Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Expeditious One-Pot and Solvent-Free Synthesis of Dihydroquinazolin-4(1H)-ones in the Presence of Microwaves

Mandar P. Surpur [a], Pankajkumar R. Singh [a], Sachin B. Patil [a] & Shriniwas D. Samant [a]

[a] Organic Chemistry Research Laboratory, Department of Chemistry, Institute of Chemical Technology, Mumbai, India

Version of record first published: 22 Jun 2007.

To cite this article: Mandar P. Surpur , Pankajkumar R. Singh , Sachin B. Patil & Shriniwas D. Samant (2007): Expeditious One-Pot and Solvent-Free Synthesis of Dihydroquinazolin-4(1H)-ones in the Presence of Microwaves, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 37:12, 1965-1970

To link to this article: http://dx.doi.org/10.1080/00397910701354699

Synthetic Communications®, 37: 1965–1970, 2007

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910701354699

Expeditious One-Pot and Solvent-Free Synthesis of Dihydroquinazolin-4(1H)-ones in the Presence of Microwaves

Mandar P. Surpur, Pankajkumar R. Singh, Sachin B. Patil, and Shriniwas D. Samant
Organic Chemistry Research Laboratory, Department of Chemistry, Institute of Chemical Technology, Mumbai, India

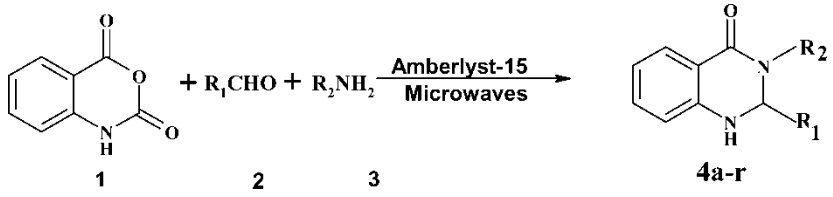
Abstract: Dihydroquinazolin-4(1H)-ones were synthesized for the first time by a novel three-component condensation of isatoic anhydride, a primary amine, and an aldehyde catalyzed by Amberlyst-15 in the presence of microwaves under neat conditions. The catalyst is reusable, thus making the process more environmentally friendly.

Keywords: dihydroquinazolin-4(1H)-ones, Amberlyst-15, microwaves, multicomponent reactions

INTRODUCTION

Dihydroquinazolin-4(1H)-ones (1) are an important class of heterocycles that exhibit biological and pharmaceutical activities. These compounds are known to be antitumur agents, diuretics, plant-growth regulators, herbicidal agents, anticonvulsants, and anticancer agents.[1] These compounds can be easily oxidized to their quinazolin-4(3H)-one analogues,[2] which are important biologically active heterocyclic compounds[3] and are found in some natural products.[4] A three-component, one-pot reaction of isatoic anhydride, primary amine, and aldehyde could be envisaged to give **1**. Recently, these compounds have been synthesized by this route, using silica-sulfuric acid,[5]

Received October 27, 2006
Address correspondence to Shriniwas D. Samant, Organic Chemistry Research Laboratory, Department of Chemistry, Institute of Chemical Technology, N. M. Parekh Road, Matunga, Mumbai 400 019, India. E-mail: samantsd@udct.org



Scheme 1.

p-TSA,[6] and Montomorillonite K10.[7] However, these methodologies have long reaction times and use hazardous chemicals. Therefore, discovery of new, inexpensive, and environmentally benign catalysts for the preparation of dihydroquinazolinones is of prime importance. In continuation of our ongoing research toward the synthesis of heterocyclic compounds by greener and environmentally benign approaches, we report the synthesis of dihydroquinazolin-4(1H)-one derivatives by the condensation of isatoic anhydride, primary amines, and aldehydes in the presence of Amberlyst-15 under microwave irradiation.

