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Facile preparation of 3-substituted 2-quinazolinones via electrogenerated base

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ABSTRACT

A new series of 3,4-disubstituted quinazolin-2-ones, with potential T-type calcium channel antagonist activity, and new 4-methylene-quinazolin-2-ones, promising catalysts as *N*-heterocyclic olefins, have been prepared in good yield by a simple reaction between 2-aminobenzophenone, or 2-aminoacetophenone, and cyanomethyl anion electrogenerated by acetonitrile reduction at a graphite electrode, followed by the addition of different organic isocyanates and subsequent heterocyclization.

1. Introduction

Quinazolinone and their derivatives are building block for approximately 150 naturally occurring alkaloids isolated from plants, microorganisms and animals.[1] Some compounds incorporating quinazolinone motif possess antitumor activities[2,3] and exhibit a variety of biological functions like DNA binding agents[4] non-steroidal anti-inflammatory potential or sedative analgesic effects.

A vast number of 4-quinazolinones have been synthesized[5] to provide synthetic drugs and to design more effective medicines. However there have been few reports about the synthesis of 2-quinazolinones. The general protocol involves the cyclization of *o*-disubstituted benzene derivatives such as 2-acyl or 2-cyanoanilines in combination with appropriate electrophiles or nucleophiles. Conley et al.[6] utilized a direct metalation approach starting with 3,4-dimethoxyanilin with n-butyllithium, then treating with potassium cyanate and followed by cyclization in polyphosphoric acid. Vicente et al.[7] reported the first ortho-palladated arylurea complexes, obtained by oxidative addition reactions, and studied their reactivity toward different reagents to prepare 2-quinazoline-2,4-dione derivatives. Ivanov[8] synthesized 6,7-dimethoxy-3,4-diphenyl-2(1*H*)-quinazolinone from 1-(3,4-dimethoxyphenyl)-3-phenyl-urea and benzoic acid. Zhu et al.[9] described an efficient synthesis of 4-alkyl-2(1*H*)-quinazolinones by cyclization of 1-(2-alkynyl-phenyl)ureas catalyzed by TfOH. More recently Odell et al.[10] published a rapid access to polyfunctionalized 3,4-dihydroquinazolinones through a sequential *N*-acyliminium ion Mannich reaction cascade.

Merck[11] was interested in the synthesis of a series of 4-(arylethynyl)-6-chloro-4-cyclopropyl-3,4-dihydroquinazolin-2 (1*H*)-ones as novel non-nucleoside HIV-1 reverse-transcriptase inhibitors. Modification at the 3- and 4-positions of the quinazolinone ring by different substituents afforded potent and selective T-type calcium channel antagonist[12,13] that displayed in vivo central nervous system efficacy in epilepsy and tremor models.[14] Furthermore these antagonists are attracting a lot of interest for the treatment of peripheral and central nervous system (CNS) disorders[15] or as effective agents for pain therapies.[16]

The first 4-alkenylquinazolinone synthesis was described by Brack[17] as an acidic rearrangement reaction starting from quinoline-1-carboxamides. This procedure was applied by Zolotykh.[18]

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Similarly, Molina et al.[19] described the 4-methylene derivatives formation when refluxing 2-[(aminocarbonyl) amino]- 3,1-benzoxazines. However in the last 30 years only a few new approaches to prepare them have been achieved. In the synthesis of 4-methylene-3,4-dihydroquinazolin-2-ones it has been found that 1-(*o*-alkynylaryl)ureas are privileged substrates that provide an adequate framework to explore alternative reaction pathways in the metal-catalyzed hydroamidation of alkynes.[20,21] This effective gold(I)complex-catalyzed approach to 4-methylenequinazolin-2-ones, similarly to their formation via the palladium oxidative alkoxycarbonylation of 2-ethynylaniline derivatives,[22] suffer however the drawbacks that these transition metal reagents entail.

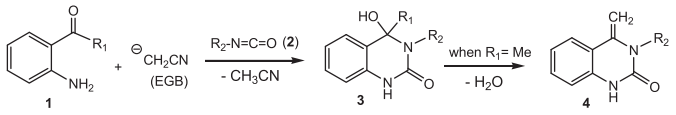
4-Methylene quinazolin-2-one core structures represent, as recently discovered,[23] new potential inhibitors of FGFR kinases with substantial therapeutic value in different cancers, including breast, pancreatic or prostate cancers. On the other hand, 4-methylene N-substituted quinazolin-2-one frameworks, due to their structural exocyclic double bond, could be promising compounds to be applied as organocatalyst in polymer chemistry, similarly to *N*-heterocyclic olefins (NHO), with demonstrated ability to promote or catalyse such reactions.[24]

Electrogenerated radical anions and anions are basic reagents, called EGBs which can be used to deprotonate and to initiate many base catalyzed reactions. The use of EGB in organic synthesis is well documented.[25] Carbanions, as strong bases, may be used to generate nucleophiles from other acidic components of the reaction mixture. Moreover radical anions as EGBs have a great potential in organic synthesis, as demonstrated in the stereoselective cyclopropanation to homoquinones from phenacyl carbenes, that we have recently highlighted.[26]

