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On Water: Catalyst−free chemoselective synthesis of highly functionalized tetrahydroquinazolines from 2-aminophenylacrylate

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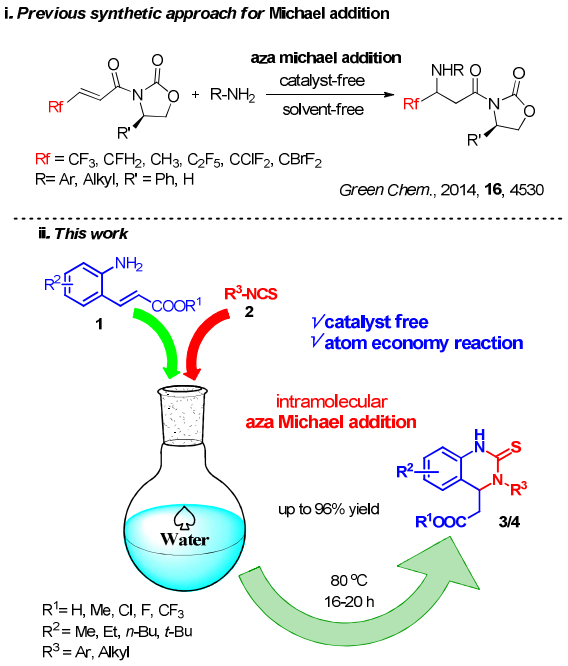
A green and catalyst free atom-ecomonic straightforward tandem approach for the synthesis of highly functionalized tetrahydroquinazolines by the reaction of 2-aminophenylacrylates with isothiocyanates using water as an environmental friendly solvent via amidation and concomitant chemoselective Michael-addition is described.

Various organic protocols have been reported using environment friendly solvents.[1–3] Water, in contrast to other toxic organic solvents, is an eco-friendly and economical reaction medium that has an incomparable effect on the rate and selectivity of organic reactions.[4] Remarkably, the reaction of water insoluble organic substrate usually takes place in an aqueous suspension and the reactivity is conducted through hydrophobic interactions and enrichments of organic substrates in the local hydrophobic surroundings.[5]

Quinazoline are an important class of benzheterocycles that serves as essential building blocks for a variety of biologically and pharmaceutically active agents.[6-8] A rapid and experimentally simple synthesis of quinazolines nucleus under mild conditions is in high demand. Micheal-addition is one of the most common methods that has been utilized for the synthesis of a variety of biologically active compounds.[9-11] Literature revealed that intermolecular conjugate addition of amines has been much explored[12]; however intramolecular conjugate additions of uredioacrylates using water as a solvent have not been much explored.[13]

In 1998, Molina[14a] reported a protocol for the formation of 2-oxo-tetrahydroquinazolines by using *ortho*-amino phenylacrylate. Xin[14b] and co-workers reported the synthesis of quinazolines starting from 2-aminophenylacrylate using NaOH as base and THF as solvent. In 2011, Glorius[12] developed a significant methodology for the synthesis of teterahydroquinazolines via Rh-catalyzed oxidative C-H olefination followed by intramolecular aza-Michael addition. Recently, Huang[15] developed an interesting approach for the aza-Michael addition with β-fluoroalkylated oxazolidinone under catalyst and solvent-free conditions (Scheme 1, i). In continuation of our ongoing research on heterocyclic synthesis;[16-17] herein, we report an efficient catalyst−free one-pot approach for the synthesis of tetrahydroquinazolines using water as solvent from an easily accessible and inexpensive starting substrate (Scheme 1, ii).

