A Greener Protocol for Accessing 2,3-Dihydro/spiroquinazolin-4(1*H*)-ones: Natural Acid-SDS Catalyzed Three-Component Reaction

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Abstract: A novel green and energy-efficient synthesis of 2,3-dihydro/spiroquinazolin-4(1*H*)-ones via three-component cyclocondensation reaction involving isatoic anhydride, amines and aldehydes/ketones utilizing recyclable tartaric acid–SDS catalyst system has been achieved. With simple requirements of mechanical stirring or mechanochemical activation at room temperature and one of the shortest reported times as of yet, it is a significant improvement on previously described methods for the synthesis of such compounds. Moreover the catalyst system can also be efficiently applied in large-scale reactions which indicates the potential for applications in industry.

Key words: 2,3-dihydroquinazolin-4(1*H*)-one, mechanochemical activation, multicomponent reaction, sodium dodecyl sulfate (SDS), tartaric acid

To break the negative public image of chemistry and the chemical industry in particular, the international chemical community is under continuous pressure to alter current working practices and to find sustainable and greener alternatives. As a result, development of environmentally benign chemical transformations, especially syntheses of biologically relevant heterocycles, has been promoted worldwide.[1,2]

2,3-Dihydroquinazolin-4(1*H*)-one, a well-documented heterocyclic scaffold, widely occurs in natural products and shows a wide range of biological activities.[3] In addition, these molecules can be further oxidized to their respective quinazolin-4(3*H*)-one analogues,[4] another important class of biologically active heterocyclic compounds.[5] The unique biological significance of the 2,3-dihydroquinazolin-4(1*H*)-one skeleton prompted several research groups to develop new protocols for its synthesis. However, most of the reported methods[6] are either not environmentally benign, suffer from harsh reaction conditions, have prolonged reaction time, use hazardous/expensive catalysts and/or use specialized equipment. Therefore, development of a simple and convenient approach for the preparation of 2,3-dihydroquinazolinone class of compounds is still required.

Accordingly, comprising the twelve principles of green chemistry formulated by Anastas and Warner,[2a] herein we report two parallel novel approaches for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives, (A) mechanical stirring under mild conditions (ambient temperature and pressure) and (B) mechanochemical activation (grinding). Mechanochemical conditions can accelerate various bond-forming reactions compared to solution-based methods and simultaneously minimize the use of solvents.[7] Grinding with a minimal amount of solvent, known as 'solvent-drop grinding', offers higher efficiency with respect to time, materials and energy usage.

The significance of our findings lies not only in avoiding the use of organic solvents as potentially toxic and hazardous materials and use of natural acid–SDS as eco-friendly and cheap catalytic system but also in the emphasis on energy efficiency of the reaction. With the increasing prices of energy and global awareness on energy crises, significance of energy efficient chemical transformations can be expected to increase considerably. Simplicity, energy efficiency, high throughput and inherent lower cost of the methodology make it superior compared to the previously reported ones and well suited for industrial applications.

At the onset of this research, we investigated the model one-pot three-component cyclocondensation reaction using mechanical stirring between isatoic anhydride, benzaldehyde and *n*-butylamine to optimize the reaction conditions (Table 1). The model reaction performed in water with tartaric acid as catalyst in stoichiometric amount was found to be sluggish with an unsatisfactory yield (entry 2). It was determined by visual inspection that the reaction mixture was not homogenous in nature and probably a factor contributing towards low yield of the reaction. Out of the two available options to obtain a homogenous mixture providing external energy or using phase-transfer agents/anionic surfactant, the later was chosen to keep the methodology energy efficient. Interestingly, phase-transfer agents such as TBAB (entry 3), TBAHS (entry 4), TMAI (entry 5) were not successful in terms of reaction time and yield but in case of anionic surfactant sodium dodecyl sulfate (SDS) (20 mol%) the reaction was complete in 40 minutes with 73% yield (entry 6). Out of the various phase-transfer agents and surfactants screened, since only SDS forms micellar aggregates, it is believed that localization which creates a favorable microenvironment for the catalyzed reaction rather than phase transfer has contributed to the acceleration of reaction rate.[8] Screening of the solvent and/or solvent systems suggested that water–ethanol mixture (3:1) is the best one and afforded the highest yield among several solvent ratios optimized (entries 7–9). Further the reaction was performed with tartaric acid as catalyst in water–ethanol (3:1)

