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

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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

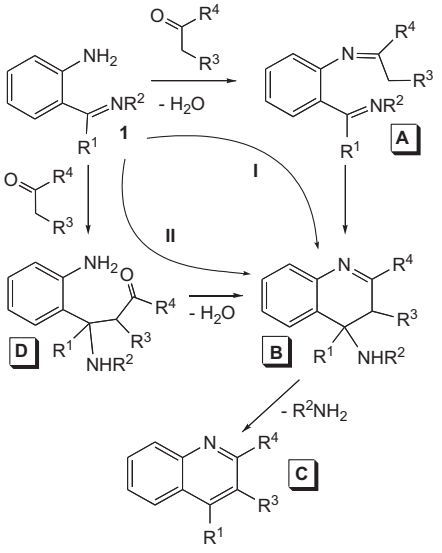
Spontaneously or under various heating conditions, 2-alkyl- or 2-aryl-(iminoalkyl)benzenamines react with ketones and triflic acid (1:1:1) to give quinolinium salts. When working under milder thermal conditions, intermediate 1,2-dihydroquinazolinium derivatives can be isolated or detected in solution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

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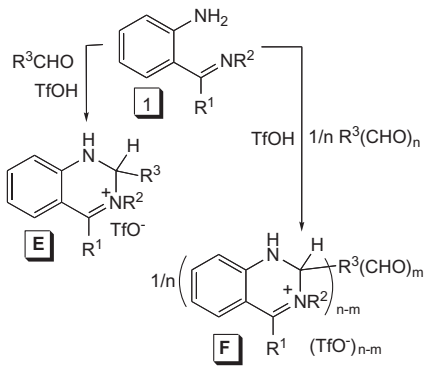
doi:10.1016/j.tetlet.2011.09.053



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]

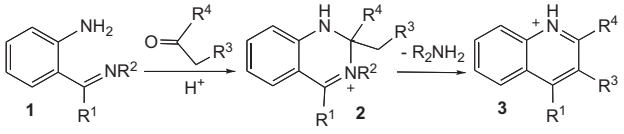
In this paper, we study the reaction between 2-amino substituted arylimines, various ketones bearing at least one α-methylene group (MeC(O)R (R = Me, Et, *i*-Pr, Bz, Ph) or $Et_2C(O)$) and TfOH (Table 1). At low temperature, DHQS form but, spontaneously or after soft heating, they convert into quinolinium 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.

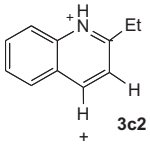
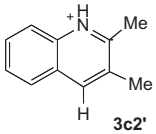
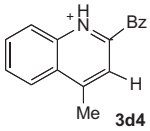
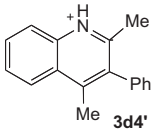
2. Results and discussion

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.

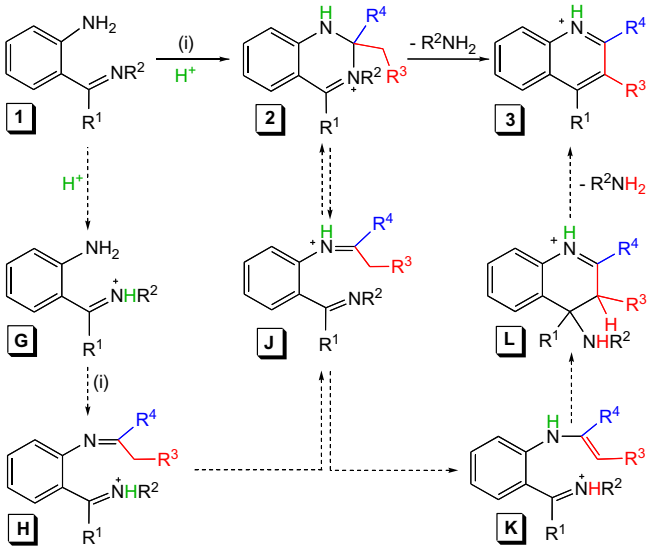
The instability of all these DHQS derived from ketones contrasts with the great stability of their 1,2-dihydroquinazolinium-4-yl palladium homologues,[16] or with that of DHQS derived from alde-

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^-.