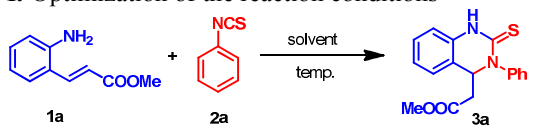


Scheme 1 Designed tandem approach

In order to identify the optimal conditions for the reaction, various Pd(II) complexes were examined with a variety of polar organic solvents in the reaction of (*E*)-methyl 3-(2-aminophenyl)acrylate **1a** with phenylisothiocyanate **2a,** the desired product **3a** was obtained in low to moderate yields (Table 1, entries 1-5). On applying the Molina's condition for isothiocyanates the desire product **3a** was obtained in 69%

yield (Table 1, entry 6). Organic solvents such as THF, DMF, MeCN, DCE provided the desire product **3a** in lower yields (Table 1, entries 7−10). Interestingly use of EtOH as a solvent provided the desired product **3a** in good yield (Table 1, entries 11-12). When the reaction of acrylate **1a** with isothiocyanates **2a** was performed in water at 80°C for 16 h, the desire product **3a** was obtained in 90% yield (Table 1, entry 13). Inferior results were observed when the reaction was performed at 25 °C for 24 h (Table 1, entry 14). On applying the Huang reaction condition, the desire product **3a** was obtained in poor yield (Table 1, entry 15). Reaction product was fully characterized by the ^{1}H, ^{13}C NMR and HRMS data. The broad singlet at ~9.0 ppm in ^{1}H NMR and the characteristic peak of C=S at ~177.0 ppm clearly indicates the formation of the product **3a**.

Table 1. Optimization of the reaction conditions[a]



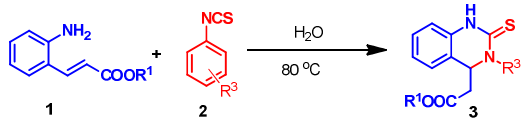
1a 2a 3a

Entry	Catalyst	Solvent	T (h)	*T* (°C)	Yield (%)[b]
1	$Pd(OAc)_2$	MeCN	8	70	25
2	$Pd_2(dba)_3$	MeCN	8	70	35
3	$PdCl_2$	MeCN	8	70	48
4	$PdCl_2$	DMF	8	70	59
5	$PdCl_2$	THF	8	60	40
6[9a]	NaOH	THF	8	60	69
7	-	THF	12	60	38
8	-	DMF	16	70	45
9	-	MeCN	16	70	30
10	-	$ClCH_2CH_2Cl$	16	80	15
11	-	EtOH	12	70	70
12	-	EtOH	16	80	75
13	**-**	**H_2O**	**16**	**80**	**90**
14	-	H_2O	24	25	15
15[11]	-	-	24	80	25

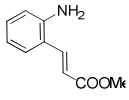
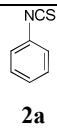
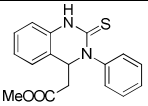
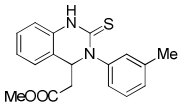
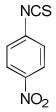
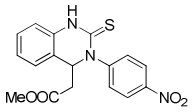
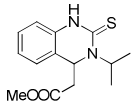
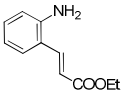
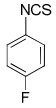
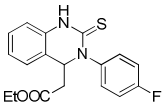
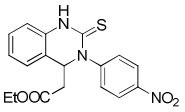
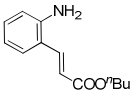
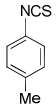
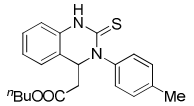
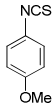
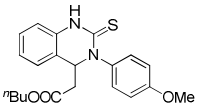
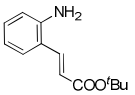
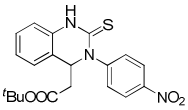
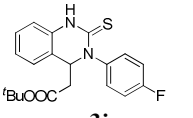
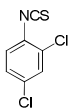
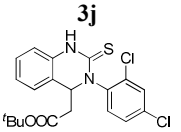
[a] Reactions were performed using 0.5 mmol of 2-aminophenylacrylate **1a** and isothiocyanates **2a** (0.5 mmol) with 5 mol% of catalyst in 2.0 mL solvent. [b] Isolated yield.