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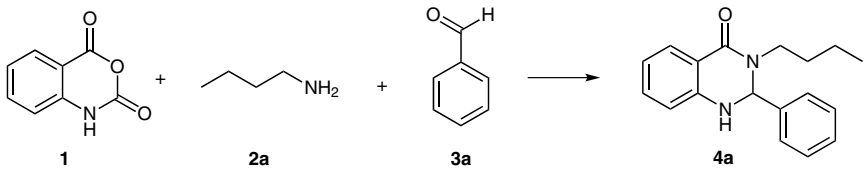
solvent system which afforded the product in 135 minutes with 81% yield (compare entries 10 and 2) while SDS alone was sufficient to provide 74% yield in 315 minutes (entry 11). To explore the efficiency of other natural acids,[6c,9] the reaction was performed successfully with citric acid (entry 12), succinic acid (entry 13), oxalic acid (entry 14) and ascorbic acid (entry 15) in stoichiometric amount but tartaric acid (entry 7) was found to be the best choice in terms of yield and reaction time.

Encouraged with our green findings, we further looked for greener alternatives in terms of time, yield and energy input and found mechanochemical activation (grinding) as a very promising technique. The above protocol proceeded successfully in a porcelain mortar and pestle using minimal amount of water–ethanol (3:1) mixture as solvent. Reaction with the grinding in slurry form provided the product **4a** in two minutes with 94% yield (entry 16). As conversion was quantitative, only washing with water to remove tartaric acid and SDS was deemed sufficient for spectroscopic analysis without any further purification.

Further to explore the scope of both green protocols (methods A and B), the reaction was investigated with an array of aromatic aldehydes appended with various substituents (Table 2)[10] under the optimized conditions (entries 7 and 16, Table 1). Reactions with electron-releasing substituents were in general better as compared to those with electron-withdrawing substituents in terms of reaction time (entries **4c**, **4d** and **4j**). Reactions in case of aryl aldehydes with electron-withdrawing substituents at *para* position took longer time as compared to electron-withdrawing substituents at *meta* position (entries **4j** and **4k**) but in case of electron-withdrawing substituents at *ortho* position, the reaction failed to provide the expected product even after 24 hours (entries **4i** and **4l**), which suggests that steric effect has a significant impact on the reaction rate. The products were isolated and purified by simple filtration/water washing. Further, the efficiency of this methodology was explored with heteroaryl aldehydes including 2-thiophene aldehyde and 5-nitrofurfural (entries **4o** and **4p**). Considering medicinal value of ferrocene-

Table 1 Optimization of Reaction Conditions with Isatoic Anhydride (**1**), *n*-Butyl Amine (**2a**) and Benzaldehyde (**3a**)



1 **2a** **3a** **4a**

Entry	Catalyst	Additive[a]	Solvent	Time (min)	Yield (%)[b]
1	–	–	H_2O	–	no reaction[c]
2	tartaric acid	–	H_2O	960	59
3	tartaric acid	TBAB[d]	H_2O	110	48
4	tartaric acid	TBAHS[d]	H_2O	420	23
5	tartaric acid	TMAI[d]	H_2O	480	trace
6	tartaric acid	SDS	H_2O	40	73
7	tartaric acid	SDS	H_2O–EtOH (3:1)	20	87
8	tartaric acid	SDS	H_2O–EtOH (1:1)	15	78
9	tartaric acid	SDS	H_2O–EtOH (1:3)	120	56
10	tartaric acid	–	H_2O–EtOH (3:1)	135	81
11	–	SDS	H_2O–EtOH (3:1)	315	74
12	citric acid	SDS	H_2O–EtOH (3:1)	15	62
13	succinic acid	SDS	H_2O–EtOH (3:1)	45	72
14	oxalic acid	SDS	H_2O–EtOH (3:1)	40	70
15	ascorbic acid	SDS	H_2O–EtOH (3:1)	45	58
16[e]	tartaric acid	SDS	H_2O–EtOH (3:1)	2	94

