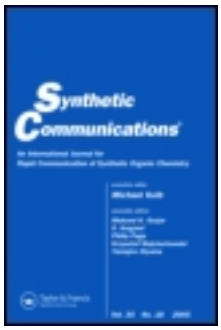

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Frédéric Lassagne [a], Floris Chevallier [a] & Florence Mongin [a]

[a] Institut des Sciences Chimiques de Rennes, Equipe Chimie et Photonique Moléculaires, UMR 6226 CNRS-Université de Rennes 1, 35042 Rennes, France

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Saccharin as an Organocatalyst for Quinoxalines and Pyrido[2,3-*b*]Pyrazines Synthesis

Frédéric Lassagne[1], Floris Chevallier[1], Florence Mongin[1]

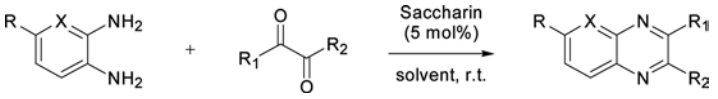
[1]Institut des Sciences Chimiques de Rennes, Equipe Chimie et Photonique Moléculaires, UMR 6226 CNRS-Université de Rennes 1, 35042 Rennes, France

Address correspondence to Frédéric Lassagne, Chimie et Photonique Moléculaires, UMR 6226 CNRS-Université de Rennes 1, Bâtiment 10A, Case 1003, Campus Scientifique de Beaulieu, 35042 Rennes, France E-mail: frederic.lassagne@univ-rennes1.fr

Abstract

A room temperature procedure using saccharin as catalyst has been described for the cyclocondensation of different 1,2-arylenediamines with various 1,2-dicarbonyl compounds, yielding either quinoxalines or pyrido[2,3-b]pyrazines. The reactions proceed in very short reaction times in methanol, and the target heterocycles are isolated in quantitative yields after addition of water, filtration and drying. Substituted pyrido[2,3-b]pyrazines can also be reached regioselectively by reacting α-ketoaldehydes with 2,3-diaminopyridine.

[Supplementary materials are available for this article. Go to the publisher's online edition of *Synthetic Communications*® for the following free supplemental resource(s): Full experimental and spectral details.]



KEYWORDS: Saccharin, Quinoxaline, Pyrido[2,3-*b*]pyrazine, Room temperature reaction

INTRODUCTION

Quinoxalines and pyrido[2,3-*b*]pyrazines are polynitrogen heterocyclic compounds possessing interesting biological activities and used as therapeutics, for example acting as antimicrobial,[1a] antiinflammatory,[2] antimalarial,[3] anticancer,[1b] and antidepressant.[4] Their skeleton is also present in various organic dyes,[5] efficient electroluminescent materials,[6] and organic semiconductors.[7]

The most common synthetic route to reach these scaffolds is the condensation of 1,2-diketones with 1,2-arylenediamines in refluxing ethanol or acetic acid (Scheme 1).[8]

In the last decade many methods were investigated for the preparation of quinoxalines, and different catalysts and solvents were evaluated in order to improve the yield of this cyclocondensation. Among the different systems used for this purpose, we can cite sulfamic acid in methanol,[9] molecular iodine,[10] 2-iodoxybenzoic acid,[11] Montmorillonite K-10,[12] polyaniline sulfate,[13] heteropolyacids,[14] and citric acid,[15] as well as metal precursors such as cerium(IV) ammonium nitrate,[16] Zn/L-proline,[17] nickel nanoparticles,[18] zirconium tetrakis(dodecyl sulfate),[19] gallium(III) triflate,[20] and carbon-doped MoO_3–TiO_2.[21]

Most of the traditional processes suffer from several disadvantages such as pollution, waste treatment, high cost, poor chemical yields, long reaction times, and tedious workup procedures, which limit their use. Despite remarkable efforts, the development of environmentally benign processes and effective method for the synthesis of quinoxalines is still an important challenge. Keeping these aspects in mind, efforts were focused to develop green chemistry for quinoxaline synthesis in both solvent and catalyst respects.

To the best of our knowledge, the acidic form of saccharin (1,1-dioxo-1,2-benzothiazol-3-one, Figure 1), cheaply available benign (edible) chemical, with mild acidity (pK_a 1.9), hydrolytic stability, and absence of volatibility or corrosivity has never been used as a Brønsted acid to catalyse the synthesis of quinoxaline derivatives.

