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N-Unsubstituted 2- and 3-thiophenimines†

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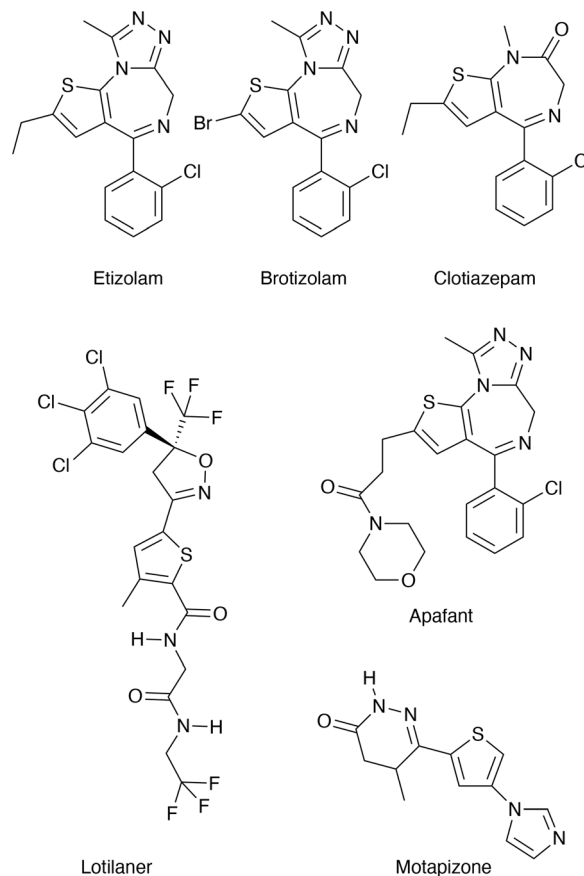
N-Unsubstituted 2-thiophenemethanimine and 3-thiophenemethanimine are the simplest derivatives of a family of imines, the thienyl imines. These two thienyl aldimines and the *C*-methyl derivatives were prepared in a gas solid reaction by dehydrocyanation of the corresponding α -aminonitriles or in the gas phase by a retro-ene reaction from *N*-allyl derivatives, then characterized by IR and NMR spectroscopy at low temperature and used in transimination reactions. From several angles, these compounds in the free or complexed state have been compared to the corresponding recently synthesized furanimines and to other *N*-unsubstituted imines, with the aim of studying the specificity of each of them.

Introduction

The synthesis and spectroscopic characterization of *N*-unsubstituted 2- and 3-furanaldimines have recently been reported.¹ These species are the parent compounds of numerous derivatives, including a significant number of drugs containing the 2-furanimine moiety.^{2–5} For thienylimines also called thiophenimines, the corresponding compounds where the furan moiety has been substituted by a thiophene moiety, biological activity has been found for 2- and 3-derivatives but mainly, for the latter, with a particular type of bicyclic compound (Scheme 1). Thus Etizolam,⁶ brotizolam⁷ and clotiazepam⁸ are thienodiazepines, compounds comparable to benzodiazepines. Apafant acts as a potent, selective inhibitor of the phospholipid mediator platelet-activating factor (PAF).⁹ Examples of 2-thienylimines include lotilaner,¹⁰ an ectoparasiticide (anti-parasitic) medication for the treatment of eyelid inflammation, or motapizone¹¹ for the inhibition of thrombocyte aggregation. The comparison of biological activity between furanimines and thienylimines is limited, since the synthesis of sulphur analogues of cefuroxime axetil or nifuratel, for example, have never been reported, while dantrolene analogues have proved far less effective.¹²

The aim of this article is to prepare hitherto unknown 2- and 3-thiophenemethanimines, which are the parent compounds of many synthesized 2- and 3-thienylimines, to characterize them spectroscopically, to compare these aldimines with

the corresponding *C*-methylated ketimines and complexed thienyl aldimine derivatives, as well as with the corresponding furanimines and *N*-unsubstituted imines, in order to deter-



Scheme 1 Some drugs containing the thiophenimine motif.

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mine whether any of their physicochemical properties are peculiar.¹³

Although often kinetically unstable, the simplest derivative of a family of compounds, such as formaldehyde for aldehydes or ethenamine for enamines, is essential in understanding this group.

Results and discussion

The difficulty of synthesizing N-H imines has already been reported including in the case of ketimines and is essentially associated with the kinetic instability.^{14–18} For the same kinetic instability, species isolation is easier for volatile compounds than for high-boiling compounds. At similar decomposition temperatures, the former can often be re-vaporized, whereas the latter cannot, as their decomposition temperature is lower than their vaporization temperature. As sulphur derivatives of furanimines, for which revaporisation was limited to ketimines that were more stable than aldimines, thienylaldimines – assuming similar kinetic stability – should again be more difficult to revaporize since the boiling point of thiophene (84 °C) is higher than that of furan (31.3 °C).

