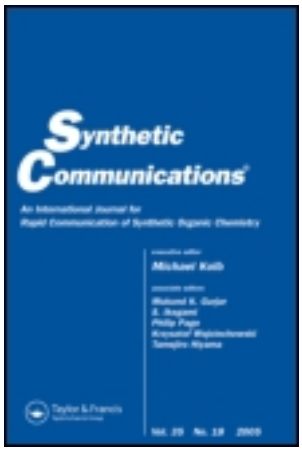

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One Pot Synthesis of 4(3H)-Quinazolinones

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One Pot Synthesis of 4(3*H*)-Quinazolinones[#]

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ABSTRACT

Anthranilamides undergo cyclocondensation with aldehydes in presence of iodine in a single-pot reaction to afford 2-substituted 4(3*H*)-quinazolinones in moderate to excellent yield (40–95%). 2,3-Substituted 4(3*H*)-quinazolinones are synthesized in moderate to good yield by three-component condensation of isotoic anhydride, amine, and aldehyde in presence of iodine.

Key Words: 4(3*H*)-Quinazolinones; Iodine; Three-component reaction; One pot synthesis.

4(3*H*)-Quinazolinones **1** are known since more than a century.[1] They belong to an important class of heterocyclic compounds in medicinal chemistry having anticonvulsant,[2] antihypertensive,[3] antidiabetic,[4] and other

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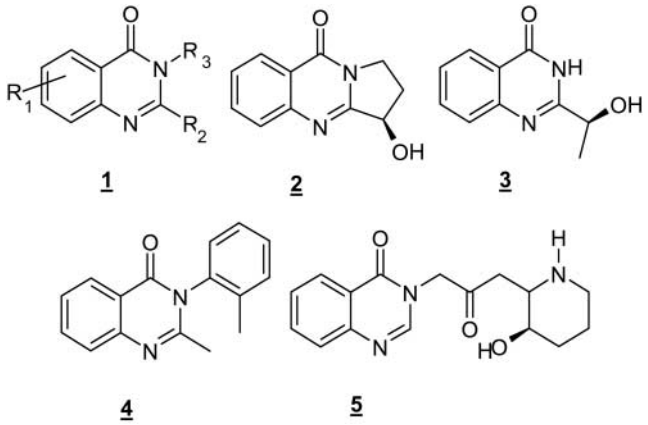
biological activities.[5] The important natural and synthetic 4(3*H*)-quinazolinones include l-vasicinone **2**,[6] chrysogine **3**,[7] methaquinalone **4**[8] a sedative, febrifugine **5**[9] an antimalarial.

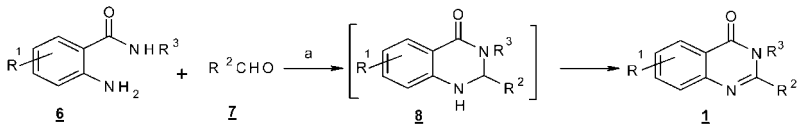


1 **2** **3**

4 **5**

While there exists numerous methods for the synthesis of 4(3*H*)-quinazolinones, only a few general methods[10] (for recent review on 2-hetero-substituted 4(3*H*)-quinazolinone, see Ref.[10b]) are capable to provide their synthesis under drastic condition in multi-step protocol. The synthetic approach to 2,3-disubstituted 3(*H*)-quinazoline-4-one **1** are based on two stage protocol, i.e., acylation of anthranilamides[11] followed by cyclization. Alternately, **1** can be synthesized in moderate yield from anthranilamide **6** and aldehydes **7** in two steps by cyclocondensation under drastic condition to afford 1,2-dihydro-4(3*H*)-quinazolinones **8** followed by oxidization mediated by potassium permanganate[10] (for recent review on 2-hetero-substituted 4(3*H*)-quinazolinone, see Ref.[10b]), MnO_2[12] to **1** in the subsequent step. Oxidative dehydrogenation of **8** in same pot during its synthesis can be envisaged to furnish **1**.

Synthesis of these compounds under mild conditions in a single-pot reaction is non-existent. We, herein, report a single pot synthesis of



6 **7** **8** **1**

a = I_2 or DDQ, DMF.

Scheme 1.

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4(3*H*)-quinazolinones **1** in moderate to high yield under mild conditions based on oxidative cycloaddition of aldehydes **7** with anthranilamides **6** (Sch. 1).