Herein, we wish to report an efficient and facile methodology for high purity quinazoline synthesis using saccharin as a white crystalline solid catalyst at room temperature in different solvents.

RESULTS AND DISCUSSION

In order to determine the optimum conditions, we screened the impact of both solvent and catalyst to substrate ratio on the course of the reaction using as model condensation the reaction between 1,2-phenylenediamine (**1a**) and benzil (**2a**).

Initially, the reaction in the presence of saccharin (10 mol%) was carried out using five polar solvents: methanol, ethanol, isopropanol, water and acetonitrile (Table 1). This

evaluation showed reactions in quantitative yields within 5 min using polar organic solvents methanol and acetonitrile (Table 1, entries 1 and 5) while ethanol and isopropanol gave lower yields under the same reaction conditions (Table 1, entries 2 and 3). In pure water, and even after 1 h reaction time, the compound **3a** was obtained in only 60 % yield (Table 1, entry 4).

Ethyl acetate, dichloromethane, diethyl ether and toluene were also screened and afforded the product in excellent yields. Using dichloromethane, the reaction was finished after 5 min (Table 1, entry 7) whereas 10 min were necessary using ethyl acetate and diethyl ether (Table 1, entries 6 and 8), and 15 min using toluene (Table 1, entry 9).

This study shows that methanol, acetonitrile and dichloromethane are better solvents as regards short reaction times than ethanol, which leads to a lower 90% yield after 5 min reaction time. Compared with acetonitrile and dichloromethane, methanol is a solvent more in accordance with sustainable chemistry, and it was thus considered as the best solvent for further studies.

Different catalyst loadings (1 mol%, 5 mol% and 10 mol% of saccharin) were next tested using methanol as solvent. All these reactions afforded **3a** in a quantitative yield after 5 min reaction time (Table 2, entries 2-4) whereas the reaction proved much slower without catalyst (Table 2, entry 1).

Using 5 mol% of saccharin, the scope of the present method was then further determined by condensation of different 1,2-arylenediamines with various 1,2-dicarbonyl compounds (Table 3).

As regards the 1,2-arylenediamine, extended reaction times for the reaction with benzil (**2a**) were logically noted in the case of π-deficient 2,3-diaminopyridine (**1c**, entry 3, 3 h reaction time) and, above all, using 4-nitro-1,2-phenylenediamine (**1d**, entry 4, 4 h reaction time) against 5 min for 1,2-phenylenediamine (**1a**, entry 1) and its 4-methyl derivative (**1b**, entry 2). Nevertheless, all the products were still obtained in excellent yields.

Concerning the 1,2-dicarbonyl compounds, 1,2-diketones such as pyruvophenone (**2b**, entry 5), 1,2-indanedione (**2c**, entry 6) and 2,3-butanedione (**2d**, entry 7), as well as aryl glyoxal hydrates such as both phenyl and 2-thienyl derivatives (**2e** and **2f**, entries 8 and 9) also reacted with 1,2-phenylenediamine (**1a**) with success in short reaction times.

The reaction between 2, 3-diaminopyridine (**1c**) and 2-thienyl glyoxal hydrate (**2f**) can theoretically lead to two regioisomeric thienyl-substituted pyrido[2,3-*b*]pyrazines. Besides a total conversion under the same reaction conditions, the predominant formation of the regioisomer **3j** (isolated by chromatography over silica gel in 95% yield) was surprisingly noticed (entry 10). The structures of **3j** and **3j'** were unequivocally identified on the basis of NMR experiments. The crude reaction mixture containing **3j** and the other regioisomer **3j'** showed two singlet peaks at 9.26 and 9.45 ppm, respectively

corresponding to their H2 and H3 protons. In addition, there is possible correlation between H2 and Ca in **3j**, and between H3 and Cb (which is more deshielded than Ca) in **3j'** (see Figure 2). The HMBC NMR experiment performed on each compound **3j** and **3j'** showed that the proton at 9.26 ppm correlates with the less deshielded Ca (136.5 ppm, withdrawing effect of only one nitrogen) of **3j** (main product) and that the proton at 9.45 ppm correlates with the more deshielded Cb (150.2 ppm, withdrawing effect of two nitrogens) of **3j'** (minor product). Such a regioselectivity could result from a favoured reaction between the stronger nucleophile site of 2,3-diaminopyridine (**1c**) at its 3 position and the stronger electrophilic site of 2-thienyl glyoxal hydrate (**2f**) which is the aldehyde function. Finally, using aryl glyoxal hydrates as 1,2-dicarbonyl compound led to shorter reaction times than using 1,2-diketones, as evidenced for example by the reaction of 2,3-diaminopyridine (**1c**) with 2-thienyl glyoxal hydrate (**2f**) and benzyl (**2a**) in respectively 15 min (entry 10) and 3 h (entry 3).