To synthesize the simpler 2-thiophenemethanimine **1a** and 3-thiophenemethanimine **1b** and the corresponding C-methyl derivatives, the ketimines **1c** and **1d** (Chart 1), dehydrocyanation over KOH powder of the corresponding α -aminonitriles was considered by analogy with the synthesis of many kinetically unstable imines (route A).^{1,14–17} However, due to the difficulty observed in vaporizing this type of precursor as the substituent size increases, retro-ene reactions starting from more volatile and kinetically stable N-allyl derivatives were also investigated (route B) (Scheme 2). Such retro-ene reactions have enabled the synthesis of a wide range of compounds.¹⁹

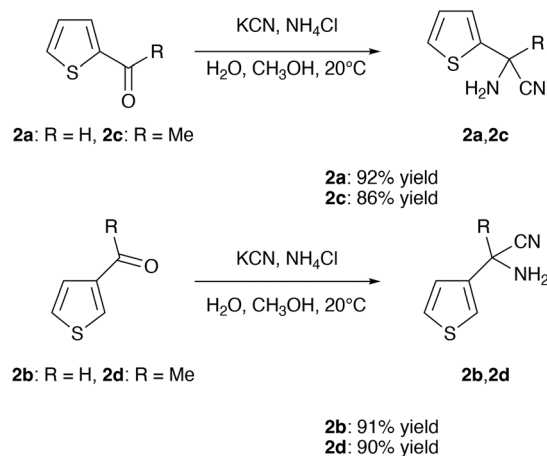
The thiophenyl α -aminonitriles **2a–2d**,^{20,21} potential precursors of imines **1a–1d**, were synthesized in a Strecker reaction

in good yields ranging from 86 to 92%, the C-methyl derivatives requiring a longer reaction time as generally observed for ketones (Scheme 3).¹ They should be stored in the freezer (–20 °C).

On the other hand, N-allylamines **4a–4d** were easy to synthesize, as is generally the case for many secondary N-allylamines.^{22–26} The condensation reaction between thienaldehydes or thienylketones and allylamine, followed by reduction of the imine formed with sodium borohydride as reducing agent, gave the N-allylamines **4a–4d** in yields ranging from 77 to 92% (Scheme 4).²⁵ Such compounds are stable at room temperature.

Using a heat gun, α -aminonitriles **2a–2d** were slowly vaporized in a vacuum line (0.1 mbar) through a reactor half-filled with powdered KOH heated to 90 °C, where they underwent dehydrocyanation.

Ketimines **1c**, **1d** were obtained in 53 (**1c**) and 56% (**1d**) yields, and N-unsubstituted 2-thienylimine **1a** and 3-thienylimine **1b** in only 33 (**1a**) and 38% (**1b**) yields, probably because the precursors partially decompose during vaporization or the aldimines are less stable on hot KOH (Scheme 5). In addition to imines, we observed, by ¹H NMR spectroscopy, the presence



Scheme 3 Synthesis of α -aminonitriles **2a–2d**.

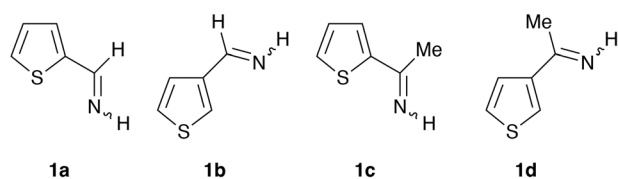
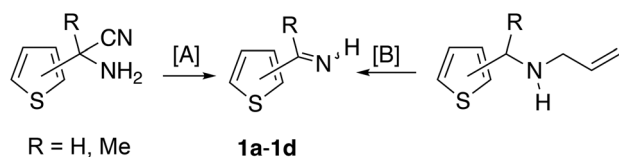
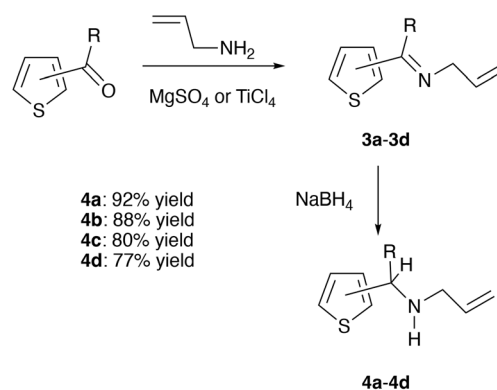


Chart 1

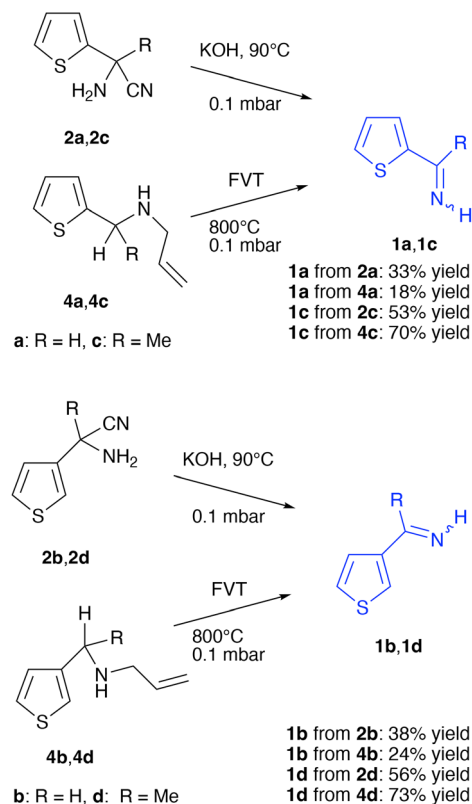


Scheme 2 Two possible routes for the synthesis of the N-unsubstituted thienylimines **1a–1d**.



