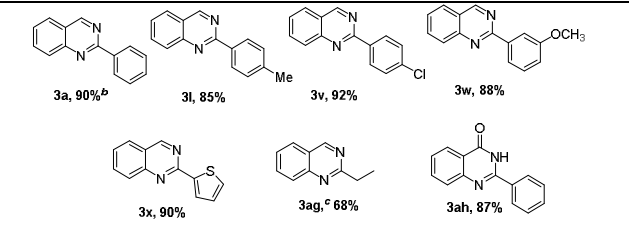


[a] reaction conditions: **1a** (1.0mmol), aldehyde (1.0mmol), DCM (3 mL), PIDA (2.0mmol) were stirred for 0.7h. [b] yield.

In view of the above impressive results, we have then tried to extend the scope of these protocols in realizing

Table 3.Synthesis of quinazolines from arylamines[a]



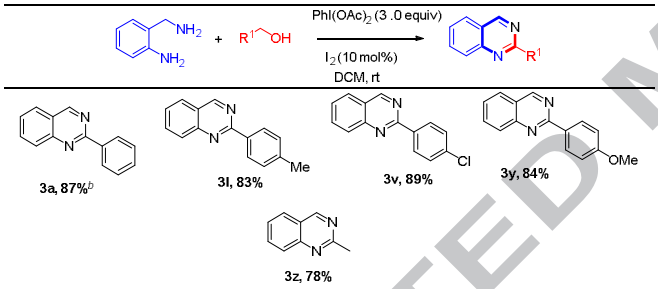


[a]reaction conditions : **1a** (1.0 mmol), aryl amines (1.0 mmol), PIDA (3.0 mmol), and DCM (3mL) at rt for 1.0h. [b] yield. [c] reaction time was 4.0h.

quinazolines from 2-aminobenzylamine and aryl and alkyl amine derivatives. Initially benzylamine derivatives (1.0 mmol) were stirred in 3 mL DCM in presence of 1.0 mmol of PIDA for 15 min and then to it **1a** (1.0 mmol) and 2.0 mmol PIDA were added at rt. Satisfyingly, the reaction proceeded well by affording the corresponding quinazolines in excellent yield (Table 3, entry **3a**, **3l**, **3v**, **3x and 3ag**). Interestingly, quinazolinone **3ah** was also obtained in excellent yield from 2-aminobenzamide and benzyl amine by applying this protocol (Table 3, entry **3ah**)

In order to synthesize quinazolines from arylalcohols we have then reacted arylalcohol derivatives (1.0 mmol) with 1.0 mmol of PIDA and molecular iodine (10 mol%) for 15 min in 3 mL DCM and then to it **1a** (1.0 mmol) and 2.0 mmol PIDA were added at rt. Benzyl alcohol derivatives with electron donating as well as electron withdrawing groups have been employed and corresponding products were obtained in excellent yield (Table 4, entry **3a**, **y**, **l**, **v**). Interestingly, when we have employed ethanol in place of benzyl alcohol derivatives the reaction have proceeded with equal efficacy affording the corresponding quinazolines in excellent yield (Table 4, entry **3z**). It is noteworthy to mention that without the addition of catalytic amount of I_2 the formation of the desired quinazolines was not observed.

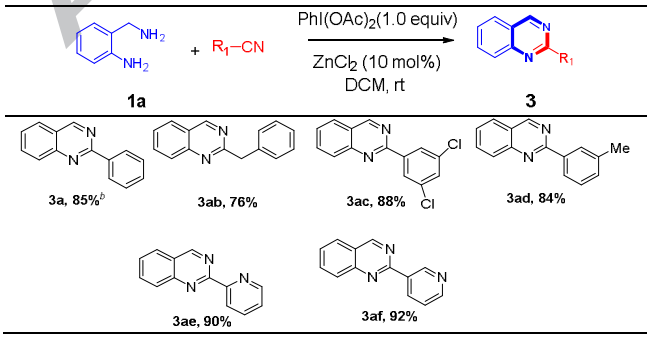
Table 4.Synthesis of quinazolines from aryl and aliphatic alcohols[a]



[a]reaction conditions : **1a** (1.0 mmol), alcohols (1.0 mmol), PIDA (3.0 mmol), I_2 (10 mol%) and DCM (3mL) at rt for 1.2h. [b] yield.