On stirring a mixture of aldehyde **7** with equimolar amount of anthranilamide **6** in dioxane or DMF at ambient temperature for 20 hr did not afford **1**. When half molar amount of I_2 was added to a stirred mixture of **6h** and **7h**, it warmed up. On stirring the mixture at ambient temperature for 5 hr, 4(3*H*)-quinazolinone **1h** was isolated 67.5% in yield, while on stirring 60–80°C for 5 hr with equimolar I_2 and potassium carbonate the yield obtained was 95%. The product can be conveniently isolated by quenching the reaction mixture with crushed ice-water and then filtering the solid precipitate thus obtained. Evidently, iodine catalyses the cyclocondensation aldehyde with anthranilamide to 1,2-dihydro-4(3*H*) quinazolinone **8**, and it is in situ the oxidation to 4(3*H*)-quinazolinone **1**. We employed DDQ in place of iodine, the conversation to 4(3*H*)-quinazolinone **1** is completed within 1/3 hr. The yield of **1b** obtained from the aliphatic aldehydes **7b** is moderate whereas aromatic aldehydes furnished corresponding quinazolinones in excellent yield (Table 1).[a]

To synthesize 2,3-disubstituted 4(3*H*)quinazolinones, we attempted three-component reaction[13],[b] comp'rising of isotoic anhydride, an amine and aldehyde following the developed protocol. Thus, when to the stirred solution of isotoic anhydride in DMF, the amine, the aldehyde, iodine, and powdered KOH are sequentially added and stirred the mixture for 5 hr at 60–80°C (Sch. 2).

The 2,3-disubstituted quinazolinone were isolated in moderate yield (entry 1k–1n, Table 1).[c] Examination reaction mixture by TLC and spectroscopic

[a]Typical example: to a solution of anthranilamide **6** (R^3 = H, 5 mmol) dissolved in 20 mL of anhydrous DMF, 3,4,5-trimethoxybenzaldehyde (5 mmol) is added. To the resulting mixture while stirring, iodine (6 mmol) and anhydrous potassium carbonate (5 mmol) are added and then heated at 60–80°C for 6 hr. The mixture is poured into crushed ice-water in (200 mL). The precipitated product is filtered, washed with water, and then recrystallized from alcohol. IR (KBr): 3442, 2935, 1673, 1605, 1457 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) (ppm): 3.71 (s, 3H), 3.73 (s, 3H), 3.87 (s, 3H), 7.24–7.34 (m, 3H), 7.59–7.61 (m, 2H), 8.06 (bs, 1H), FAB mass: m/z 213 ($M^+ + 1$, 100%), 154, 136.

[b]2,3-Dihydro 4(3*H*)-quinazolinones have been synthesized in moderate yield from isotoic anhydride and aromatic aldimines under drastic conditions.

[c]Typical example: to a solution of isotoic anhydride (1 mmol) dissolved in 5 mL of anhydrous DMF, *N*-butyl amine (1 mmol) and benzaldehyde (2 mmol) are added. The resulting mixture is while stirring; iodine (1.2 mmol) and powdered KOH (1.2 mmol) are added and then heated at 60–80°C for 8 hr. The product mixture is diluted with crushed ice-water and extracted with ethyl acetate. After usual work-up, liquid product is purified by silica gel chromatography and recrystallized from alcohol to obtain **1k**. IR (KBr): 1662, 1605, 1457 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) (ppm): 0.83 (t, 3H), 1.42 (m, 4H), 3.86 (m, 3H), 7.43 (s, 5H), 7.44–93 (m, 4H), FAB mass: m/z 279 ($M^+ + 1$).

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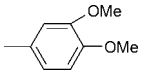
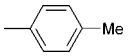
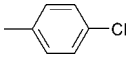
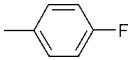
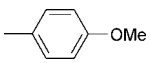
Table 1. 4(3*H*)-Quinazolinones: variation of aldehydes (R^2).

Entry	R^1	R^2	R^3	Yield (%)	M.p. (°C)	Reference
1a	H		H	85.2	231–232	[15]
1b	H		H	62	176–178	
1c	7-Cl		H	87	292–294	[14]
1d	H		H	91	241	[15]
1e	H		H	90	306	[16]
1f	H		H	87	258–260	
1g	H		H	88	247	[15]
1h	H		H	98,[x] 95,[y] 67.5[z]	170–172	

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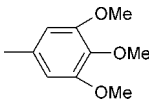
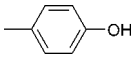
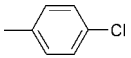
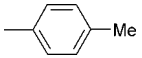
1i	H		H	75.3	255	[15]
1j	H		H	80	262–264	
1k	H			50	116–118	[17]
1l	H			53	137–139	[18]
1m	H			60	170–172	[17]
1n	H			55	229–231	[19]

Note: x = DDQ, room temperature; $y = I_2$, 1 molar heat 5 hr; $z = I_2$, 1/2 molar, room temperature.