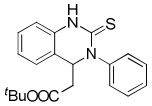
Under the optimized reaction conditions, we examined the substrate scope of the developed chemistry by using a variety of 2-aminoaryl acrylates **1a**–**d** and isothiocyanates **2a**–**h** (Table 2). Reaction of acrylate **1a** with phenylisothiocyanate **2a** provided the desired product **3a** in 90% yield (Table 2, entry 1). In case of isothiocyanates, bearing an electron-donating group **2b** the desire product **3b** was obtained in 83% yields (Table 2, entry 2); however, isothiocyanates bearing electron−withdrawing groups **2c** afforded the product **3c** comparatively in higher yield (Table 2, entry 3). Interestingly, when 2-isothiocyanatopropane **2d** was reacted with **1a,** the product **3d** was successfully obtained in 75% yield (Table 2, entry 4). Products **3e**–**f** were obtained in 92% and 94% yields respectively, when *para*-fluoro and *para*-nitro were employed as isothiocyanates (Table 2, entries 5−6). The reaction was well implemented in the case of *n*-butyl acrylate **1c** to form intriguing cyclized product **3g**–**h** in 84–80% yields (Table 2, entries 7−8). A comparable yield of the desire product was obtained when *tert*-butyl acrylate **1d** was used with isothiocyanate **2c, 2e**, **2h** and **2a** (Table 2, entries 9−12).

Table 2. Tandem synthesis of tetrahydroquinazolines[a]



1 2 3

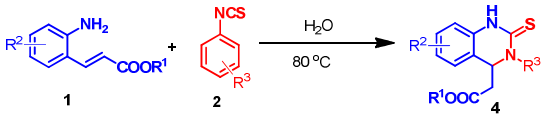
Entry	Acrylate **1**	Isothiocyanate **2**	Product **3**	Yield (%)[b]
1	 **1a**	 **2a**	 **3a**	90
2	**1a**	 **2b**	 **3b**	83
3	**1a**	 **2c**	 **3c**	95
4	**1a**	 **2d**	 **3d**	75[c]
5	 **1b**	 **2e**	 **3e**	92
6	**1b**	**2c**	 **3f**	94
7	 **1c**	 **2f**	 **3g**	84
8	**1c**	 **2g**	 **3h**	80
9	 **1d**	**2c**	 **3i**	90
10	**1d**	**2e**	 **3j**	92
11	**1d**			93

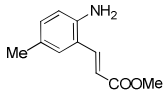
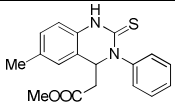
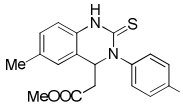
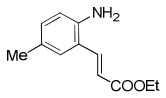
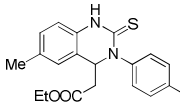
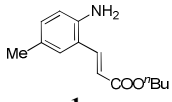
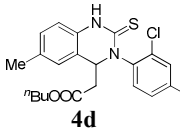
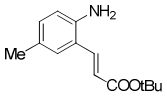
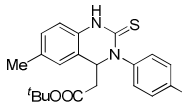
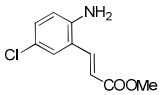
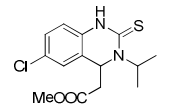
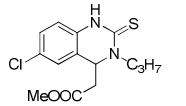
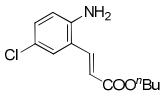
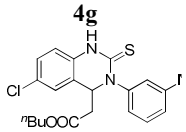
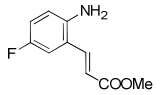
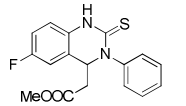
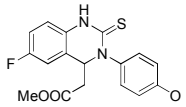
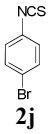
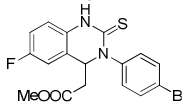
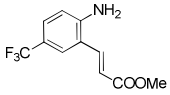
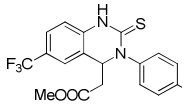
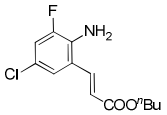
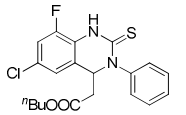
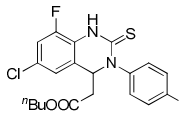
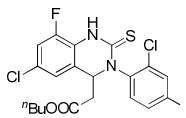
		2h	**3k**	
12	**1d**	**2a**	 **3l**	84