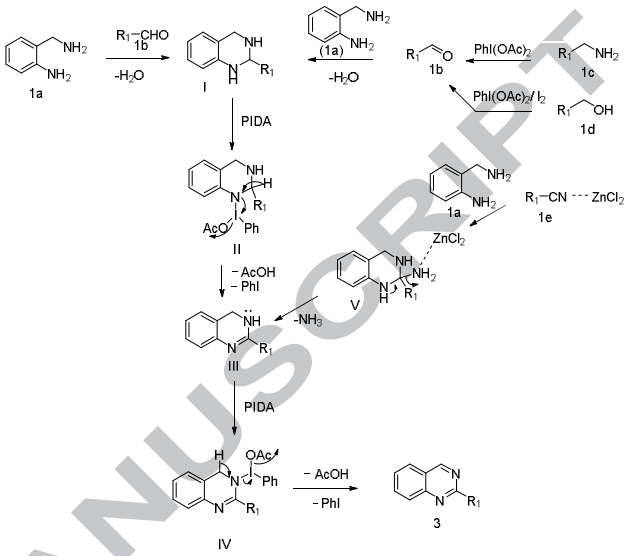
We have further extended this protocol to construct quinazoline scaffold from aryl, alkyl and heteroaryl nitriles by reacting **1a** (1.0 mmol) with nitrile derivatives (1.0 mmol) using PIDA as the oxidants in presence of $ZnCl_2$ (10 mol%) in DCM at rt. In this particular case however the presence of Lewis acid catalyst is essential to facilitate the attack of 2-aminobenzylamine to the nitrile group. The reaction proceeded well at rt affording the corresponding quinazolines in excellent yields.

Table 5.Synthesis of quinazolines from aryl and aliphatic nitriles[a]



[a]reaction conditions : **1a** (1.0 mmol), nitriles (1.0 mmol), PIDA (1.0 mmol), $ZnCl_2$ (10 mol%) and DCM (3mL) at rt for 1.3h. [b] yield.

A tentative mechanism for the formation of quinazoline is also shown in Scheme 2. After the formation of intermediate **I** from the reaction between **1a** and **1b**, PIDA reacts with **I** to generate the intermediate **II**. An elimination reaction in II then leads to



Scheme3: Plausible mechanism for the synthesis of quinazolines

the formation of **III**. **III** then gets attacked by another molecule of PIDA to produce the product **3** following a similar course via intermediate **IV**. In case of arylamines (**1c**) and arylalcohol derivatives (**1d**), their initial oxidation takes place in presence of PIDA and PIDA/I_2 respectively to generate their corresponding aldehydes. It is noteworthy to mention that the conversion of 1d to 1b was not observed in absence of molecular iodine. The role of catalytic amount of molecular iodine in this transformation is probably the formation of IOAc which may impart the key role in generating the intermediate 1b which then follows the desired course of reaction and ultimately produces the product **3**. For nitrile derivatives, coordination of $ZnCl_2$ with –CN group[11] facilitates the reaction of 2-aminobenzylamine with nitrile moiety thereby allowing the formation of **V** which then releases a molecule of NH_3 in presence of $ZnCl_2$ to form **III**. **III** then follows the similar course of mechanism to afford the product **3**.

3. Conclusions

In summary, PIDA has been successfully employed to synthesize 2-substitutedquinazolinesfrom 2-aminobenzylamine and a variety of easily available aldehydes, arylamines, aryl as well as aliphatic alcohols and nitriles. The versatility of this protocol is well established by exploiting PIDA in absence or presence of different additives in order to synthesize 2-substituted quinazolines from diverse starting materials. Additionally, this protocol offers mild and robust conditions to synthesize quinazoline scaffold in excellent yields by promoting the C-N bond formation at room temperature.

4. Acknowledgments

We acknowledge the financial support from the centre of CAS-V (Synthesis and functional materials) (support offered by UGC, New Delhi) of the department of Chemistry, University of Calcutta. MS and PM are thankful to U.G.C, New Delhi, India for the grant of their Junior and Senior Research fellowships

respectively. Crystallography was performed at the DST-FIST, India-funded Single Crystal Diffractometer Facility at the Department of Chemistry, University of Calcutta.