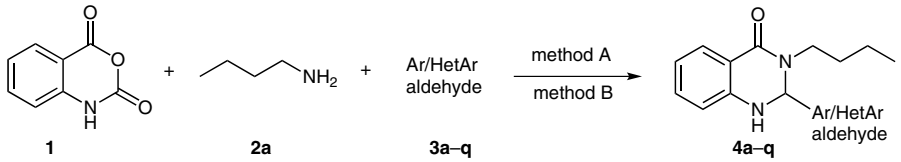
[a] Amount: 20 mol%.
[b] Isolated yield.
[c] No product was observed after 24 h.
[d] TBAB: tetrabutylammonium bromide; TBAHS: tetrabutylammonium hydrogen sulfate; TMAI: tetramethylammonium iodide.
[e] Reaction was performed with grinding: method B.

containing heterocycles,[11] our methodology was successfully applied to obtain 3-butyl-2-ferrocenyl-2,3-dihydroquinazolin-4(1*H*)-one in very good yield from ferrocenecarboxaldehyde (entry **4q**). As expected from preliminary results, the average time span of reaction with different aryl/heteroaryl aldehydes in case of method A (8 min to 9 h) decreased to one to eight minutes with appreciable increase in yield via method B.

Subsequently, the substrate scope regarding amines was also examined. Aliphatic amines, aromatic amines, cyclic amines and hydroxyl amines were found to be effective substrates and afforded the corresponding 2,3-dihydroquinazolin-4(1*H*)-one derivatives in excellent yields. Method B again proved to be better than method A in terms of reaction time and yields (Table 3). The reaction worked well with aqueous ammonia as well (entry **4u**), however the product 2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one could not be obtained with ammonium acetate.[6c,e]

The methodology was further extended to cyclic ketones such as cyclohexanone, 3,4-dihydronaphthalen-2(1*H*)-one and 1-ethyl-1*H*-indole-2,3-dione to provide respective spirocyclized products **4v**, **4w** and **4x** (Table 4). Although a few methods of synthesis of such class of spirocyclized compounds are known in literature,[12] to the best of our knowledge, no such synthesis using isatoic anhydride has been reported yet. Further exploration of this methodology with other ketones is underway in our laboratory.

Table 2 Synthesis[10] of Quinazolinone Derivatives **4a–q** Using Isatoic Anhydride (**1**), *n*-Butyl Amine (**2a**) and Different Aromatic and Heteroaromatic Aldehydes (**3a–q**) via Methods A[a] and B[b]

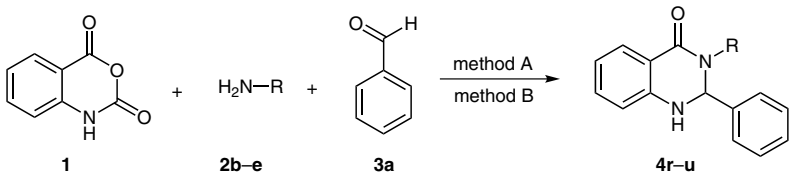


1 **2a** **3a–q** **4a–q**

Product	Ar/HetAr aldehyde	Method A		Method B	
		Time (min)	Yield (%)[c]	Time (min)	Yield (%)[c]
4a[d]	benzaldehyde (**3a**)	20	87	2	94
4b	4-isopropylbenzaldehyde (**3b**)	8	84	1	93
4c	4-methoxybenzaldehyde (**3c**)	12	89	1	96
4d	4-cyanobenzaldehyde (**3d**)	150	78	5	86
4e	4-hydroxybenzaldehyde (**3e**)	90	81	3	89
4f	4-fluorobenzaldehyde (**3f**)	10	83	1	93
4g	4-cholorobenzaldehyde (**3g**)	45	80	3	91
4h	4-bromobenzaldehyde (**3h**)	55	79	3	90
4i	2-nromobenzaldehyde (**3i**)	–	–[e]	–	–[e]
4j	4-nitrobenzaldehyde (**3j**)	335	73	6	84
4k	3-nitrobenzaldehyde (**3k**)	60	79	3	87
4l	2-nitrobenzaldehyde (**3l**)	–	–[e]	–	–[e]
4m	terephthalaldehyde (**3m**)	70	62	4	78
4n	9-anthraldehyde (**3n**)	540	80	8	83
4o	2-thiophenecarboxaldehyde (**3o**)	28	81	2	88
4p	5-nitrofurfural (**3p**)	10	86	1	95
4q[d]	ferrocenecarboxaldehyde (**3q**)	33	72	3	81