Cationic exchange resins, particularly the macroporous ones, are versatile catalysts that offer several advantages over the homogeneous catalysts with respect to corrosion, product recovery, and selectivity.[8] Amberlyst-15 is a cationic exchange resin with a Hammett acidity function of -2.2.[9] It has a cross-linking density (i.e., percentage of divinylbenzene) 20, surface area of 45 m^2/g, and pore volume of 0.35 ml/g.[8] When the condensation of isatoic anhydride, aniline, and benzaldehyde was carried out in the presence of Amberlyst-15 at 130°C, the reaction took a long time for completion (i.e., 3–4 hr).

Microwave irradiation of organic reactions has rapidly gained popularity because it accelerates a variety of synthetic transformations.[10,11]

Table 1. Effect of various solid Brønsted acid catalysts on the condensation of isatoic anhydride, benzaldehyde, and aniline under microwave irradiation

Catalyst	Time (min)	Yield (%)[a]
Amberlyst-15	3	81
Indion 130	12	68
Indion FF-IP	16	65
Sulphamic acid	5	77

Notes. Isatoic anhydride (1 mmol, 0.163 g); aniline (1.2 mmol, 0.091 ml); benzaldehyde (1 mmol, 0.101 ml); catalyst (50% by wt of isatoic anhydride). Microwave power: 360 W. Solvent free.

[a]Isolated and unoptimized yield.

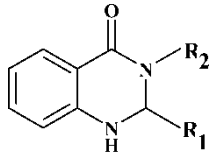
Table 2. Recyclability study of Amberlyst-15

Run	Time (min)	Yield (%)[a]
1	3	81
2	3	81
3	4	80
4	4	78

Notes. Isatoic anhydride (1 mmol, 0.163 g); aniline (1.2 mmol, 0.091 ml); benzaldehyde (1 mmol, 0.101 ml); Amberlyst-15 (80 mg, 50% by wt of isatoic anhydride). Microwave power: 360 W, Solvent free.

[a]Isolated and unoptimized yield.

Table 3. Microwave-assisted one-pot synthesis of dihydroquinazolin-4-(1H)-one derivatives catalyzed by Amberlyst-15



4a-s

Product	R^1	R^2	Time (min)	Yield (%)[a]
4a	Ph	Ph	3	81
4b	3-NO_2Ph	Ph	6	83
4c	4-ClPh	Ph	6	84
4d	4-NO_2Ph	Ph	5	64
4e	2-CH_3Ph	Ph	3	72
4f	4-BrPh	Ph	5	85
4g	4-FPh	Ph	6	68
4h	Ph	H	3	78
4i	4-ClPh	H	3	86
4j	3-NO_2Ph	H	6	77
4k	4-BrPh	H	4	87
4l	4-CH_3OPh	H	7	75
4m	3,4-$(CH_3O)_2$Ph	H	7	70
4n	4-NO_2Ph	Pr	6	73
4o	Ph	Me	6	71
4p	4-ClPh	Me	5	74
4q	4-BrPh	Me	5	75
4r	4-CH_3OPh	Me	7	69

Notes. Isatoic is anhydride (1 mmol); amine (1.2 mmol); aldehyde (1 mmol); Amberlyst-15 (80 mg, 50% by wt of isatoic anhydride). Microwave power: 360 W. Solvent free.

[a]Isolated and unoptimized yield.

The application of microwaves with the use of certain catalysts or reagents provides unique chemical processes with special attributes such as enhanced reaction rates, higher yields, greater selectivity, and ease of manipulation. Thus, the reaction was also attempted under microwave irradiation (Scheme 1).

RESULTS AND DISCUSSION

Isatoic anhydride (**1**) was treated with aniline (**2**) and benzaldehyde (**3**) in the presence of different solid Brønsted acid catalysts under microwave irradiation (Table 1). Amberlyst-15 was found to be the best catalyst, as it gave 81% yield of the product in a short time of (3 min).

To check the reusability of the catalyst, the reaction of isatoic anhydride, aniline, and benzaldehyde was carried out three to four times using Amberlyst-15, and the effect on yield and time required for the reaction was seen (Table 2).