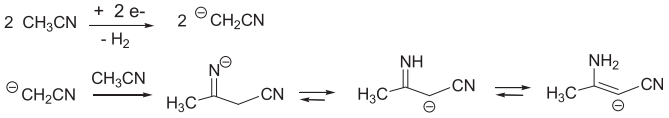
Intrigued now by promising further expectation of acetonitrile anion, as strong EGB, in the preparation of many heterocyclic molecules, we focused our attention on using the electrochemistry as a tool to prepare quinazolin-2-one moieties. Herein we report, as outlined in Scheme 1, a novel strategy for the conversion of readily available substrates into 3,4-disubstituted quinazolin-2-ones (**3**) and 4-methylene-3-substituted quinazolin-2-ones (**4**). Electrogenerated cyanomethyl anion (EGB) and 2-aminophenones evolve to **3** (or **4**) when reacted with aryl (or alkyl) isocyanates by heterocyclization.

2. Results and discussion

It is well established that the electrochemical reduction of acetonitrile in the presence of a quaternary ammonium salt as supporting electrolyte yields the corresponding cyanomethyl anion, a strong basic entity, with a pKa value of c.a. 32[27] capable of removing a weak acidic proton. When this reduction is carried out at a platinum, graphite or stainless steel cathode, under an argon atmosphere, the anion of 3-aminocrotonitrile[28,29] is also formed after the nucleophilic attack of the cyanomethyl anion to a new solvent molecule, as indicated in Scheme 2. However, the use of low temperatures and a sacrificial magnesium anode, in an undivided cell, avoids to a large extent this undesired reaction. It occurs because the subsequently formed magnesium cations, present in solution, stabilize the cyanomethyl anions by ion-pair association.[30]



Scheme 1. Outline of the synthetic procedure described in this paper.



Scheme 2. Cathodic formation of 3-amino-crotonitrile anion.

The quantity of the electrogenerated cyanomethyl anion (EGB) depends on the total circulated charge through the electrochemical cell (solution). In absence of a proton donor the carbanion is produced in a 1 F/mol process, however at the present work, to synthesize 2-quinazolinones, a significant excess of the EGB was necessary. It was because a complete proton abstraction from anilines (as acidic substrates) requires a higher base concentration, but also due to the inherent dimerization of cyanomethyl anion that, even minimized, takes place in some extend.

Once the optimal quantity of electrogenerated base was formed, the current supplier was switched off and then the corresponding 2-aminophenone (**1**) was added to the reaction medium. Subsequent deprotonation of the amine to a nitride occurs by the effect of the EGB, as indicated in Scheme 3.

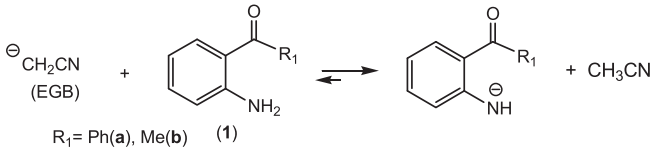
Aromatic ketones are well known electro-reducible carbonyl substrates, both under protic and aprotic solvents. For this reason compounds **1** are avoided to be present in the electrolytic solution at the applied galvanostatic conditions, needed to produce the EGB.

The freshly generated nitride attacks further an organic isocyanate molecule (**2**), subsequently introduced into the reaction medium, providing a new anionic intermediate. The latter finally cyclises through an addition reaction to the carbonyl group of the ketone, leading, as detailed in Scheme 4, to the 2-quinazolinone scaffolds after protonation during the work-up.

Moreover, the electrolytic conditions were optimized in terms of reaction times (once selected a constant current value of 120 mA, see experimental section) in order to get the best obtained yield on **3** or **4**, regarding the cyanomethyl anion dimerization product, 2-aminocrotonitrile, finally formed by the excess of EGB.

The afforded yields of a variety of substituted products **3** (**a-g**) and **4** (**a-g**), when alkyl: benzyl (**a**), ethyl (**b**), propyl (**c**), butyl (**d**) and cyclohexyl (**e**) or aryl: phenyl (**f**) and 4-chlorophenyl (**g**) isocyanates were used, are summarized in the experimental section of the manuscript. The complete characterization of these quinazolin-2-ones was performed according to their spectroscopic and spectrometric properties, becoming curious, at time that relevant, the final spontaneous dehydration of 4-hydroxy derivatives from starting acetophenone to the corresponding isolated compounds **4**, while 2-amino benzophenone derivatives were isolated as 4-hydroxy-4-phenyl-2-quinazolinones (**3**).

The heterocyclization reaction that evolves to the quinazolinone ring was further supported by the heteronuclear multiple bond correlation (gradient HMBC) two-dimensional spectrum (^{13}C and ^{1}H NMR data) of 4-hydroxy-4-phenyl-3-butyl-2-quinazolinone (**3d**), that is shown in Fig. 1. The two un-equivalent methylene hydrogen atoms, directly joined to the nitrogen at 3-position of the ring (that appear at $\delta = 3.20$ ppm and 3.40 ppm) correlate,



Scheme 3. Deprotonation of 2-aminophenones (**1a**) and (**1b**) by EGB.