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), 80 °C, 2 mL H_2O, 16 h. [b] Isolated yields. [c] Time = 20 h

Success of the chemoselective addition of the unsubstituted aminoacrylates onto isothiocyanates encouraged us for the addition of the substituted acrylates onto isothiocyanates to synthesize functionalized tetrahydroquinazolines. Under the optimized reaction conditions (Table 1, entry 13); the reaction of the acrylates **1e**–**m** with isothiocyanates **2a**–**j** provided the corresponding products **4a**–**o** in good yields (Table 3, entries 1−15). During the course of the reaction it was observed that the nature of the substituent's attached to the aryl ring of isothiocyanates and the acrylates were responsible for the success of the reaction. The presence of electron-releasing methyl group in anilines increases the nucleophilicity of $-NH_2$ group which enhances the yield of the compounds **4a-e** (Table 3, entries 1−5). Reaction proceeded well with aliphatic isothiocyanate **2d** and **2i**, which provided the corresponding fused product **4f**–**g** in 68% and 62% yields respectively (Table 3, entries 6 and 7). We further employed the same protocol bearing halogen substituent on anilines moieties, the declines in the yield of the compounds **4h-k** was observed which might be due to the low nucleophilicity of $-NH_2$ group (entries 8−11). Presence of electron-withdrawing groups on aniline ring afforded the desire product **4l** in 65% yield (entry 12). Interestingly, when sterically hindered chloro-fluoroaniline **1m** was reacted with isocyanates **2a**, **2c** and **2h** provided the desire product **4m-4o** in moderate yields (entries 13−15).

Table 3. Synthesis of substituted tetrahydroquinazolines[a]

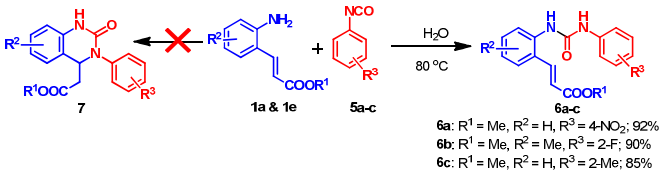


Entry	Acrylate **1**	Isothiocyanate **2**	Product **4**	Yield (%)[b]
1	 **1e**	**2a**	 **4a**	92
2	**1e**	**2f**	 **4b**	87
3	 **1f**	**2e**	 **4c**	93
4	 **1g**	**2h**	 **4d**	94
5	 **1h**	**2c**	 **4e**	92
6	 **1i**	**2d**	 **4f**	68 [c]
7	**1i**	 **2i**	 **4g**	62 [c]
8	 **1j**	**2b**	 **4h**	77
9	 **1k**	**2a**	 **4i**	75
10	**1k**	**2g**	 **4j**	68
11	**1k**	 **2j**	 **4k**	78
12	 **1l**	**2c**	 **4l**	65
13	 **1m**	**2a**	 **4m**	68
14	**1m**	**2c**	 **4n**	75
15	**1m**	**2h**	 **4o**	72

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), 80 °C, 2 mL H_2O for 16 h. [b] Isolated yields. [c] Time = 20 h

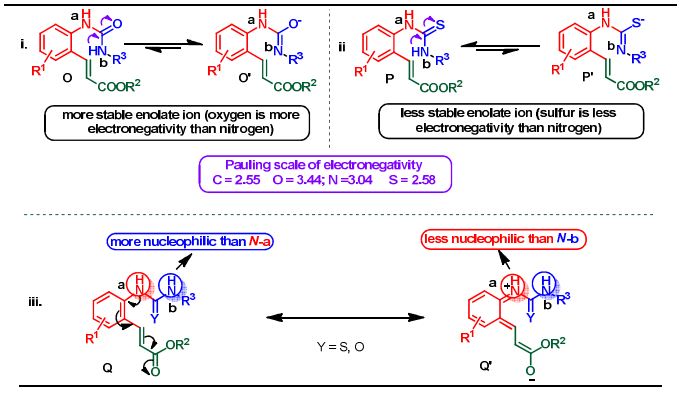
Encouraged by our previous results with isothiocyanates, we further employed the same eco-friendly protocol to examine the scope for the reaction using 2-aminoaryl acrylates **1** with functionally varied isocyanates **5** to obtain 2-oxo-tetrahydroquinazolines **7** as desire product; unfortunately the reaction fails to provide the cyclized product. The reaction of