In order to strengthen the novelty of present method, we have compared our results with some reported procedures using conventional methods to prepare the compound **3a**. The results are summarized in Table 4.

As we can see, saccharin gave quantitative yields after short reaction times. Furthermore, according to the optimized procedure, we evaluated the reusability of saccharin as follows. To 1,2-phenylenediamine (10 mmol) in methanol (10 mL) were added saccharin (0.5 mmol) and benzil (10 mmol). After 5 min reaction time, the mixture was cooled

using an ice bath, the solid was filtered, and the filtrate was used for the next run with fresh reactants within five cycles without noticeably decreasing catalytic activity.

CONCLUSION

In summary, we have developed a safe and economical process for the catalytic synthesis of quinoxaline and pyrido[2,3-*b*]pyrazine derivatives from 1,2-arylenediamines and 1,2-dicarbonyl compounds at room temperature. The reusability of saccharin, a catalyst easy to handle, its availability and commercial low cost, its environmental acceptability and absence of toxicity, the mild reaction conditions, the simple work-up procedure, and the short reaction times are the strong practical points of the presented method.

EXPERIMENTAL

Column chromatography was performed using silica gel 60 (230–400 mesh). Melting points were measured on a Kofler apparatus and are uncorrected. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance III spectrometer at 300 and 75 MHz, respectively. ^{1}H chemical shifts (δ) are given in ppm relative to the solvent residual peak, and ^{13}C chemical shifts relative to the central peak of the solvent signal.[30] High- resolution mass spectra (HRMS) were recorded on a Bruker micrOTOF Q II instrument. 1,2-Diketones, 1,2-arylenediamines, acetophenone, 2-acetylthiophene, phenyl glyoxal hydrate (**2e**), 1,2-indanedione (**2c**) were purchased from Aldrich and 2-thienyl glyoxal hydrate (**2f**) from Alfa Aesar.

General Procedure For The Quinoxalines And Pyrido[2,3-*B*]Pyrazines Synthesis

To the required 1,2-dicarbonyl compound **2** (10 mmol) in methanol (10 mL) were successively added saccharin (92 mg, 0.5 mmol) and the required 1,2-arylenediamine **1** (10 mmol). The mixture was stirred for the appropriate time at room temperature (reaction monitored by TLC), and poured into water (10 mL). The solid was collected by filtration and dried to afford the product **3**. The isomers **3j** and **3j'** were separated by chromatography over silica gel (CH_2Cl_2-AcOEt 8:2). All products were characterized by ^{1}H NMR, and ^{13}C NMR and were identified by comparison of the spectral data and melting points with those reported in literature (supporting information).

Spectral (^{1}H NMR, and ^{13}C NMR) and HRMS data of new compounds are given.

11*H*-Indeno[1,2-*B*]Quinoxaline (3f)

White solid, mp 160 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 4.06 (s, 2H), 7.47-7.70 (m, 5H), 8.02-8.20 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 36.0, 122.7, 125.8, 128.0, 128.8, 129.0, 129.1, 129.2, 131.1, 138.0, 141.2, 142.0, 143.5, 154.6, 159.4. HRMS (ESI) *m/z* calcd for $C_{15}H_{12}N_2$: 219.0922 $[M+H]^+$; found: 219.0926.

3-(2-Thiophenyl)Pyrido[2,3-*B*]Pyrazine (3j)

Yellow crystals, mp 160 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 7.16 (dd, 1H, J = 3.8 and 5.0), 7.56 (dd, 1H, J = 1.1 and 5.0), 7.59 (dd, 1H, J = 4.2 and 8.3), 7.93 (dd, 1H, J = 1.1 and 3.8), 8.35 (dd, 1H, J = 1.9 and 8.3), 9.07 (dd, 1H, J = 1.9 and 4.2), 9.26 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 124.4, 128.6, 128.7, 131.6, 136.5, 138.1, 141.4, 143.3, 150.3, 150.7, 154.4. HRMS (ESI) *m/z* calcd for $C_{11}H_9N_3S$: 214.0439 $[M+H]^+$; found 214.0440.