Scheme 3. Proposed reaction pathway for the synthesis of 1,2-dihydroquinazolinium salts **2** and their decomposition into quinolinium salts **3**. Dashed arrows are proposed reaction transformations and solid arrows, observed reactions. The counterion of cationic species is TfO^-. (i) = $R^3CH_2C(O)R^4$.

hydes (**E** and **F**, Scheme 2), including those derived from acetaldehyde and therefore having an α-methylene group. In fact DHQS **E** with R^1 = Me, R^2 = cyclohexyl = Cy or CH(Me)Ph, R^3 = Me (Scheme 2)[15] or that with R^1 = H, R^2 = Tol, R^3 = R^4 = H (**2c5**, entry 7) were recovered quantitatively after heating them at 65 °C.

Trying to account for these observations, we propose in Scheme 3 a plausible reaction pathway for the syntheses of quinolinium salts **3** from the reactions of 2-(amino)benzenimines (**1**), the appropriate ketone, and TfOH (a Friedländer–Borsche synthesis of quinolinium salts in an acidic medium). The DHQS **2** would likely form through the reaction pathway **1** → **G** → **H** → **J** → **2** as confirmed by the isolation of some intermediates (e.g., of type **G**)[15] and a DFT study (to be published). We propose that the decomposition of **2** into quinolinium salts **3** occurs through the reaction pathway **2** → **J** → **K** → **L** → **3**. The **2** → **J** transformation, which seems to be the key step, would be facilitated by CH_2R^3 and R^4 having electron donor ability (+I or +M effect). This would favour the cleavage of the C(2)–N(3) bond displacing the equilibrium towards **J**. From here, the positive charge on N(1) in **J** would increase the acidic character of the α-methylene protons facilitating the protonation of the NR^2 nitrogen (**K**) and the attack of the resulting methylene carbon to the partly positive iminium carbon producing a new heterocycle (**L**) with an exocyclic NHR^2 fragment. Abstraction of one proton of the α-methylene group by the NHR^2 fragment in **L** would give quinolinium salt **3**, with concomitant loss of R^2NH_2. This decomposition way of **2** through **J**, is related to pathway **I** proposed for the Friedländer–Borsche reaction (Scheme 1) in which **A** and **B** protonated at N(1) correspond to intermediates **J** and **L** in Scheme 3.

The successful synthesis of **3c3** from **1c**, acetophenone and TfOH (entry 5) suggests that the π donor ability (+M effect) of the Ph group in **2c3**, likely enhanced by the positive charge at N(3), is crucial in this reaction given that the homologous reaction between **1c**, acetaldehyde and TfOH, produces the stable DHQS 2-methyl-3-tolyl-1,2-dihydroquinazolinium triflate (**2c5**) (entry 7) and not even traces of the corresponding quinolinum salt were detected. In view of the similar electronic effects of phenyl and vinyl groups, the failed attempt to decompose **2d5** into a quinolinium salt could be attributed to steric reasons or to alternative decomposition pathways competing with that leading to the quinoline.

The influence of the R^1 and R^2 substituents seems not to be as important as that of CH_2R^3 or R^4. For instance, although the electron withdrawing ability of both R^1 and R^2 would favour the **K** → **L** step, their actual influence in the process seems to be scarce in view of the stability of **2a** (R^1 = H, R^2 = Xy) being greater than that of **2b** (R^1 = H, R^2 = Cy) and much greater than that of **2d1** (R^1 = Me, R^2 = Cy).

In the reactions where CH_2R^3 = R^4 or when only one of these substituents bears an α-methylene group, only one quinolinium salt is obtained. However, when CH_2R^3 is different from R^4 and both bear an α-methylene group, both substituents are available for deprotonation by the NR^2 group in **J** giving rise to two isomeric quinolinium salts. This is the case of the reaction of **1c** with TfOH in MeC(O)Et producing a mixture containing $TolNH_2$ (Tol = 4-Tolyl), **3c2** and **3c2′** in a 2:1:1 molar ratio (entry 4). Recrystallization of the isolated mixture allowed us to enrich it in one of the isomers (**3c2**:**3c2′** = 7:1, see Experimental Section) thus facilitating the NMR assignments. When the reaction was repeated at room temperature for 30 min and Et_2O was added to the concentrated reaction mixture, an orange solid insoluble in $CDCl_3$ was obtained. In its ^1H NMR spectrum in CD_3CN, we detected some of the resonances that could be assigned to the intermediate DHQS **2c2**. Similarly, the reaction of **1d** with MeC(O)Bz and TfOH produced a mixture containing $CyNH_2$, **3d4** and **3d4′** in 10:7:3 molar ratio (entry 11). The easier deprotonation of the Me group compared to Bz could be attributed to steric reasons or, again, to the phenyl group acting as a net electron releasing group.