[a] Method A: magnetic stirring, reaction conditions: **1** (0.61 mmol), **2a** (0.61 mmol), **3a–q** (0.61 mmol), tartaric acid (0.61 mmol), SDS (20 mol%), H_2O–EtOH (3:1, 4 mL) as solvent.
[b] Method B: grinding using mortar and pestle, reaction conditions: **1** (0.61 mmol), **2a** (0.61 mmol), **3a–q** (0.61 mmol), tartaric acid (0.61 mmol), SDS (20 mol%), few drops of H_2O–EtOH (3:1) as solvent.
[c] Isolated yield.
[d] Analytical data provided.[10]
[e] No product was observed after 24 h.

Table 3 Synthesis of Quinazolinone Derivatives **4r–u** Using Isatoic Anhydride (**1**), Benzaldehyde (**3a**) and Different Amines **2b–e** via Methods A[a] and B[b]

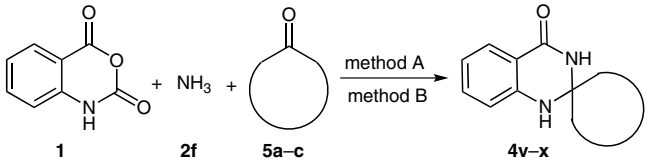


1 **2b–e** **3a** **4r–u**

Product	R	Method A		Method B	
		Time (min)	Yield (%)[c]	Time (min)	Yield (%)[c]
4r	**2b** (cyclohexyl)	23	73	2	84
4s	**2c** (3-hydroxypropyl)	8	81	1	92
4t[d]	**2d** (Ph)	130	74	6	86
4u[d]	**2e** (H)	15	89	1	96

[a] Method A: magnetic stirring, reaction conditions: **1** (0.61 mmol), **2b–e** (0.61 mmol), **3a** (0.61 mmol), tartaric acid (0.61 mmol), SDS (20 mol%), H_2O–EtOH (3:1; 4 mL) as solvent.
[b] Method B: grinding using mortar and pestle, reaction conditions: **1** (0.61 mmol), **2b–e** (0.61 mmol), **3a** (0.61 mmol), tartaric acid (0.61 mmol), SDS (20 mol%), few drops of H_2O–EtOH (3:1) as solvent.
[c] Isolated yield.
[d] Analytical data provided.[10]

Table 4 Synthesis of Spiroquinazolinone Derivatives **4v–x** Using Isatoic Anhydride (**1**), Aqueous Ammonia (**2f**) and Cyclic Ketones **5a–c** via Methods A[a] and B[b]



1 **2f** **5a–c** **4v–x**

Product	Ketone **5**	Method A		Method B	
		Time (min)	Yield (%)[c]	Time (min)	Yield (%)[c]
4v[d]	cyclohexanone (**5a**)	25	71	3	86
4w	3,4-dihydronaphthalen-2(1*H*)-one (**5b**)	120	68	6	83
4x[d]	1-ethyl-1*H*-indole-2,3-dione (**5c**)	135	76	9	85

[a] Method A: magnetic stirring, reaction conditions: **1** (0.61 mmol), **2f** (0.61 mmol), **5a–c** (0.61 mmol), tartaric acid (0.61 mmol), SDS (20 mol%), H_2O–EtOH (3:1; 4 mL) as solvent.
[b] Method B: grinding using mortar and pestle, reaction conditions: **1** (0.61 mmol), **2f** (0.61 mmol), **5a–c** (0.61 mmol), tartaric acid (0.61 mmol), SDS (20 mol%), few drops of H_2O–EtOH (3:1) as solvent.
[c] Isolated yield after recrystallization.
[d] Analytical data provided.[10]

Finally, the recyclability of the tartaric acid–SDS catalyst system in method A was investigated. As shown in Figure 1, the reaction medium was reused for four runs in the preparation of **4a** without any significant loss of activity (with the yield of the product **4a** being 86%, 84%, 82%, and 83%, respectively).