acrylates **1a** and **1e** with electron−withdrawing isocyanates **5a**–**b** afforded the uncyclized urea derivates **6a**−**b** in 92% and 90% yields respectively. However the reaction of acrylate **1a** with electron-releasing isocyanates **5c** afforded the urea product in 85% yield (Scheme 2). The probable reason could be due to the low nucleophilicity of amide nitrogen as described in Scheme 3.



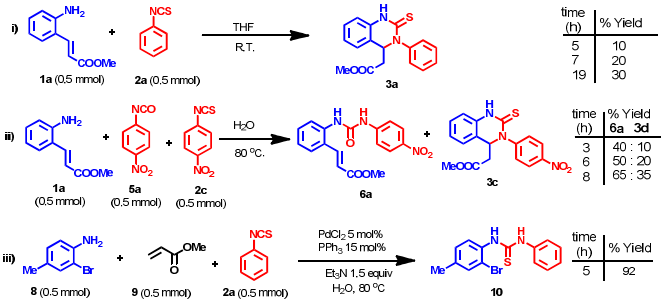
Scheme 2. Reaction of phenylisocyanates with acrylates.

The reactivity behaviour of thiourea and urea intermediates is explained in Scheme 3. Theoretically it was known that the reactivity of thia-amide (S=CNHR) is greater than that of amide (O=CNHR); the probable reason could be due to the higher electronegativity of oxygen in comparison to sulphur.[18] This effect, in turn, decreases the nucleophilicity of nitrogen-*b* in uredio intermediate **O** (Scheme 3; i) in comparison to thia-uredio intermediate **P** (Scheme 3; ii). According to Pauling electronegativity scale (C = 2.55; O = 3.44; S = 2.58; N = 3.04) uredio intermediate **O** generates more stable enolate than thia-uredio intermediate **P**, hence enolate **O**' is less nucleophilic than enolate **P**' (Scheme 3). It is proposed that lone pair of nitrogen-b take part in the reaction/enolate formation as lone pair of nitrogen-*a* are delocalized with adjacent acrylate, making it less nucleophilic than nitrogen-*b*. In case of thia-uredio **P** compounds the electronegativity of sulphur is inferior to that of nitrogen-b; however in case of intermediate **Q**, the lone pair of nitrogen-**a** is involved in both resonance with the benzene ring and towards the sulphur-atom. Hence we conclude that the nitrogen-b is more nucleophilic than nitrogen-*a* (Scheme 3; iii).