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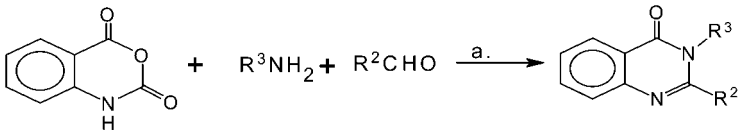

6 **7** **1**

Scheme 2.

means showed that it is a mixture of desired product, anthranilamide and aldehyde. *N*-substituted anthranilamide formed by facile condensation of amine with isotoic anhydride requires drastic condition to undergo cyclocondensation with aldehyde compared to *N*-unsubstituted anthranilamide.

Iodine catalyses the cyclocondensation of aldehyde with anthranilamide through polarization of its C═O bond. Apparently, the oxidizing rate with DDQ is higher than that of iodine; hence the formation **1** with it is more facile.

The quinazolinone **1** prepared have been characterized by NMR, IR, and FAB mass spectra. The other physical properties of known product have comparable as reported. In conclusion, 4(3*H*)-quinazolinone are synthesized by single-pot reaction of either anthranilamide with aldehyde or isotoic anhydride, amines and aldehyde mediated by iodine or DDQ in moderate to excellent yield.

REFERENCES

1. Widdege, A. Synthesis of 4(3H)-quinazolinones. Prakt. Chem. **1887**, *36*, 141–145.
2. Mannschreck, A.; Koller, H.; Davies, M.A.; Traber, J. The enantiomers of methaquinalone and their unequal anticonvulsive activity. Eur. J. Med. Chem. **1984**, *19*, 381.
3. (a) Hess, H.J.; Cronin, T.H.; Scriabine, A. Antihypertensive 2-amino-4(3H)-quinazolinones. J. Med. Chem. **1968**, *11*, 130; (b) Hussain, M.A.; Chin, A.T.; Price, W.A.; Timmermans, P.B.; Shefter, E. Pharm. Res. **1988**, *5*, 242.
4. (a) Malamas, M.S.; Miller, J. Quinazolineacetic acids and related analogs as aldose reductase inhibitors. J. Med. Chem. **1991**, *34*, 1492; (b) Gupta, C.M.; Bhaduri, A.P.; Khanna, N.M. Drugs acting on the central nervous system. Syntheses of substituted quinazolinones and quinazolines and triazepino- and triazocinoquinazolinones. J. Med. Chem. **1968**, *11*, 392.