In conclusion, an energy efficient and green synthetic methodology has been developed for the facile synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones at room temperature via mechanical stirring and mechanochemical activation. The protocol was shown to be successfully applicable to a wide range of aryl/heteroaryl aldehydes

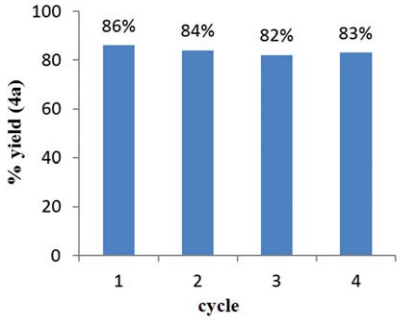


Figure 1 Recyclability of tartaric acid–SDS catalyst system

and amines with the shortest reaction time reported so far at ambient temperature besides obtaining high yields. Further, it was extended to the synthesis of spiro compounds as well. Thus the developed methodology provides opportunity for the construction of diverse bioactive molecules with numerous other advantages such as: (1) theoretically, this combination of MCR (multicomponent reaction) spans a chemical space of greater than $1000 \times 1000 \times 100 = 10^8$ molecules,[12] (2) high bond-forming efficiency[13] as three C–N bonds are formed, (3) economic methodology which offers a great possibility for applications in industry,[14] (4) use of water–ethanol mixture as green solvent and (5) simple purification process/clean synthesis.

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References

(1) (a) Baird, C. *Environmental Chemistry*; W. H. Freeman and Company: New York, **1999**. (b) Anastas, P.; Heine, L. G.; Williamson, T. C. *Green Chemical Syntheses and Processes*; Oxford University Press: New York, **2000**. (c) Matlack, A. S. *Introduction to Green Chemistry*; Marcel Dekker: New York, **2001**. (d) Lancaster, M. *Green Chemistry: An Introductory Text*; Royal Society of Chemistry: Cambridge, **2002**.

(2) (a) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: Oxford, **1998**. (b) Bruckmann, A.; Krebs, A.; Bolm, C. *Green Chem.* **2008**, *10*, 1131. (c) Horvath, I. T. *Green Chem.* **2008**, *10*, 1024. (d) *Handbook of Green Chemistry*; Crabtree, R. H.; Anastas, P. T., Eds.; Wiley-VCH: Weinheim, **2009**.

(3) (a) Liverton, N. J.; Armstrong, D. J.; Claremon, D. A.; Remy, D. C.; Baldwin, J. J.; Lynch, R. J.; Zhang, G.; Gould, R. J. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 483. (b) Zhang, W.; Mayer, J. P.; Hall, S. E.; Weigel, J. A. *J. Comb. Chem.* **2001**, *3*, 255.

(4) Abdel-Jalil, R. J.; Voelter, W.; Saeed, M. *Tetrahedron Lett.* **2004**, *45*, 3475.

(5) (a) Maia, R. C.; Silva, L. L.; Mazzeu, E. F.; Fumian, M. M.; de Rezende, C. M.; Doriguetto, A. C.; Correa, R. S.; Miranda, A. L. P.; Barreiro, E. J.; Fraga, C. A. M. *Bioorg. Med. Chem.* **2009**, *17*, 6517. (b) Jalali-Heravi, M.; Asadollahi-Baboli, M. *Eur. J. Med. Chem.* **2009**, *44*, 1463. (c) Maskey, R. P.; Shaaban, M.; Grun-Wollny, I.; Laatsch, H. *J. Nat. Prod.* **2004**, *67*, 1131.

