Tetrahedron Letters 52 (2011) 6298–6302

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

About the intermediacy of 1,2-dihydroquinazolinium salts in the Friedländer–Borsche synthesis of quinolinium salts in acidic medium

José Vicente *, María Teresa Chicote, Antonio Jesús Martínez-Martínez

Grupo de Química Organometálica, Departamento de Química Inorgánica, Universidad de Murcia, Apartado 4021, 30071 Murcia, Spain

ARTICLE INFO

Article history:
Received 1 August 2011
Accepted 12 September 2011
Available online 17 September 2011

Keywords:
Quinolinium salts
1,2-Dihydroquinazolinium salts
Friedländer–Borsche reaction
Nitrogen heterocycles
Ketones

ABSTRACT

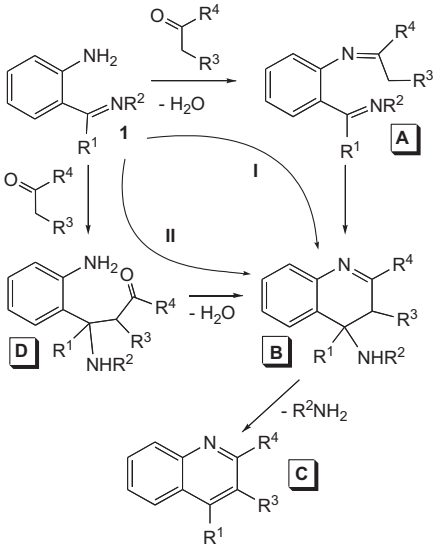
Spontaneously or under various heating conditions, 2-alkyl- or 2-aryl-(iminoalkyl)benzenamines react with ketones and triflic acid (1:1:1) to give quinolinium salts. When working under milder thermal conditions, intermediate 1,2-dihydroquinazolinium derivatives can be isolated or detected in solution but decompose upon standing or heating to give the corresponding quinolinium salts.

1. Introduction

Compounds based on the quinoline ring structure have found important applications related to their biological activity,[1] their ability to form polymers with excellent electronic or optical properties[2,3] and, recently, as efficient corrosion inhibitors for steel.[4] This explains the ongoing interest in finding new and efficient routes for their syntheses.[2,5,6] The Friedländer reaction, which involves the condensation of 2-(aminoaryl)carbonyl compounds with aldehydes or ketones containing α-methylene groups, is one of the most simple, efficient and straightforward methods for the synthesis of quinolines.[7] The limitation arising from the tendency of 2-(aminoaryl)aldehydes to undergo self-condensation, can be overcome by using 2-(aminoaryl)imines instead (Friedländer–Borsche reaction). Two alternative reaction pathways[6–8] for the mechanism of the Friedländer reaction have been proposed. The Borsche version of these two ways is shown in Scheme 1.

In pathway **I** the first step, rate determining, consists of the formation of a Schiff base (**A**). An intramolecular aldol-like reaction follows, to give a 3,4-dihydro-4-NHR^2-quinoline (**B**) that leads to quinoline (**C**) upon loss of R^{2}NH$_2$. Pathway **II** proposes that the intermolecular aldol-like condensation occurs first to give (**D**), followed by a dehydration/cyclization process that gives (**C**) through the intermediacy of (**B**). Although most of the evidence is in favour of the first reaction pathway, recent experimental works support pathway **II**.[6,8,9]

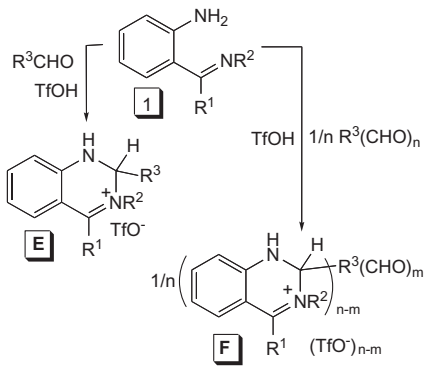
A few reactions have been described in which quinazoline itself[10] or some oxo-[11] or dihydro-derivatives[12] react with active α-methylene compounds or with enamines or ynamines,[13] to give quinoline derivatives, and some alkylquinazolinium salts react with quaternary heterocyclic salts yielding substituted heteroaryl quinolines.[14]



Scheme 1. Proposed reaction pathways for the Friedländer–Borsche synthesis of quinolines.

* Corresponding author. Tel.: +34 868 884143; fax: +34 868 887785.
E-mail address: jvs1@um.es (J. Vicente).

0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.09.053



Scheme 2. Synthesis of 1,2-dihydroquinazolinium salts from 2-alkyl or 2-aryl(iminoalkyl)benzenamines, aldehydes and TfOH. The counterion of cationic species is TfO^-.

We have recently reported[15] the reactions taking place between 2-alkyl- or 2-aryl(iminoalkyl)benzenamines $H_2NC_6H_4C(R^1)=NR^2$-2 (**1**, Scheme 2), aldehydes R^3CHO and triflic acid (TfOH) to give 1,2-dihydroquinazolinium triflate salts (DHQS, **E**, Scheme 2). The reaction worked also using the appropriate amounts of di- and tri-aldehydes to afford the corresponding mono-, bis- or tris-DHQS (**F**),[15] but failed with most ketones; it also worked when the iminoacyl Pd(II) complex *trans*-[PdI{C(=NXy)$C_6H_4NH_2$-2}$(CNXy)_2$] (i.e., a compound of type **1** with R^1 = *trans*-PdI$(CNXy)_2$ and R^2 = $C_6H_3Me_2$-2,6 = Xy) was treated with TfOH and with a variety of carbonyl compounds, including aldehydes and ketones, to afford the corresponding 1,2-dihydroquinazolinium-4-yl palladium complexes.[16,17]