In summary, all the DHQS of type **2** shown in Table 1 decomposed in solution, spontaneously or after soft heating to give the corresponding quinolinium derivatives **3** (with the exception of the DHQS obtained from MVK). This contrasts with the great stability of their 1,2-dihydroquinazolinium-4-yl palladium homologues[16] and the DHQS derived from aldehydes.[15]

3. Conclusion

When working in an acidic medium, DHQS can be intermediates in the Friedländer–Borsche synthesis of quinolinium salts involving 2-(aminoaryl)imines and ketones containing an α-methyl or α-methylene functionality.

4. Experimental section

The syntheses of compounds **2a, 2b** and **2c1** were reported by us.[15] The following DHQS salts were identified in the reaction mixture by some of their resonances (others were obscured by the resonances corresponding to other components in the mixture):Compound **2c1** (400 MHz, $CDCl_3$, 25 °C, TMS) δ 1.75 (s, 6H, Me_2C), 2.46 (s, 3H, Me^{Tol}), 6.85 ("dt", 1H, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 0.8 Hz), 7.14 (m, 2H), 7.23–7.44 (m obscured by the resonances of other components, 4H, *ortho*-Tol + *meta*-Tol), 7.58 (ddd, 1H, $^3J_{HH}$ = 8.4 Hz, $^3J_{HH}$ = 7.2 Hz, $^4J_{HH}$ = 1.6 Hz), 8.07 (s, 1H, H4), 8.34 (s br, 1H, NH). Compound **2c2**: ^1H NMR (200 MHz, CD_3CN, 25 °C, TMS): 0.91 (t, 3H, CH_3^{Et}, $^3J_{HH}$ = 7.4 Hz), 1.93 (s, 3H, Me), 2.41 (q, 2H, CH_2^{Et}, $^3J_{HH}$ = 7.2 Hz). Compound **2c3**: ^1H NMR (400 MHz, $CDCl_3$, 45 °C, TMS): δ 2.28 (s, 3H, Me^{Tol}), 2.33 (s, 3H, Me), 8.86 (s, 1H, *CH*=NTol). Compound **2c4**: ^1H NMR (400 MHz, $CDCl_3$, 10 °C, TMS): δ 2.37 (s, 3H, Me), 7.92 (d, 1H, $^3J_{HH}$ = 8.7 Hz, Ar), 8.67 (s, 1H, CH=NTol). Compound **2d1**: ^1H NMR (200 MHz, $CDCl_3$, −30 °C, TMS): δ 1.75 (s, CMe_2), 2.92 (s, *Me*C=N), 4.05 (m, CH, Cy). Compound **2d2**: ^1H NMR (600 MHz, $CDCl_3$, −10 °C, TMS): δ 1.21–2.18 (several m, 10H, Cy), 2.72 (s, 3H, MeC=N), 3.68 (m, CH^{Cy}), 6.80 (m, 2H, $^3J_{HH}$ = 7.8 Hz, Ar), 6.93 (d, 1H, $^3J_{HH}$ = 7.8 Hz). Compound **2d3**: (^1H NMR (600 MHz, $CDCl_3$, −10 °C, TMS): δ 2.66 (s, 3H, MeC=N), 3.66 (m, CH^{Cy}) 6.92 (d, 1H, $^3J_{HH}$ = 7.8 Hz, Ar), 7.31 (t, 1H, $^3J_{HH}$ = 7.6 Hz, Ar). Compound **2d4** at ^1H NMR (300 MHz,