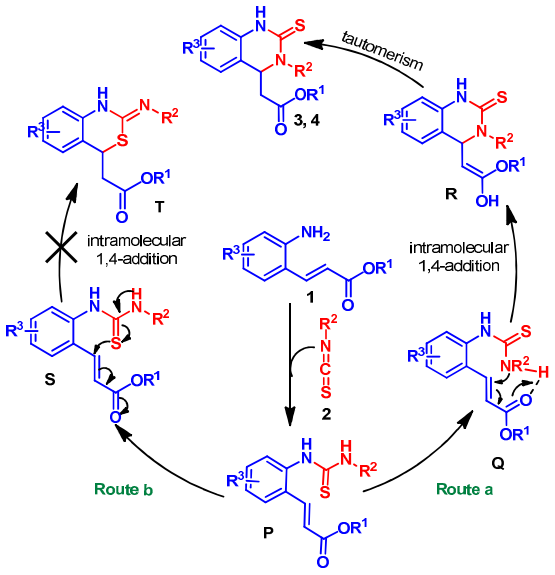


Scheme 3. Reactivity behaviour of amide

To validate the reactivity behaviour of isothiocyanate and isocyanates onto acrylate, we performed three sets of reactions and monitored the formation of products in different conditions and time intervals (Scheme 4). In first set of reaction we reacted **1a** with isothiocyanate **2a** using THF as solvent at room temperature and monitored the reaction products after 5, 7 and 19 h intervals. We observed that after 5 h product **3a** was obtained in 10% yield; however after 7 h, the yield was increased upto 20% and after 19 h product **3a** was observed in 30% yield (Scheme 4, i). The combined reaction of isocyanates **5a** and isothiocyanates **2c** was performed using water as solvent, after 8 h it was observed that the urea product **6a** and quinazoline product **3d** were obtained in 65% and 35% yields respectively (Scheme 4, ii). A three compontent reaction of aniline **8** and methylacrylate **9** with isothiocyanate **2a** using water and Pd-catalyst at 80°C for 5 h provided the thiourea product **10** in 92% yield (Scheme 3, iii); These observations suggest the formation of urea intermediates over thiourea intermediates and also suggest that the thia-amide is more Michael-donor in water as comparison to amide. The probable reason for the above reactivity could be due to electronegativity of the C=O and C=S groups.



Scheme 4. Control experiments



Scheme 5. Plausible mechanism.

With these observations in hand, a plausible mechanism is proposed in Scheme 5. The nucleophilic addition of 2-aminoaryl acrylates **1** and isothiocyanates **2** generates the condensation species **P**, that results in the intramolecular hydrogen bonding which favor the aza-Michael addition and subsequently leads to the formation of cyclized product **R**. After rapid tautomerization the desire products

3/**4** is obtained (Route **a**). The intermediate **P** renders the regioselective 2nd intramoleular nucleophilic attack due to the lack of hydrogen bonding which inhibits the formation of product **T** (Route b).

Conclusions

In conclusion, we have described an environmentally benign catalyst-free tandem approach for the synthesis of highly functionalized fused bicyclic quinazolines with excellent chemoselectivity in good to excellent yields. Water, in contrast to other organic solvents, is non-flammable, inexpensive and environment friendly which remarkably effect on the rate and selectivity of organic reaction through hydrophobic interactions. The atom economic conversion in water proceeded with high functional group tolerance. This developed chemistry can be used for the generation of a variety of biologically active quinazoline derivatives from 2-aminoacrylate and isothiocyanates *via* in situ formation of thiouredioamides and concomitant chemoselective intramolecular aza-Michael addition.

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Notes and references

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†Electronic Supplementary Information (ESI) available: Datas and spectral Copies of ^{1}H, ^{13}C NMR and HRMS for target compounds. See DOI: 10.1039/b000000x/

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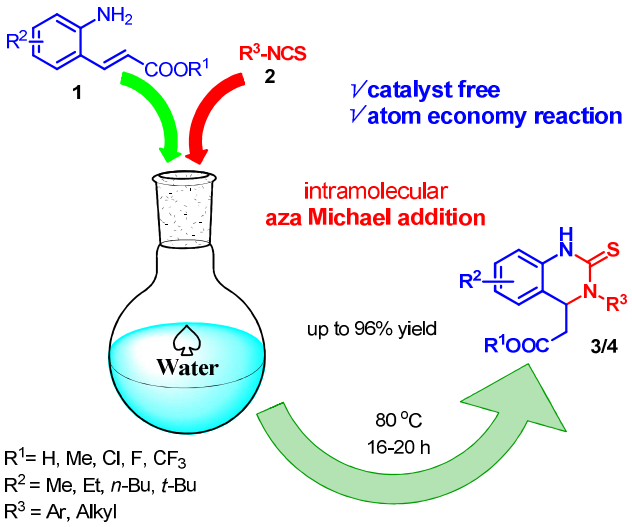
Graphical Abstract



ABSTRACT: A catalyst free atom-ecomonic straightforward tandem approach for the synthesis of highly functionalized tetrahydroquinazolines by the reaction of 2-aminophenylacrylate **1** with isothiocyanates **2** using water as an environmental friendly solvent via amidation and concomitant chemoselective Michael-addition is described.