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SHORT COMMUNICATION

DABCO AS A NOVEL AND EFFICIENT CATALYST FOR THE SYNTHESIS OF 4(3*H*)-QUINAZOLINONE DERIVATIVES

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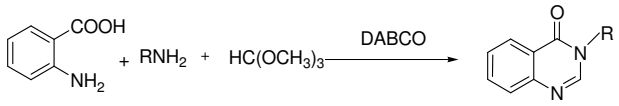
ABSTRACT. 4(3*H*)-Quinazolinones were synthesized in high to excellent yields through the one-pot condensation of anthranilic acid, trimethyl orthoformate and primary amines in the presence of DABCO under solvent free conditions.

KEY WORDS: 4(3*H*)-Quinazolinone, DABCO (1,4-diazabicyclo[2,2,2]octane), Trimethyl orthoformate, Anthranilic acid

INTRODUCTION

In recent years there has been an increasing interest in the chemistry of 4(3*H*)-quinazolinones because of their biological significance. The quinazolinone moiety is a building block for approximately 150 naturally occurring alkaloids [1] such as glycosminine [2], echinozolinone [3], deoxyvasicinone [4], rutaecarpine [5] and drugs like methaqualone [6]. Many of them show antifungal, antibacterial, anticancer, anti-inflammatory, anticonvulsant, immunotropic, hypolipidemic, antitumor, antiulcer analgesic and antiproliferative activities as well as inhibitory effects for thymidylate synthase and poly-(*ADP*-ribose) polymerase (*PARP*) [7-19]. Recently quinazolinone chemistry has got new direction due to some resemblance with folic acid [20-22]. Thus, due to the diverse range of the pharmacological activities of quinazolinones and their derivatives, there are numerous methods available for their synthesis [23]. Most of these procedures have significant drawbacks such as long reaction times, low yields, harsh reaction conditions, difficult work-up and use of environmentally toxic reagents or media. Therefore, demand for increasingly clean and efficient chemical synthesis is important from both economic and environmental points of view. In continuation of our work to develop new synthetic methodologies, we report a facile and efficient method for the synthesis of 4(3*H*)-quinazolinone derivatives by the condensation reaction of anthranilic acid, trimethyl orthoformate and primary amines in the presence of DABCO under solvent free conditions in an oil bath (80˚C).



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

RESULTS AND DISCUSSION

DABCO (1,4-diazabicyclo[2,2,2]octane) has been widely used as a catalyst for the Baylis–Hillman reaction [24]. It has also been reported as a catalyst for acceleration of benzoylation reactions [25]. DABCO has been applied for the synthesis of zeolite as a structure directing agent [26] and can catalyze the self and cross-condensation of α-acethylenic ketones [27]. It has also been used to catalyze the coupling of α-keto-esters with acrylonitrile [28] and for the dimerization of α,β-unsaturated ketones and nitriles [29].

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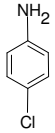
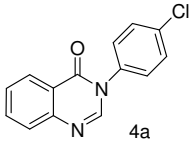
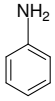
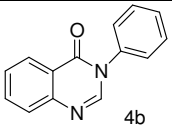
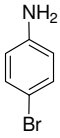
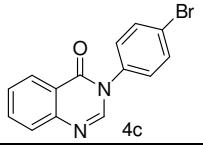
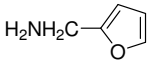
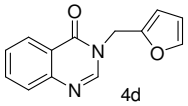
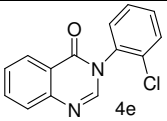
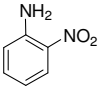
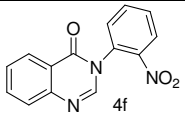
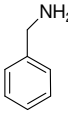
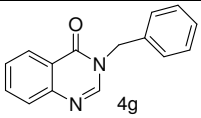
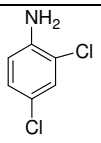
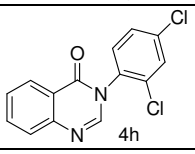
Table 1. Synthesis of 4(3*H*)-Quinazolinones in the presence of DABC.