$CDCl_3$, 55 °C, TMS): δ 1.21–2.16 (several m, 10H, Cy), 2.54 (s, 3H, MeC=N), 3.62 (m, CH^{Cy}), 6.63 (d, 1H, $^3J_{HH}$ = 8.1 Hz, Ar). We describe below the synthesis and characterization of the isolated DHQS **2c5** and **2d5.**

Chloride salts of the quinolinium cations present in **3a**,[18] **3c2**,[18] **3c2′**[19] and **3d1**[20] have been reported. The NMR data of **3a**, **3c2**,[18] are almost identical to those in our triflates (see below), while the NMR data of the chlorides of **3c2′**,[19] and **3d1**[20] were not reported. The quinolinium salt **3c3**[18] has been identified by its previously reported ^{1}H NMR spectrum. The remaining quinolinium salts (**3c4**, **3d2**, **3d4** and **3d4′**) were characterized upon treating a $CDCl_3$ solution with one drop of concentrated aqueous NaOH to afford the corresponding quinoline (**3** + NaOH → **Q3** + NaTfO). The mixture was briefly shaken until the yellow colour vanished and filtered through a short column of anhydrous $MgSO_4$. The quinolines were identified by their previously reported ^{1}H NMR (**Q3c4**,[21] **Q3d2**,[22] **Q3d4**)[23] or UV–Vis (**Q3d4′**)[24] spectra. As the quinolinium salt **3d3** and its corresponding quinoline were unknown, we report below its synthesis and characterization.

4.1. Synthesis of 2c5 from 1c, acetaldehyde and TfOH

To a solution of **1c** (150 mg, 0.71 mmol) in $CHCl_3$ (5 mL, 0 °C) were successively added acetaldehyde (70 μL, 1.24 mmol) and TfOH (70 μL, 0.80 mmol) and the reaction mixture was stirred at room temperature for 30 min. The resulting orange solution was concentrated under vacuum to dryness to give an oily material which was dissolved in CH_2Cl_2 (5 mL), filtered through a short pad of anhydrous $MgSO_4$, and concentrated to dryness. The residue was washed three times with a 1:20 mixture of CH_2Cl_2 and Et_2O (21 mL), and vacuum dried to give **2c5** as a dark orange solid. Yield: 164.9 mg, 0.4268 mmol, 60%. Mp: 69 °C. HRMS (ESI) *m*/*z* calcd for $C_{16}H_{17}N_2$ $[M]^+$, 237.1386; found 237.1388. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ 1.58 (d, 2H, $^3J_{HH}$ = 6.4 Hz, *Me*CH), 2.39 (s, 3H, Me^{Tol}), 6.08 (q, 1H, $^3J_{HH}$ = 6.0 Hz, MeC*H*), 6.84 (“dt”, 1H, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 0.8 Hz), 6.99 (d, 1H, $^3J_{HH}$ = 8.0 Hz), 7.33 (d, 2H, $^3J_{HH}$ = 8.4 Hz, Tol), 7.44 (d, 2H, $^3J_{HH}$ = 8.4 Hz, Tol), 7.52 (ddd, 1H, $^3J_{HH}$ = 8.4 Hz, $^3J_{HH}$ = 6.8 Hz, $^4J_{HH}$ = 1.2 Hz), (dd overlapped v br s, 1H each, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 1.2 Hz), 8.64 (s, 1H, CH=N). IR (Nujol, cm^{-1}): *ν*(NH) 3272, *ν*(C=N + C=C) 1630, 1601, 1566.