5. References and notes

1. (a) Yoshimura, A. and ZhdankinV. V.*Chem. Rev*. **2016**, *116*, 3328–3435; (b) Zhdankin V. V. and StangP. J. *Chem. Rev*. **2008**, *108*, 5299–5358; (c) Banks, D. F. *Chem. Rev*. **1966**, *66*, 243–266.
2. (a) Dohi, T., Takenaga, N., Goto, A., Maruyama, A., Kita, Y., *Org. Lett*. **2007**, *9*, 3129-3132; (b) Yoshimura, A., Middleton, K. R., Todora, A. D., Kastern, B. J., Koski, S. R., Maskaev, A. V., Zhdankin V. V, *Org. Lett.* **2013**, *15*, 4010-4013.
3. (a) Liu, G.Q., Li, Y.M. *J. Org. Chem.* **2014** *79*, 10094–10109; (b) Zhang, L.H., Kauffman, G.S., Pesti, J. A., Yin, J. *J. Org. Chem.* **1997** *62*, 6918–6920; (c) Xu, J.H., Jiang, Q., Guo, C.C. *J. Org. Chem.* **2013** *78*, 11881–11886.
4. Saha, M., Mukherjee, P., Das, A. R. *Tetrahedron Lett*. **2017**, *58*, 1046–1049.
5. (a) Connolly, D. J., Cusack, D., Sullivan, T. P. O., Guiry, P. J. *Tetrahedron* **2005**, *61*, 10153; (b) Foster, B. A., Coffrey, H. A., Morin, M. J., Rastinejad, F. *Science* **1999**, *286*, 2507; (c) Gundla, R., Kazemi, R., Sanam, R., Muttineni, R., Sarma, J. A. R. P., Dayam, R., Neamati, N. J. *J. Med. Chem.* **2008**, *51*, 3367; (d) Lüth, A., Löwe, W. *Eur. J. Med. Chem.* **2008**, *43*, 1478.
6. (a) Selvam T. P. and Kumar P. V. *Research in Pharmacy* **2011**, *1*, 1; (b) Henderson, E. A., Bavetsias, V., Theti, D. S., Wilson, S. C., Clauss, R., Jackman, A. L. *Bioorg. Med. Chem.* **2006**, *14*, 5020; (c) Chien, T.C., Chen, C.S., Yu, F.H., Chern, J.W *Chem. Pharm. Bull.* **2004**, *52*, 1422.
7. Ravez, S., Castillo-Aguilera, O., Depreux, P., Goossens, L. Expert OpinTher Pat. **2015**, *25*, 789-804.
8. (a) VandenEynde, J. J., Godin, J., Mayence, A., Maquestiau, A., Anders, E. *Synthesis* **1993**, 867; (b) Peng, Y., Zeng, Y., Qiu, G., Cai, L., Pike, V. W. *J. Heterocycl. Chem*. **2010**, *47*, 1240; (c) C. Maheswari, U., Kumar, G. S., Venkateshwar, M., Kumar, R. A., Kantam, M. L., Reddy, K. R. *Adv. Synth. Catal*. **2010**, *352*, 341; (d) Huang, C., Fu, Y., Fu, H., Jiang, Y.,Zhao, Y., *Chem. Commun*. **2008**, 6333; (e) Malakar, C. C., Baskakova, A., Conrad J., Beifuss, U. *Chem. Eur. J*. **2012**, *18*, 8882; (e) Han, B., Yang, X. L., Wang, C.,Bai, Y. M., Pan, T. C., Chen, X., Yu, W. *J. Org. Chem.* **2012**, *77*, 1136; (f) Wang, C., Li, S., Liu, H., Jiang,Y., Fu, H. *J. Org. Chem*. **2010**, *75*, 7936; (g) Chen, Z., Chen, J., Liu, M., Ding, J., Gao, W., Huang, X. and Wu, H. *J. Org. Chem.* **2013**, *78*, 11342−11348; (h) Zhao, D., Shen, Q., Zhou, Y. R., Li, J. X. *Org. Biomol. Chem*. **2013**, *11*, 5908; (i) Truong, V. L., Morrow, M., *Tetrahedron Lett*. **2010**, *51*, 758–760; (j) Xu, C., Jia, F.C., Zhou, Z.W., Zheng, S.J., Li, H. and Wu, A.X. *J. Org. Chem*. **2016**, *81*, 3000–3006; (k) Cai, Q., Li, D.K., Zhou, R.R., Zhuang, S.Y., Ma , J.T., Wu, Y.D and Wu, A.X.*J. Org. Chem*. **2016**, *81*, 8104–8111;(l) Zhao, D., Zhou, Y.R., Shen, Q.and Li, J.X. *RSC Adv*. **2014**, *4*, 6486; (m) Zhang, Z., Wang, M., Zhang, C., Zhang, Z., Lu, J. and Wang, F. *Chem. Commun. 2015*, **51**, 9205-9207; (n) Tangella, Y., Manasa, K. L., Sathish , M., Alarifi , A. and Kamal , A. *Chemistry Select* **2016**, *1*, 2895 – 2899.
9. (a) Su, C., Tandiana, R., Tian, B., Sengupta, A., Tang, W., Su, J. and Loh, K. P. *ACS Catal*. **2016**, *6*, 3594–3599; (b) Yamaguchi, T., Sakairi, K., Yamaguchi, E., Tada, N., Itoh, A. *RSC Adv*. **2016**,*6*, 56892-56895; (c) Hati, S., Sen, S., *Synthesis* **2016**, *48*, 1389-1398; (d) Li, C., An, S., Zhang, Y. J., Kang, Y., Liu, P., Wang, Y. and Li, J. *RSC Adv*. **2014**, *4*, 49888.
10. Mukherjee, P. and Das, A. R. *J. Org. Chem*.DOI**:** 10.1021/acs.joc.7b00089.
11. Vorona, S., Artamonova, T., Zevatskii, Y., Myznikov, L. *Synthesis* **2014**, *46*, 0781–0786.

.

- 2-substituted quinazolines from 2-aminobenzylamine.
- Diverse aldehydes, aryl and alkyl amines, alcohols and nitriles can be employed.
- $PhI(OAc)_2$ shows the promise in presence or absence of $ZnCl_2$ or I_2.
- Mild and versatile protocol does not demand high thermal or photochemical energy.
- Protocol offers well tolerance towards oxidation prone functional groups.