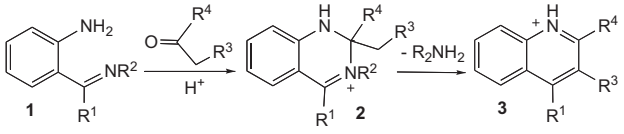
In this paper, we study the reaction between 2-amino substituted arylimines, various ketones bearing at least one α-methylene group (MeC(O)R (R = Me, Et, *i*-Pr, Bz, Ph) or $Et_2C(O)$) and TfOH (Table 1). At low temperature, DHQS form but, spontaneously or after soft heating, they convert into quinolinium salts upon loss of R^2NH_2. This suggests that DHQS could be intermediates in the Friedländer–Borsche synthesis of quinolinium salts in an acidic medium. This transformation has not been reported in the literature.

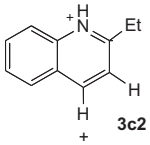
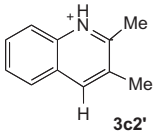
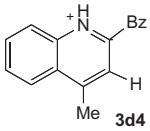
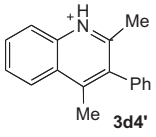
2. Results and discussion

When we reported the syntheses of DHQS **E** and **F** (Scheme 2) with R^1 different from [Pd],[15] we mentioned that the reactions using ketones ($Me_2C(O)$ or MeC(O)Et) showed differences with respect to those with aldehydes, regarding both the stability and the nature of the resulting products. In this Letter, we report the results obtained when decided to study these decomposition processes in depth, following the reactions by variable temperature ^1H NMR spectroscopy, and including in the study various other ketones bearing at least an α-methylene group which we reacted with compounds **1a–d** and TfOH (Table 1). The reactions were carried out by dissolving the appropriate compound **1** and ketone in $CDCl_3$ at −30 °C and adding the equimolar amount of TfOH. The temperature was then raised (1 °C/min) and one spectrum was measured every 10 min. The spectra showed that the reaction did not start until TfOH was added and that DHQS (**2**, Table 1), started to form immediately or after a few minutes, even at low temperature. In the case of **1d**, a protonated species (**G** in Scheme 3) was also detected after mixing the reagents.[15] The stability in solution of these DHQS varies from **2a** (entry 1) or **2d5** (entry 12) which are stable up to room temperature and can be isolated and fully characterized, to **2c1–4** (entries 3–6) which are stable up to 10–20 °C for a short period of time, or **2d1–4** (entries 8–11) which are identified in the interval of −30 to −10 °C, and decompose gradually upon raising the temperature. In turn, **2b** (entry 2) could be isolated, analysed and studied by ^1H NMR but its $^{13}C\{^1H\}$ NMR showed some impurities formed during the acquisition time, indicating its limited stability in solution.[15] The NMR spectra also showed the transformation of the DHQS **2** derived from ketones, spontaneous or induced by soft heating, into the corresponding quinolinium triflates **3** upon loss of R^2NH_2. The exception was the reaction of **1d** with methyl vinyl ketone (MVK) and TfOH ($CDCl_3$ at 25 °C), which afforded **2d5** (entry 12) as the only species present in solution. Its concentration did not change with time at 25 °C but, when rising the temperature to 45 °C, the reaction proceeded slowly and no more changes were observed after 10 h. At this point the NMR showed a complex mixture in which we could not assess or deny the presence of the expected quinolinium salt or the 4-iminium-1,2,3,4-tetrahydroquinoline compound resulting after an isomerization process, as we have observed for other DHQS bearing a Me group at the 4-position and electron withdrawing substituents on C(2).[15] In all other cases, complete conversion of **2** into **3** + R^2NH_2 occurred in less than 10 h at 50 °C and no further transformation of the quinolinium salts was observed.

The instability of all these DHQS derived from ketones contrasts with the great stability of their 1,2-dihydroquinazolinium-4-yl palladium homologues,[16] or with that of DHQS derived from alde-

Table 1
Friedländer–Borsche synthesis of quinolinium salts **3** mediated by 1,2-dihydroquinazolinium salts in acidic medium



Entry	R^1, R^2 (1)	R^3, R^4	DHQS (2)	Quinolinium salt (3)
1	H, Xy (1a)	H, Me	2a	3a
2	H, Cy (1b)	H, Me	2b	3a
				3a
3	H, Tol (1c)	H, Me	2c1	 **3c2**
				+
4	H, Tol (1c)	H, Et	2c2	 **3c2'**
5	H, Tol (1c)	H, Ph	2c3	3c3
6	H, Tol (1c)	Me, Et	2c4	3c4
7	H, Tol (1c)	H, H	2c5	[a]
8	Me, Cy (1d)	H, Me	2d1	3d1
9	Me, Cy (1d)	H, *i*-Pr	2d2	3d2
				3d3
10	Me, Cy (1d)	Me, Et	2d3	 **3d4**
				+
11	Me, Cy (1d)	H, Bz	2d4	 **3d4'**
12	Me, Cy (1d)	H, CH=CH_2	2d5	[b]

[a] The DHQS is stable after heating at 65 °C.
[b] The DHQS is stable at room temperature but decomposes at T >45 °C to give a mixture of unknown compounds. Xy = xylyl, Cy = cyclohexyl, Tol = 4-tolyl, *i*-Pr = isopropyl. The counterion of cationic species is TfO^-.