4.2. Synthesis of 2d5 from 1d, MVK and TfOH

To a solution of **1d** (150 mg, 0.69 mmol) in CH_2Cl_2 (5 mL, 0 °C) were successively added MVK (60 μL, 0.73 mmol) and TfOH (70 μL, 0.80 mmol). After 45 min of stirring at 0 °C, the yellow solution was concentrated under vacuum to dryness to give an oily residue which was converted into a suspension by stirring it with a CH_2Cl_2/Et_2O mixture (1:15, 16 mL, 0 °C, 20 min). The suspension was filtered under a nitrogen stream, and the yellow solid collected, **2d5**, was dried by suction. Yield: 187.3 mg, 0.4476 mmol, 65%. Mp: 133 °C. HRMS (ESI) *m*/*z* calcd for $C_{18}H_{25}N_2$ $[M]^+$, 269.2012; found 269.2015. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ 1.11–1.92 (several m, 10H, CH_2Cy), 2.79 (s, 3H, Me), 2.81 (s, 3H, Me), 3.99 (m, 1H, CHCy), 6.78–6.83 (m, 2H), 6.88 (m, 1H), 6.94 (dd, 1H, $^3J_{HH}$ = 8.1 Hz, $^4J_{HH}$ = 1.5 Hz), 7.31 (m, 2H), 7.38 (dd, 1H, $^3J_{HH}$ = 8.5 Hz, $^4J_{HH}$ = 1.5 Hz). IR (Nujol, cm^{-1}): *ν*(NH) 3270, *ν*(C=N + C=C) 1633, 1615, 1567.

4.3. Synthesis of 3a from 1c, acetone and TfOH

To a solution of **1c** (90 mg, 0.43 mmol) in acetone (20 mL) was added TfOH (40 μL, 0.46 mmol). The reaction mixture was stirred at room temperature for 1 h and then refluxed for 6 h. The resulting orange solution was concentrated under vacuum (1 mL) and Et_2O was added (20 mL, 0 °C). A suspension formed, which was stirred at 0 °C for 15 min and filtered. The solid collected was washed with Et_2O (3 × 5 mL, 0 °C) and dried under a N_2 stream to give **3a** as a light brown solid. Yield: 82 mg, 0.28 mmol, 65%. Mp: 105 °C. HRMS (ESI) *m*/*z* calcd for $C_{10}H_{10}N$ $[M]^+$, 144.0808; found 144.0812. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ 3.11 (s, 3H, Me), 7.78 (d, 1H, $^3J_{HH}$ = 8.7 Hz), 7.87 (t, 1H, $^3J_{HH}$ = 7.6 Hz), 8.05 (t, 1H, $^3J_{HH}$ = 7.8 Hz), 8.14 (d, 1H, $^3J_{HH}$ = 8.4 Hz), 8.46 (d, 1H, $^3J_{HH}$ = 8.4 Hz), 8.83 (d, 1H, $^3J_{HH}$ = 8.7 Hz). $^{13}C\{^1H\}$ NMR (100.8 MHz, $CDCl_3$, 25 °C, TMS): δ 20.8, 120.3 (q, $^1J_{CF}$ = 319 Hz), 120.6, 123.2, 127.0, 128.7, 129.8, 135.1, 137.8, 146.4, 157.6. IR (Nujol, cm^{-1}): *ν*(NH) 3302, *ν*(C=N + C=C) 1653, 1607, 1544.

Alternatively, **3a** formed quantitatively, along with the equimolar amount of $XyNH_2$ or $CyNH_2$, when a solution of **2a** or **2b** in $CDCl_3$ was heated for 6 h at 45 or 60 °C, respectively, as shown by ^{1}H NMR.