The catalyst was active even after four consecutive runs. Encouraged by these results, we decided to further explore the scope of the reaction by carrying out the condensation of a variety of substituted primary amines and aldehydes with isatoic anhydride. The condensation went smoothly, giving the desired products in less time and in good yields (Table 3). No side products were formed.

CONCLUSION

In conclusion, a simple, short, and environmentally friendly method for the synthesis of a novel class of dihydroquinazolin-4(1H)-ones is described. The workup procedure is simple, and chromatography is not required. Starting materials are inexpensive and commercially available. By the reaction of a range of amines and aldehydes with isatoic anhydride, novel libraries of dihydroquinazolinones could be developed, which would make this process suitable for parallel synthesis in drug discovery.

EXPERIMENTAL

All the products are known and were characterized by comparison of their spectroscopic and physical data with authentic samples synthesized by the reported procedure.[6] The microwave irradiation was carried out using a domestic microwave oven (LG: Little Chef) at power of 360 W.

Typical Experimental Procedure

Isatoic anhydride (1 mmol), aniline (1.2 mmol), benzaldehyde (1 mmol), and Amberlyst-15 (80 mg) were put in a 25-ml, round-bottom flask. The reaction mixture was stirred at room temperature with the help of a magnetic stirrer. The flask was kept in the domestic microwave oven, and the contents were irradiated with microwaves at 360 W, with irradiation pulses of 1 min each followed by a cooling period of 30 s at room temperature after every pulse. After the completion of the reaction (as indicated on TLC), the reaction mixture was cooled to room temperature, and hot ethanol (10 ml) was added. The reaction mixture was filtered using a G-3 filter to separate the catalyst. The filtrate was concentrated under vacuum to obtain the solid product. The product was crystallized from absolute alcohol. To study the recyclability of the catalyst, the catalyst was isolated after each run, washed with hot ethanol, and dried at 100°C for 6 h.

REFERENCES

1. (a) Hamel, E.; Lin, C. M.; Plowman, J.; Wang, H.; Lee, K.; Paull, K. D. *Biochem. Pharmacol.* **1996**, *51*, 53; (b) Biressi, M. G.; Cantarelli, G.; Carissimi, M.; Catteneo, A.; Ravenna. *Ed. Sci.* **1969**, *24*, 199; (c) Bhalla, P. R.; Walworth, B. L. *Chem. Abstr.* **1983**, *98*, 1669; (d) Bhalla, P. R. Walworth, B. L. *Chem. Abstr.* **1984**, *100*, 174857; (e) Hour, M.; Huang, L.; Kuo, S.; Xia, Y.; Bastow, K.; Nakanishi, Y.; Hamel, E.; Lee, K. 6-Alkylamino- and 2,3-dihydro-3′-methoxy-2-phenyl-4-quinazolinones and related compounds: Their synthesis, cytotoxicity and inhibition of tubilin polymerization. *J. Med. Chem.* **2000**, *43*, 4479–4487.
2. (a) Rao, V. B.; Hanumanthu, P.; Ratnam, C. V. *Indian J. Chem.* **1979**, *18B*, 493; (b) Lopez, S. E.; Rosales, M. E.; Urdaneta, N.; Godoy, M. V.; Charris, J. E. *J. Chem. Res., Synop.* **2000**, 258; (c) Abdel-Jalil, R. J.; Volter, W.; Saeed, M. A novel method for the synthesis of 4(3H)quinazolinone. *Tetrahedron Lett.* **2004**, *45*, 3475–3478.
3. (a) Wolf, J. F.; Rathman, T. L.; Sleevi, M. C.; Campbell, J. A.; Greenwood, T. D. Synthesis and anticonvulsant activity of some new 2-substituted 3-aryl-4(3H)-quinazolinones. *J. Med. Chem.* **1990**, *33*, 161–166; (b) Padia, J. K.; Field, M.; Hinton, J.; Meecham, K.; Pablo, J.; Pinnock, R.; Roth, B. D.; Singh, L.; Suman-Chauhan, N.; Trivedi, B. K.; Webdale, 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*, 1042–1049; (c) Kung, P.-P.; Casper, M. D.; Cook, K. L.; Wilson-Lingard, L.; Risen, L. M.; Vickers, T. A.; Ranken, R.; Blyn, L. B.; Wyatt, R.; Cook, P. D.; Ecker, D. J. Structure–Activity relationship of novel 2-substituted quinazoline antibacterial agents. *J. Med. Chem.* **1999**, *42*, 4705–4713; (d) Tsou, H.-R.; Mamuya, N.; Johnson, B. D.; Reich, M. F.; Gruber, B. C.; Y.-F.; Wissner, A. 6-Substituted-4-(3-bromophenylamino) quinazolines as putative irreversible inhibitors of the epidermal growth factor receptor(EFGR) and human epidermal growth factor receptor (HER-2) tyrosine kinases with enhanced anti-tumour activity. *J. Med.*