(6) (a) Gao, L.; Ji, H.; Rong, L.; Tang, D.; Zha, Y.; Shi, Y.; Tu, S. *J. Heterocycl. Chem.* **2011**, *48*, 957. (b) Niknam, K.; Jafarpour, N.; Niknam, E. *Chin. Chem. Lett.* **2011**, *22*, 69. (c) Ghorbani-Choghamarani, A.; Taghipour, T. *Lett. Org. Chem.* **2011**, *8*, 470. (d) Zeng, L. Y.; Cai, C. *J. Heterocycl. Chem.* **2010**, *47*, 1035. (e) Zhang, Z. H.; Lu, H. Y.; Yang, S. H.; Gao, J. W. *J. Comb. Chem.* **2010**, *12*, 643. (f) Rostamizadeh, S.; Amani, A. M.; Mahdavinia, G. H.; Sepehrian, H.; Ebrahimi, S. *Synthesis* **2010**, 1356. (g) Shaterian, H. R.; Oveisi, A. R.; Honarmand, M. *Synth. Commun.* **2010**, *40*, 1231. (h) Dabiri, M.; Salehi, P.; Baghbanzadeh, M.; Zolfigol, M. A.; Agheb, M.; Heydari, S. *Catal. Commun.* **2008**, *9*, 785. (i) Chen, J.; Wu, D.; He, F.; Liu, M.; Wu, H.; Ding, J.; Su, W. *Tetrahedron Lett.* **2008**, *49*, 3814. (j) Chen, J.; Su, W.; Wu, H.; Liu, M.; Jin, C. *Green Chem.* **2007**, *9*, 972. (k) Baghbanzadeh, M.; Salehi, P.; Dabiri, M.; Kozehgary, G. *Synthesis* **2006**, 344. (l) Yoo, C. L.; Fettinger, J. C.; Kurth, M. J. *J. Org. Chem.* **2005**, *70*, 6941. (m) Dabiri, M.; Salehi, P.; Otokesh, S.; Baghbanzadeh, M.; Kozehgarya, G.; Mohammadi, A. A. *Tetrahedron Lett.* **2005**, *46*, 6123. (n) Shi, D. Q.; Rong, L. C.; Wang, J. X.; Zhuang, Q. Y.; Wang, X. S.; Hu, H. W. *Tetrahedron Lett.* **2003**, *44*, 3199. (o) Khurana, J. M.; Kukreja, G. *J. Heterocycl. Chem.* **2003**, *40*, 677. (p) Su, W. K.; Yang, B. B. *Aust. J. Chem.* **2002**, *55*, 695.

(7) (a) Beyer, M. K.; Clausen-Schaumann, H. *Chem. Rev.* **2005**, *105*, 2921. (b) Choudhary, G.; Peddinti, R. K. *Green Chem.* **2011**, *13*, 276. (c) Aakeroy, C. B.; Chopade, P. D. *Org. Lett.* **2011**, *13*, 1. (d) van den Ancker, T. R.; Cave, G. W. V.; Raston, C. L. *Green Chem.* **2006**, *8*, 50. (e) Trask, A. V.; Motherwell, W. D. S.; Jones, W. *Chem. Commun.* **2004**, 890. (f) Cave, G. W. V.; Raston, C. L. *Chem. Commun.* **2000**, 2199.

(8) (a) Rosati, F.; Oelerich, J.; Roelfes, G. *Chem. Commun.* **2010**, *46*, 7804. (b) Scott, J. L.; Raston, C. L. *Green Chem.* **2000**, *2*, 245. (c) Molteni, G.; Ponti, A.; Orlandi, M. *New J. Chem.* **2002**, *26*, 1340. (d) Chiba, K.; Jinno, M.; Nozaki, A.; Tada, M. *Chem. Commun.* **1997**, 1403. (e) Kobayashi, S.; Busujima, T.; Nagayama, S. *Chem. Commun.* **1998**, 19.

(9) (a) Miyake, H.; Nakaob, Y.; Sasaki, M. *Tetrahedron Lett.* **2006**, *47*, 6247. (b) Zhou, B.; Yang, J.; Li, M.; Gu, Y. *Green Chem.* **2011**, *13*, 2204.