4.4. Synthesis of 3c2 + 3c2′ from 1c, MVK and TfOH

To a solution of **1c** (150 mg, 0.71 mmol) in methyl ethyl ketone (20 mL) was added TfOH (65 μL, 0.74 mmol). The reaction mixture was stirred at room temperature for 1 h and then heated at 80 °C for 24 h. The reaction mixture was concentrated under vacuum to dryness to give an oily residue, which was shown by ^{1}H NMR to contain only **3c2**, **3c2′** and $TolNH_2$, in a 1:1:2 molar ratio. The reaction crude was washed with a mixture of CH_2Cl_2/n-pentane (1:20, 21 mL) and vacuum dried for 1 h to give a pale brown solid consisting of a 1:1 mixture of isomers **3c2** and **3c2′**. Yield: 147 mg, 0.48 mmol, 67%. HRMS (ESI) *m*/*z* calcd for $C_{11}H_{12}N$ $[M]^+$, 158.0964; found 158.0966. The isolated 1:1 mixture of isomers was enriched in **3c2′** (**3c2′**:**3c2** = 7:1) by recrystallizing it twice from CH_2Cl_2/Et_2O (1:20, 2 × 21 mL, 0 °C). Yield: 93 mg, 0.30 mmol, 42%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): **3c2**: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ 1.52 (t, 3H, Me, $^3J_{HH}$ = 7.8 Hz, Me), 3.39 (q, 2H, CH_2, $^3J_{HH}$ = 7.8 Hz), 7.79–7.88 (t + d obscured by the resonances of the **3c2′** isomer, 2H), 8.05 (t obscured by the resonances of **3c2′**, 2H), 8.13 (d, 1H, $^3J_{HH}$ = 8.4 Hz), 8.52 (d, 1H, $^3J_{HH}$ = 8.7 Hz), 8.85 (d, 1H, $^3J_{HH}$ = 8.7 Hz). $^{13}C\{^1H\}$ NMR (100.8 MHz, $CDCl_3$, 25 °C, TMS): δ 13.4, 27.9, 120.3 (q, $^1J_{CF}$ = 319 Hz), 121.0, 121.6, 127.2, 128.5, 129.7, 135.2, 138.0, 146.5, 162.6. Compound **3c2′**: δ 2.63 (s, 3H, Me), 3.03 (s, 3H, Me), 7.79–7.88 (various m obscured by the resonances of the **3c2** isomer, 1H), 7.96 (“dt”, 1H, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ = 1.2), 8.05 (d, obscured by the resonances of **3c2**, 1H), 8.41 (d, 1H, $^3J_{HH}$ = 8.4 Hz), 8.62 (s, 1H). $^{13}C\{^1H\}$ NMR (100.8 MHz, $CDCl_3$, 25 °C, TMS): δ 18.5, 19.3, 120.3 (q, $^1J_{CF}$ = 319 Hz), 120.6, 127.3, 127.7, 129.8, 132.0, 134.0, 136.7, 144.9, 157.4.

4.5. Synthesis of 3d1 from 1d, acetone and TfOH

To a solution of **1d** (90 mg, 0.42 mmol) in $CHCl_3$ (5 mL) were successively added acetone (30 μL, 0.43 mmol) and TfOH (38 μL, 0.44 mmol). The reaction mixture was heated to 55 °C for 1 h. The resulting orange solution was filtered through a short pad of Celite, concentrated under vacuum (1 mL) and a mixture Et_2O/*n*-pentane (1:2, 30 mL, 0 °C) was added. The suspension was filtered and the solid collected was dried by suction to give **3d1** as a pale yellow solid. Yield: 94.6 mg, 0.31 mmol, 71%. Mp: 151 °C. HRMS (ESI) *m*/*z* calcd for $C_{11}H_{12}N$ $[M]^+$, 158.0964; found 158.0958. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ 2.96 (s, 3H, Me), 3.04 (s, 3H, Me), 7.58 (s, 1H, CH=C), 7.87 (t, 1H, $^3J_{HH}$ = 8.0 Hz), 8.02 (“dt”, 1H, $^3J_{HH}$ = 8.2 Hz, $^3J_{HH}$ = 8.2 Hz, $^4J_{HH}$ = 1.2 Hz), 8.19 (d, 1H, $^3J_{HH}$ = 8.8 Hz), 8.44 (d, 1H $^3J_{HH}$ = 8.4 Hz), 15.17, (v br s, 1H, NH). $^{13}C\{^1H\}$ NMR (100.8 MHz, $CDCl_3$, 25 °C, TMS): δ 19.9, 20.6, 120.3 (q, $^1J_{CF}$ = 320 Hz), 121.6, 123.6, 124.7, 126.6, 129.5, 134.7, 137.5, 156.3, 157.3. IR (Nujol, cm^{-1}): *ν*(NH) 3303, *ν*(C=N + C=C) 1651, 1603, 1525.