Chem. **2000**, *44*, 2719–2734; (e) Matsuno, K.; Ichimura, M.; Nakajima, T.; Tahara, K.; Fujiwara, S.; Kase, H.; Vishiki, J.; Giese, N. A.; Pandey, A.; Scarborough, R. M.; Lokker, N. A.; Yu, J.-C.; Irie, J.; Tsukda, E.; Ide, S.-I.; Oda, S.; Nomoto, Y. Potent and selective inhibitors of platelet-derived growth factor receptor phosphorylation 1: Synthesis, structure-activity relationship, and biological effects of a new class of quinazoline derivatives. *J. Med. Chem.* **2002**, *45*, 3057–3066.

4. Maskey, R. P.; Shaaban, M.; Grun-Wollnu, I.; Laatsch, H. Quinazolin-4-one derivatives from *Streptomyces* isolates. *J. Nat. Prod.* **2004**, *67*, 1131–1134.
5. Salehi, P.; Dabiri, M.; Zolfigol, M. A.; Baghbanzdeh, M. A novel method for the one-pot three-component synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones. *Synlett* **2005**, 1155–1157.
6. Baghbanzdeh, M.; Salehi, P.; Dabiri, M.; Kozehgary, G. Water-accelerated synthesis of novel bis-2,3-dihydroquinazolin-4(1*H*)-one derivatives. *Synthesis* **2006**, 344–348.
7. Salehi, P.; Dabiri, M.; Baghbanzadeh, M.; Bahramnejad, M. One-pot, three-component synthesis of 2,3-dihydro-4(1H)-quinazolinones by Montmorillonite K-10 as an efficient and reusable catalyst. *Synth. Commun.* **2006**, 2287–2292.
8. Sharma, M. M. Some novel aspects of cationic ion exchange resins as catalysts: Review. *React. Funct. Polym.* **1995**, *26*, 3–23.
9. Chakrabarti, A.; Sharma, M. M. Cationic ion exchange resins as catalyst. *React. Polym.* **1993**, *20*, 1–45.
10. Caddick, S. Microwave assisted organic reactions. *Tetrahedron* **1995**, *51* (38), 10403–10432.
11. For recent reviews on microwave-assisted organic reactions, see (a) Varma, R. S. Solvent-free synthesis of heterocyclic compounds using microwaves. *J. Heterocycl. Chem.* **1999**, *36*, 1565–1571; (b) Varma, R. S. Solvent-free organic synthesis. *Green Chem.* **1999**, *1* (1), 43–55; (c) Bose, A. K.; Banik, B. K.; Lavlinskaia, N.; Jayaraman, M.; Manhas, M. S. More chemistry in a microwave. *Chemtech* **1997**, *27* (9), 18–24; (d) Majetich, G.; Hicks, R. Radiat. applications of microwave accelerated organic synthesis. *Phys. Chem.* **1995**, *45* (4), 567–569; (e) Abramovich, R. A. Applications of microwave energy in organic chemistry: A review. *Org. Prep. Proced. Int.* **1991**, *23* (6), 683–711.