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5. (a) Bartrolli, J.; Turmo, E.; Alguero, M.; Boncompte, E.; Vericat, M.L.; Coute, L.; Ramis, J.; Merlos, M.; Refaudt-Gracia, J.; Form, J. New azole antifungals. 3-Synthesis and antifungal activity of 3-substituted-4(3H)-quinazolinones. J. Med. Chem. **1998**, *41*, 1869; (b) Padia, J.K.; Field, M.; Hinton, J.; Meecham, K.; Pablo, J.; Pinnok, R.; Roth, B.D.; Singh, L.; Suman-Chauhan, N.; Trivedi, B.K.; Wesbdale, L. Novel non-peptide CCK-B antagonists: design and development of quinazolinone derivatives as potent, selective, and orally active CCK-B antagonists. J. Med. Chem. **1998**, *41*, 1042; (c) Kurogi, Y.; Inoue, Y.; Tsutsumi, K.; Nakamura, S.; Nagao, K.; Yohsitsugu, H.; Truda, Y. Synthesis and hypolipidemic activities of novel 2-[4-[(diethoxyphosphoryl)methyl] phenyl]-quinazolines and 4(3H)-quinazolinones. J. Med. Chem. **1996**, *39*, 1433.
6. Eguchi, S.; Suzuki, T.; Okawa, J.; Matsu, Y.; Yashima, E.; Okamoto, Y. Synthesis of optically active vasicinone based on intramolecular Aza–Wittig reaction and asymmetric oxidation. J. Org. Chem. **1996**, *61*, 7316–7319.
7. Bergman, J.; Brynolft, A. Synthesis of chrysogine, a metabolic of *Penicillium chrysogenum* and some related 2-substituted 4-(3H)-quinazolinones. Tetrahedron **1990**, *46*, 1295–1310.
8. Kacker, I.K.; Zaheer, S.H. Potential analgesics. Part I. Synthesis of substituted 4-quinazolones. J. Ind. Chem. Soc. **1951**, *28*, 344–346.
9. (a) Kobayashi, S.; Ueno, M.; Suzuki, R.; Ishitani, H.; Kim, H.S.; Wataya, Y. Catalytic asymmetric synthesis of antimalarial alkaloids febrifugine and isofebrifugine and their biological acitivity. J. Org. Chem. **1999**, *64*, 6833–6841; (b) Takaya, Y.; Tasaka, H.; Chiba, T.; Uwai, K.; Tanitsu, M.A.; Kim, H.S.; Wataya, Y.; Miura, M.; Takeshita, M.; Oshima, Y. New type of febrifugine analogues, bearing a quinolizidine moiety, show potent antimalarial acitivity against *Plasmodium* malaria parasite. J. Med. Chem. **1999**, *42*, 3163–3166.
10. (a) Armarego, W.L.F. Quinazolines. Adv. Heterocyclic Chem. **1979**, *24*, 1–63; (b) Reddy, P.; Reddy, P.P.; Vasantha, T. A review on 2-heteryl and heteroalkyl-4(3H)-quinazolinones. Heterocycles **2003**, *60*, 183.
11. (a) Filachione, E.M.; Lengel, J.H.; Fisher, C.H. Pyrolysis of lactic acid derivatives. Production of phenyl and *o*-tolyl acrylate. J. Am. Chem. Soc. **1944**, *66*, 494–496; (b) Bondgar, B.P. Synthesis of 4(3H)-quinazolinones from ortho amido benzonitriles using urea hydrogen peroxide. Synth. Com. **1997**, *27*, 2065–2068; (c) Meyer, J.F.; Wagner, E.C. The Niementowski reaction. The use of methyl anthranilate or isatoic anhydride with substituted amides or amidines in the formation of 3-substituted amides or amidines in the formation of 3-substituted-4-keto-3,4-dihydroquinazolines. J. Org. Chem. **1943**, *8*, 239–252.

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12. Maitraie, D.; Venkat Reddy, G.; RamaRao, V.V.V.N.S.; Ravi Kanth, S.; Shanthan Rao, P.; Narsaia, B. A simple and facile method for the synthesis of novel 5/7 trifluoromethyl-substituted 4(3H)-quinazolone regioisomers. J. Fluorine Chem. **2002**, *118*, 273–279.
13. (a) Noda, K.; Ide, H.; Nakagawa, A.; Motomura, T. 2-(Pyridyl)-4(3H)-quinazolinones. Japan Kokai 73, 62, 775 (Chemical abstracts **1973**; 79:14653); (b) Steiger, W.; Kappe, T.; Ziegler, E. Synthesis of heterocycles CXXIII. Reactions of isotoic anhydrides with anils. Montash Chemie **1969**, *100*, 146–149.
14. Desai, D.R.; Patel, V.S.; Patel, S.R. A study of reactivity of B2-substituted 3,1,4-benzoxazons Part 1. Synthesis of 2-methyl 2,2-phenyl-6(7) chloro-4-keto quinazolines. J. Ind. Chem. Soc. **1966**, *43*, 351–355.
15. Stephen, H.; Wadge, G. Conversion of *N*-arylanthralinamides to 2-aroyl-quinazol-4-ones. J. Chem. Soc. **1956**, 4420.
16. David, T.; Zentmyer Wagner, E.C. The so-called acylanthranils (3,1,4-benzoxazones). I. Preparation; reactions with water, ammonia, and aniline. J. Org. Chem. **1949**, *14*, 967–981.
17. Jackman, G.B.; Petrow, V.; Stephenson. Some 2,3-disubstituted 4(3H)-quinazolones and 3H-4-thioquinazolones. J. Pharm. Pharmacol. **1960**, *12*, 529–538.
18. Petyunin, P.A.; Kozhevnikov, Y.V.; Berdinskii, I.S. Synthesis of 2,3-diaryl-substituted 4-quinazolones with polyphosphoric acid. Uch. Zap. Perm. Gos Univ. **1966**, *141*, 309–312, CA 69:77226k.
19. Legrand, L.; Lozach, N. Heterocyclic sulphur compounds 1. Action of primary amine, 3,1-benzothiazine-4 thiones and 3,1-benzothiazin-4-one. Bull. Chem. Soc. Chim. France **1960**, *92*, 2085.

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