4.6. Synthesis of 3d3 from 1d, $Et_2C(O)$ and TfOH

To a solution of **1d** (25 mg, 0.1155 mmol) in $CHCl_3$ (0.5 mL) were successively added $Et_2C(O)$ (13 μL, 0.1229 mmol) and TfOH (12 μL, 0.1375 mmol). The reaction mixture was heated to 55 °C for 10 h. The resulting yellow solution was filtered through a short pad of Celite and Et_2O (15 mL, 0 °C) was added. The resulting suspension was filtered and the solid collected was dried by suction to give **3d3** as a yellow solid. Yield: 27.1 mg, 0.0808 mmol, 70%. Mp: 103 °C. HRMS (ESI) *m*/*z* calcd for $C_{13}H_{16}N$ $[M]^+$, 186.1277; found 186.1276. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ 1.42 (t, 3H, $^3J_{HH}$ = 7.6 Hz, Me^{Et}), 2.54 (s, 3H, Me), 2.81 (s, 3H, Me), 3.27 (q, 2H, CH_2^{Et}), 7.73 ("dt", 1H, $^3J_{HH}$ = 8.2 Hz, $^4J_{HH}$ = 1.2 Hz), 7.86 ("dt", 1H, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ = 1.2 Hz), 8.14 (d, 1H, $^3J_{HH}$ = 8.4 Hz), 8.34 (d, 1H, $^3J_{HH}$ = 8.4 Hz); NH resonance not observed. IR (Nujol, cm^{-1}): ν(NH) 3354, ν(C=N + C=C) 1637, 1611, 1535.

4.7. ^{1}H NMR resonances for the unreported quinolinium salts 3c4, 3d2, 3d4 and 3d4′

Compound **3c4**: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ 1.48 (t, 3H, $^3J_{HH}$ = 7.6 Hz, Me^{Et}), 2.69 (s, 3H, Me), 3.36 (q, 2H, $^3J_{HH}$ = 7.6 Hz, CH_2^{Et}), 7.82 (t, 1H, $^3J_{HH}$ = 8.4 Hz), 8.00 (m, 2H), 8.49 (d, 1H, $^3J_{HH}$ = 8.8 Hz), 8.62 (s, 1H); the NH resonance was not observed. Compound **3d2**: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ 1.49 (s, 6H, $^3J_{HH}$ = 6.8 Hz, $Me^{i\text{-}Pr}$), 2.93 (d, 3H, $^3J_{HH}$ = 0.8 Hz, Me), 3.66 (sept, 1H, $^3J_{HH}$ = 6.8 Hz, $CH^{i\text{-}Pr}$), 7.54 (d, 1H, $^3J_{HH}$ = 0.8 Hz), 7.78 ("dt", 1H, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 1.2 Hz), 7.97 ("dt", 1H, $^3J_{HH}$ = 8.2 Hz, $^4J_{HH}$ = 1.2 Hz), 8.14 (dd, 1H, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 0.8 Hz), 8.14 (d, 1H, $^3J_{HH}$ = 8.4 Hz); the NH resonance was not observed. Compounds **3d4** + **3d4′** (1:0.4): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS), δ 2.59 (s, 3H, Me), 2.67 (s, 3H, Me), 2.71 (s, 3H, Me), 4.45 (s, 2H, CH_2), 7.18–7.35 (m, 6H, Ph + CH), 7.52–7.57 (m, 3H, Ph), 7.69 (dd, 2H, $^3J_{HH}$ = 8.2 Hz, $^4J_{HH}$ = 1.2 Hz, Ph), 7.79 (ddd, 1H, $^3J_{HH}$ = 8.0 Hz, $^3J_{HH}$ = 6.8 Hz, $^4J_{HH}$ = 0.8 Hz), 7.85 (ddd, 1H, $^3J_{HH}$ = 8.4 Hz, $^3J_{HH}$ = 6.8 Hz, $^4J_{HH}$ = 1.2 Hz), 7.95 (ddd, 1H, $^3J_{HH}$ = 8.4 Hz, $^3J_{HH}$ = 7.2 Hz, $^4J_{HH}$ = 1.2 Hz), 8.03 (d, 1H, $^3J_{HH}$ = 8.4 Hz), 8.17 (dd, 1H, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 0.4 Hz), 8.31 (d, 1H, $^3J_{HH}$ = 8.4 Hz), 8.41 (d, 1H, $^3J_{HH}$ = 8.4 Hz); the NH resonance was not observed.

Acknowledgments

We thank Ministerio de Educación y Ciencia (MEC), FEDER (CTQ2007-60808/BQU) and Fundación Séneca (04539/GERM/06) for financial support and A.J.M.M. to MEC for a FPU grant.