Entry	Amine	Quinazolinone	Yield (%)[a]
1		 4a	92 [30]
2		 4b	95 [30]
3		 4c	93 [30]
4		 4d	95 [31]
5		 4e	92 [32]
6		 4f	92 [33]
7		 4g	93 [34]
8		 4h	95 [35]

[a]Yields refer to isolated products (reaction time = 1 h).

Therefore, we selected DABCO as a new catalyst for the synthesis of 4(3*H*)-quinazolinones. The reaction of various amines, anthranilic acid, trimethyl orthoformate in the presence of DABCO afforded products in high yields (Table 1). This method works well with a 1:1.2:1.2 mole ratio mixture of anthranilic acid, trimethyl orthoformate and primary amines in the presence of DABCO under solvent free conditions in an oil bath (80˚C) to give the desired products. This method not only affords the products in excellent yields but also avoids the problems associated with catalyst cost, handling, safety and pollution. This catalyst can act as eco-friendly for a variety of organic transformations since it is non-volatile, recyclable, non-

explosive, easy to handle and thermally robust. In view of the emerging importance of the catalyst, we wish to explore the use of DABCO as a recyclable catalyst for the synthesis of 4(3*H*)-quinazolinones.

To obtain the optimum amount of catalyst for this reaction, various amounts of catalysts for the reaction were used. The results indicate that the yields were affected by changing the catalyst moles. The reactions proceeded well with 10 mol% catalyst and use of an increased amount of catalyst does not make much difference. (As shown in Table 2).

Table 2. Comparison the results of amino alcohols in the presence of different moles of DABCO.

Entry	Mol% of DABCO	Yields (%)[a]						
		4a	**4b**	**4c**	**4d**	**4e**	**4f**	**4g**
1	2	80	79	77	76	72	76	77
2	5	88	87	89	90	89	85	87
3	10	92	95	93	95	94	92	93
4	15	93	95	94	95	95	93	93
5	20	94	95	95	96	96	93	94

[a]Yields refer to isolated products.

EXPERIMENTAL

Chemicals were purchased from the Fluka, Merck and Aldrich chemical companies. Melting points were measured with a Bamstead Electrothermal 9200 apparatus and are uncorrected. GC/MS spectra were recorded on an Agilent Technologies 6890 network GC system and an Agilent 5973 network mass selective detector. Thin layer chromatography (TLC) on commercial aluminum-backed plates of silica gel, 60 F254 was used to monitor the progress of reactions. ^{1}H NMR spectra were recorded on a Bruker AQS AVANCE-300 MHz spectrometer using TMS as an internal standard ($CDCl_3$ solution). Yields refer to isolated pure products. Products were identified by GC/MS and ^{1}H NMR and the data were compared to those of the authentic samples purchased from commercial sources.

*Synthesis of 3(4-bromophenyl)-4(3H)-quinazolinone (**4c**).* A mixture of anthranilic acid (1 mmol), trimethyl orthoformate (1.2 mmol), 4-bromoaniline (1.2 mmol), DABCO (10 mol %) was added. The reaction mixture was stirred under solvent free condition in an oil bath (80˚C) for 1 h. After completion of the reaction (monitored by TLC), 10 mL of CH_2Cl_2 was added to the reaction mixture and the catalyst was recovered by filtration. The filtrate was washed twice with HCl (5%) and subsequently twice with $NaHCO_3$ (5%). The organic layer was dried and the solvent was evaporated to afford the pure product. Yield 85%, mp 185 °C. Catalyst was recovered from the residue of the filtration of the reaction mixture by washing thoroughly (CH_2Cl_2), drying, and it then was pure enough for recycling. M.p. = 185 °C; ^{1}H NMR ($CDC1_3$, 300 MHz) δ (ppm): 8.38 (d, J = 7.43 Hz, 1H), 8.04 (s, 1H), 7.85-7.19 (m, 7H): GC/Ms 302,300 (M^+).

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