(10) **Representative Procedure**:
Method A: In a round-bottom flask, isatoic anhydride (0.1 g, 0.61 mmol) and amine (0.61 mmol) were dissolved in micellar solution of H_2O–EtOH (3:1; 4 mL) sensitized with SDS (20 mol%). Tartaric acid (0.92 g, 0.61 mmol) and aldehyde/ketone (0.61 mmol) were then successively added and the reaction was allowed to stir at r.t. for an appropriate time indicated in Tables 2–4. The solid precipitate was filtered, washed with H_2O, dried and could be used without further purification, however in case of **4r**, **4s** and **4t** recrystallization with EtOH–ice was required.
Method B: isatoic anhydride (0.1 g, 0.61 mmol) and amine (0.61 mmol) were mixed with a few drops of the solvent system (H_2O–EtOH, 3:1) in a mortar. Tartaric acid (0.92 g, 0.61 mmol), SDS (20 mol%) and aldehyde/ketone (0.61 mmol) were then successively added and ground together with a pestle until completion of the reaction (Tables 2–4). In most of the cases the product was washed with H_2O, however in case of **4r**–**t** recrystallization with EtOH–ice was required.
3-Butyl-2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (4a): colorless solid; yield: 0.15 g (87%); mp 132–135 °C. ^{1}H (300 MHz, $CDCl_3$): δ = 7.88 (d, 1 H, *J* = 6.9 Hz), 7.21 (br s, 4 H), 7.13–7.19 (m, 2 H), 6.76 (t, 1 H, *J* = 7.3 Hz), 6.44 (d, 1 H, *J* = 8.0 Hz), 5.76 (s, 1 H), 3.85–3.94 (m, 1 H), 2.64–2.74 (m, 1 H), 1.45–1.49 (m, 2 H), 1.20–1.27 (m, 2 H), 0.80 (t, 3 H, *J* = 7.3 Hz).^{13}C (50 MHz, $CDCl_3$): δ = 163.2, 145.2, 140.0, 133.4, 129.2, 128.9, 128.4, 126.5, 119.1, 116.2, 114.4, 72.1, 44.6, 29.8, 20.2, 13.8. IR (KBr): 3360, 1634 cm^{-1}. MS (ES$^+$): *m*/*z* = 281.1 [M$^+$ + 1]. HRMS (DART): *m*/*z* calcd for [$C_{18}H_{20}N_2O$ + H$^+$]: 281.1654; found: 281.1647.
3-Butyl-2-ferrocenyl-2,3-dihydroquinazolin-4(1*H*)-one (4q): yellow solid; yield: 0.17 g (72%); mp 137–140 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83 (d, 1 H, *J* = 7.4 Hz), 7.19–7.27 (m, 1 H), 6.79 (t, 1 H, *J* = 7.4 Hz), 6.64 (d, 1 H, *J* = 6.9 Hz), 5.40 (s, 1 H), 4.08–4.21 (m, 10 H), 3.75–3.79 (m, 1 H), 2.88–2.92 (m, 1 H), 1.42–1.50 (m, 2 H), 1.19–1.28 (m, 2 H), 0.82 (t, 3 H, *J* = 7.5 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 162.7, 146.4, 133.3, 128.7, 119.3, 116.5, 113.9, 88.6, 73.3,

69.1, 68.81, 68.76, 68.6, 68.2, 66.3, 44.0, 30.1, 20.3, 14.0. IR (KBr): 3285, 1631 cm^{-1}. MS (ES^+) *m*/*z* = 389.0 [M^+ + 1]. HRMS (DART): *m*/*z* calcd for [$C_{22}H_{24}FeN_2O + H^+$]: 389.1316; found: 389.1318.

2,3-Diphenyl-2,3-dihydroquinazolin-4(1*H*)-one (4t): colorless solid; yield: 0.14 g (74%); mp 212–214 ºC. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.04 (d, 1 H, *J* = 7.8 Hz), 7.19–7.38 (m, 11 H), 6.92 (t, 1 H, *J* = 7.5 Hz), 6.65 (d, 1 H, *J* = 7.8 Hz), 6.11 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$ + CD_3OD): δ = 165.6, 147.8, 142.1, 141.6, 135.8, 130.6, 130.5, 130.2, 128.7, 128.4, 120.5, 117.5, 116.5, 76.2. IR (KBr): 3327, 1649 cm^{-1}. MS (ES^+): *m*/*z* = 301.1 [M^+ + 1]. HRMS (DART): *m*/*z* calcd for [$C_{20}H_{16}N_2O + H^+$]: 301.1335; found: 301.1333.