References and notes

1. Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 166.
2. Palimkar, S. S.; Siddiqui, S. A.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V. *J. Org. Chem.* **2003**, *68*, 9371.
3. Jyothish, K.; Avirah, R. R.; Ramaiah, D. *Org. Lett.* **2006**, *8*, 111.
4. Ebenso, E. E.; Obot, I. B.; Murulana, L. C. *Int. J. Electrochem. Sci.* **2010**, *5*, 1574.
5. (a) Kozlov, N. G.; Gusak, K. N.; Kadutskii, A. P. *Chem. Heterocycl. Compd.* **2010**, *46*, 505; (b) Patteux, C.; Levacher, V.; Dupas, G. *Org. Lett* **2003**, *5*, 3061; (c) McNaughton, B. R.; Miller, B. L. *Org. Lett.* **2003**, *5*, 4257; (d) Selvam, K.; Swaminathan, M. *Tetrahedron Lett.* **2010**, 4911; (e) Martínez, R.; Ramón, D. J.; Yus, M. *J. Org. Chem.* **2008**, *73*, 9778.
6. Jiang, B.; Dong, J. J.; Jin, Y.; Du, X.-L.; Xu, M. *Eur. J. Org. Chem.* **2008**, 2693.
7. Marco-Contelles, J.; Pérez-Mayoral, E.; Abdelouahid, S.; Carreiras, M. C.; Soriano, E. *Chem. Rev.* **2009**, *109*, 2652.
8. Muchowski, J. M.; Maddox, M. L. *Can. J. Chem.* **2004**, *82*, 461; Yang, D.; Jiang, K.; Li, J.; Xu, F. *Tetrahedron* **2007**, *63*, 7654.
9. Sridharan, V.; Ribelles, P.; Ramos, M. T.; Menéndez, C. J. *J. Org. Chem.* **2009**, *74*, 5715.
10. Higashino, T.; Ito, H.; Hayashi, E. *Chem. Pharm. Bull.* **1972**, *20*, 1544.
11. Higashino, T.; Nagano, Y.; Hayashi, E. *Chem. Pharm. Bull.* **1975**, *23*, 746.
12. Higashino, T.; Suzuki, K.; Hayashi, E. *Chem. Pharm. Bull.* **1978**, *26*, 3485.
13. Miyashita, A.; Taido, N.; Sato, S.; Yamamoto, K.; Ishida, H.; Higashino, T. *Chem. Pharm. Bull.* **1991**, *39*, 282.
14. Gromov, S. P.; Razinkin, M. A.; Drach, V. S.; Sergeev, S. A. *Russ. Chem. Bull.* **1998**, *47*, 1179.
15. Vicente, J.; Chicote, M. T.; Martínez-Martínez, A. J.; Bautista, D.; Jones, P. G. *Org. Biomol. Chem.* **2011**, *9*, 2279.
16. Vicente, J.; Chicote, M. T.; Martínez-Martínez, A. J.; Bautista, D. *Organometallics* **2009**, *28*, 5915.
17. Vicente, J.; Chicote, M. T.; Martínez-Martínez, A. J.; Bautista, D. *Organometallics* **2011**, 2425.
18. Tadaoka, H.; Cartigny, D.; Nagano, T.; Gosavi, T.; Ayad, T.; Genêt, J.-P.; Ohshima, T.; Ratovelomanana-Vidal, V.; Mashima, K. *Chem. Eur. J.* **2009**, *15*, 9990.
19. Gagan, J. M. F.; Lloyd, D. *Chem. Commun.* **1967**, 1043.
20. Campbell, K. N.; Schaffner, I. J. *J. Am. Chem. Soc.* **1945**, *67*, 86.
21. Martínez, R.; Ramón, D. J.; Yus, M. *Tetrahedron* **2006**, *62*, 8988.
22. Molander, G. A.; Colombel, V.; Braz, V. A. *Org. Lett.* **2011**, *13*, 1852.
23. Brown, T. M.; Cooksey, C. J.; Dronsfield, A. T.; Wilkinson, A. S. *Appl. Organomet. Chem.* **1996**, *10*, 415.
24. Kempter, G.; Möbius, G. *J. Prak. Chem.* **1966**, *34*, 298.