2-(2-Thiophenyl)Pyrido[2,3-*B*]Pyrazine (3j')

Pale yellow solid, mp 172 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 7.23 (dd, 1H, J = 3.8 and 5.0), 7.59 (dd, 1H, J = 1.0 and 5.0), 7.71 (dd, 1H, J = 4.2 and 8.4), 7.91 (dd, 1H, J = 1.0 and 3.8), 8.43 (dd, 1H, J = 1.9 and 8.4), 9.08 (dd, 1H, J = 1.9 and 4.2), 9.45 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 125.9, 128.2, 128.9, 131.1, 137.7, 138.4, 141.3, 145.3, 148.7, 150.0, 152.7. HRMS (ESI) *m/z* calcd for $C_{11}H_9N_3S$: 214.0439 $[M+H]^+$; found: 214.0436.

SUPPLEMENTARY MATERIAL

Supporting information: general procedures, characterization data, and ^{1}H and ^{13}C NMR spectra. This material can be found via the "Supplementary Content" section of this article's webpage.

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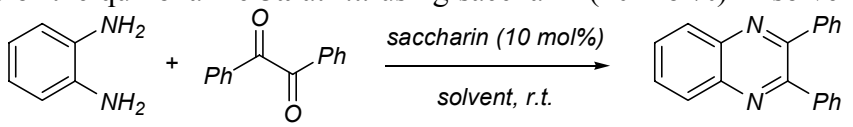
Table 1. Synthesis of the quinoxaline **3a** at r.t. using saccharin (10 mol%) in solvents of different polarities.

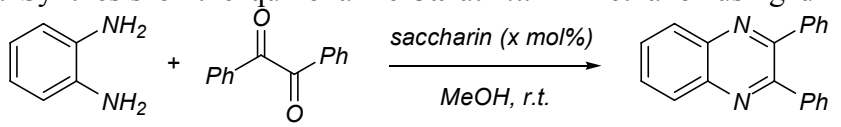


1a **2a** **3a**

Entry	Solvent	Reaction time (min)	Yield[a] (%)
1	Methanol	5	>99
2	Ethanol	5	90
3	Isopropanol	5	85
4	Water	60	60
5	Acetonitrile	5	>99
6	Ethyl acetate	10	97
7	Dichloromethane	5	>99
8	Diethyl ether	10	95
9	Toluene	15	80

[a]Isolated yield.

Table 2. Synthesis of the quinoxaline **3a** at r.t. in methanol using different saccharin loadings.

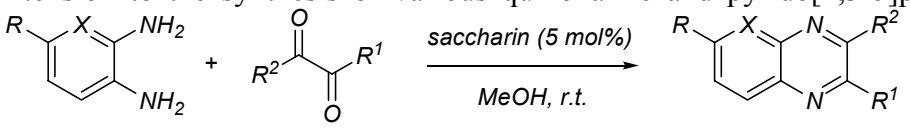


1a **2a** **3a**

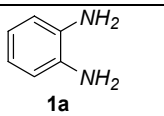
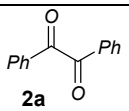
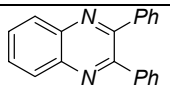
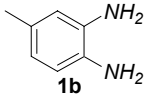
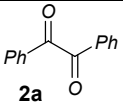
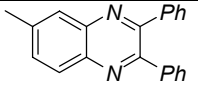
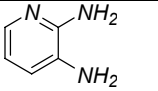
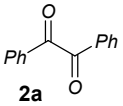
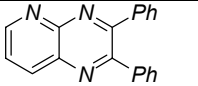
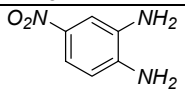
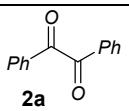
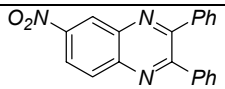
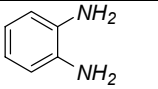
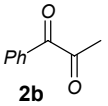
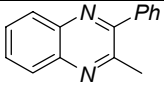
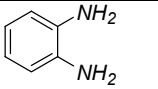
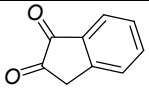
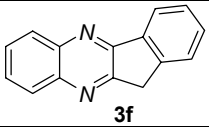
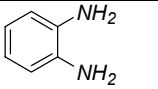
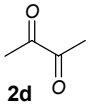
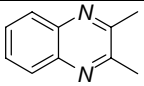
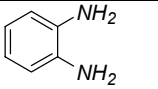
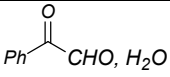
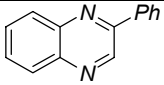
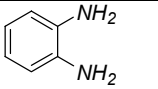
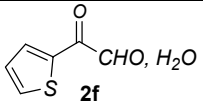
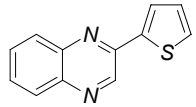
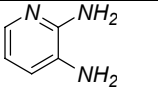
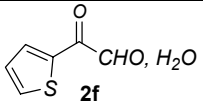
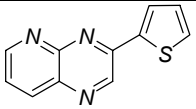
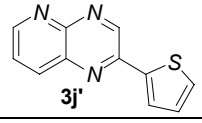
Entry	x (mol%)	Reaction time (min)	Yield[a] (%)
1	0	60	50
2	1	5	>99
3	5	5	>99
4	10	5	>99