2-Phenyl-2,3-dihydroquinazolin-4(1*H*)-one (4u): colorless solid; yield: 0.12 g (89%); mp 218–220 ºC. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.96 (d, 1 H, *J* = 8.1 Hz), 7.26–7.58 (m, 6 H), 6.94 (t, 1 H, *J* = 7.2 Hz), 6.69 (d, 1 H, *J* = 8.0 Hz), 5.90 (s, 1 H), 5.82 (s, 1 H, NH), 4.41 (s, 1 H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.5, 152.9, 145.8, 138.4, 133.8, 133.3, 132.6, 132.0, 122.6, 119.8, 119.5, 72.5. IR (KBr): 3296, 3190, 1656 cm^{-1}. MS (ES^+): *m*/*z* = 225.0 [M^+ + 1]. HRMS (DART): *m*/*z* calcd for [$C_{14}H_{12}N_2O + H^+$]: 225.1022; found: 225.1017.

1′*H*-Spiro[cyclohexane-1,2′-quinazolin]-4′(3′*H*)-one (4v): colorless solid; yield: 0.09 g (71%); mp 217–219 °C.^1H NMR (200 MHz, $CDCl_3$): δ = 7.89 (dd, 1 H, J_1 = 7.8 Hz, J_2 = 1.2 Hz), 7.28–7.33 (m, 1 H), 6.84 (t, 1 H, *J* = 7.5 Hz), 6.67 (d, 1 H, *J* = 7.8 Hz), 6.43 (s, 1 H, NH), 4.40 (s, 1 H, NH), 1.84 (br s, 4 H), 1.47–1.68 (m, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$ + CD_3OD): δ = 167.0, 148.0, 136.2, 130.3, 120.7, 117.0, 70.5, 39.7, 26.8, 24.0. IR (KBr): 3362, 3179, 1647 cm^{-1}. MS (ES^+): *m*/*z* = 217.0 [M^+ + 1]. HRMS (DART): *m*/*z* calcd for [$C_{13}H_{16}N_2O + H^+$]: 217.1335; found: 217.1326.

1-Ethyl-1′*H*-spiro[indoline-3,2′-quinazoline]-2,4′(3′*H*)-dione (4x): tan solid; yield: 0.15 g (85%); mp 227–230 °C. ^1H NMR (300 MHz, DMSO-d_6): δ = 8.29 (s, 1 H, NH), 7.62 (d, 1 H, *J* = 7.1 Hz), 7.52 (d, 1 H, *J* = 7.2 Hz), 7.42 (t, 1 H, *J* = 7.6 Hz), 7.18–7.25 (m, 2 H), 7.00–7.16 (m, 2 H), 6.69 (t, 1 H, *J* = 7.3 Hz), 6.61 (d, 1 H, *J* = 4.0 Hz), 3.57–3.68 (m, 2 H), 1.16 (t, 3 H, *J* = 6.9 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 173.8, 163.9, 146.7, 142.6, 133.3, 130.9, 129.0, 126.8, 125.1, 122.7, 117.2, 114.2, 113.9, 109.0, 70.7, 34.0, 12.3. IR (KBr): 3368, 3227, 1638, 1613 cm^{-1}. MS (ES^+): *m*/*z* = 294.0 [M^+ + 1]. HRMS (DART): *m*/*z* calcd for [$C_{17}H_{15}N_3O_2 + H^+$]: 294.1164; found: 294.1156.

(11) Bellot, F.; Cosledan, F.; Vendier, L.; Brocard, J.; Meunier, B.; Robert, A. *J. Med. Chem.* **2010**, *53*, 4103.

(12) (a) Subba Reddy, B. V.; Venkateswarlu, A.; Madan, C.; Vinu, A. *Tetrahedron Lett.* **2011**, *52*, 1891. (b) Miklós, F.; Fülöp, F. *Eur. J. Org. Chem.* **2010**, 959. (c) Wang, X.; Yang, K.; Zhou, J.; Tu, S. *J. Comb. Chem.* **2010**, *12*, 417. (d) Shi, D.; Rong, L.; Wang, J.; Zhuang, Q.; Wangb, X.; Hu, H. *Tetrahedron Lett.* **2003**, *44*, 3199.

(13) The corresponding starting materials for this reaction are broadly commercially available, mostly in numbers exceeding 1000 (RNH_2, RCHO, RCOR). However, less than 1000 substituted isatoic anhydrides are available.

(14) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.

(15) For large-scale reaction, reaction with 20 g of isatoic anhydride successfully afforded **4a** with 84% yield (29.5 g) via method A.