[a]Isolated yield.

Table 3. Extension to the synthesis of various quinoxaline and pyrido[2,3-*b*]pyrazine derivatives.



1 **2** **3**

Entry	1,2-Arylenediamine	1,2-Dicarbonyl compound	Product **3**	Reaction time (min)	Yield (%)[a]
1	 **1a**	 **2a**	 **3a**	5	>99
2	 **1b**	 **2a**	 **3b**	5	>99
3	 **1c**	 **2a**	 **3c**	180	95
4	 **1d**	 **2a**	 **3d**	240	96
5	 **1a**	 **2b**	 **3e**	10	97
6	 **1a**	 **2c**	 **3f**	5	92
7	 **1a**	 **2d**	 **3g**	10	92
8	 **1a**	 **2e**	 **3h**	15	>99
9	 **1a**	 **2f**	 **3i**	15	94
10	 **1c**	 **2f**	 **3j**	15	95[b]
			 **3j'**	15	5[b]

[a]Isolated yield.

[b] Regioisomers isolated by chromatography over silica gel (eluent: 80/20 CH_2Cl_2-AcOEt).

Table 4. Conventional quinoxaline (**3a**) preparations using different catalysts/solvents at r.t.

Entry	Catalyst	Mol%	Solvent	Time (min)	Yield	Ref.
1	Cerium(IV) ammonium nitrate	5	H_2O	10	98	[16]
2	Iodine	10	MeCN	5	95	[10]
3	2-Iodoxybenzoic acid	1	AcOH	15	98	[11]
4	Montmorillonite K-10	10	H_2O	150	>99	[12]
5	Zn[(L)-proline]	10	AcOH	5	96	[17]
6	Poly-aniline sulfate salt	5	$Cl(CH_2)_2Cl$	15	92	[13]
7	Sulfamic acid	5	MeOH	5	>99	[9]
8	$CuSO_4$, $5H_2O$	10	MeOH/H_2O	5	97	[22]
9	$H_4SiW_{12}O_{40}$	5	H_2O	60	96	[14]
10	Gallium(III) triflate	5	EtOH	5	>99	[20]
11	APTS/NaPTS	5	H_2O	7	96	[31]
12	Citric acid	3	EtOH	<1	94	[15]
13	Saccharin	1 or 5	MeOH	5	>99	This study

Scheme 1. Most common synthetic route to reach quinoxalines.

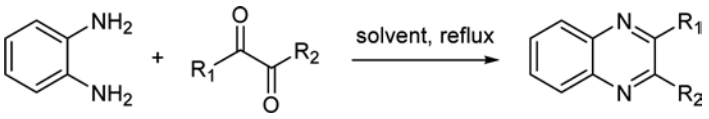


Figure 1. Saccharin as its acidic form.

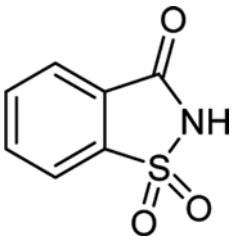
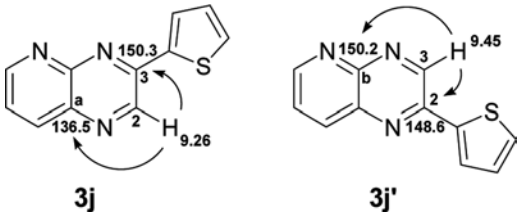


Figure 2. Identification of regioisomers **3j** and **3j'** by NMR HMBC experiment.



3j 3j'