Scheme 4 Synthesis of N-allylthiophenamines **4a–4d**.



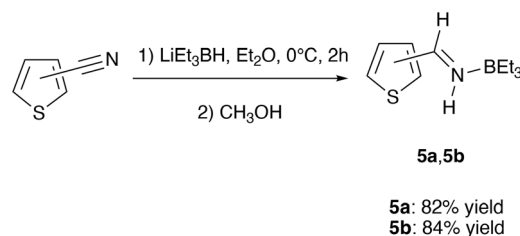
Scheme 5 Synthesis of thienylimines **1a–1d**.

of by-products such as ammonia and a few other minor products that were not identified.

N-Allyl amines **4a–4d** were vaporized under vacuum (0.1 mbar) with gentle heating in a quartz tube placed in an oven heated to 800 °C, where the chemical reaction took place. Imine and propene were formed. Ketimines **1c**, **1d** were obtained in yields of 70 and 73% respectively, but aldimines in yields of only 18 (**1a**) and 24% (**1b**), in the presence of propene and numerous minor impurities. Although simpler to implement, this approach is clearly limited to thienylketimines such as **1c** and **1d**, for which it can easily be scaled up to gram scale.

Imines synthesized by both routes were isolated using the same technique. Ketimines **1c**, **1d** were selectively trapped in a U-tube cooled to –35 °C to separate them from the more volatile by-products. Revaporization by gentle heating to around 30–40 °C led to pure compounds that could be condensed on a cold finger with a solvent for NMR analysis or on a KBr window cooled to 77 K for IR spectroscopy. Using the same approach, aldimines **1a**, **1b** led to a complex mixture of products containing small amounts of the expected imine. Consequently, in what follows, only route A was used for aldimines **1a**, **1b**; they were condensed directly on the cold finger cooled to 77 K, but the presence of ammonia could not be avoided.

NMR analysis of imines **1a–1d** was performed at low temperature (–50 °C).

Scheme 6 Formation of the thienylaldimine complexes **5a**, **5b**.

Imines **1a–1d** diluted to 5% in deuterated chloroform or dideutero methylene chloride are stable at –50 °C. At rt, a half-life time of 60 min for **1a**, 45 min for **1b** and 30 h for **1c** and **1d** was measured by ^1H NMR spectroscopy with an internal reference.

As already reported the reaction of triethylborane with imines does not lead to the complexed systems.^{1,27,28} Complexes **5a**, **5b** were obtained by reaction of superhydride with the corresponding nitriles but are therefore limited to complexes of aldimines (Scheme 6).[‡]

The (*E*) and (*Z*) isomers were observed for the 4 imines **1a–1d** by ^1H NMR spectroscopy for a sample diluted in CDCl_3 or CD_2Cl_2 and cooled to –50 °C and never previously warmed to a higher temperature: *E/Z* = 9/1 (**1a**), *E/Z* = 8/2 (**1b**), *E/Z* = 9/1 (**1c**), *E/Z* = 7/3 (**1d**). These ratios were the same at room temperature. Only (*E*) isomers were observed for complexes **5a**, **5b** as already observed for other of *N*–H aldimines complexes.^{1,27,28}

The chemical shift of the proton on the nitrogen atom was observed as a doublet at δ_{H} 9.65 (*E*) and 9.52 (*Z*) ppm for **1a**, δ_{H} 9.69 (*E*) and 9.61 (*Z*) ppm for **1b** but a rather significant difference was observed in the chemical shifts of the proton on the carbon of the imine function: 8.83 and 8.48 ppm for **1a** and 8.56 and 8.22 ppm for **1b** (Fig. 1). Coupling constant for imines **1a**, **1b** around 25 Hz ($^3J_{\text{HHtrans}}$) and 16 Hz ($^3J_{\text{HHcis}}$) are typical.

For **1c** and **1d**, the chemical shifts of the (*E*) and (*Z*) isomers were attributed following 2D NOESY NMR experiments (see ESI[†]). Two singlets at δ_{H} 8.99 (*E*) and 9.26 (*Z*) ppm were observed for **1c** and δ_{H} 9.17 (*E*) and 9.39 (*Z*) ppm for **1d**. The ^{13}C NMR chemical shifts of the corresponding carbon are at δ_{C} 163.6 (*E*) and 162.0 ppm (*Z*) for **1a** and δ_{C} 164.7 (*E*) and 163.3 ppm (*Z*) for **1b**.

The comparison of thienylimines with furanimines shows a difference in the *Z/E* ratio and chemical shifts of the imine function for 2-thiophene and 2-furan derivatives. For alkylated *N*–H aldimines, this ratio is around 1/3.¹⁵ In the case of 2-furanmethanimine, we observed a *Z/E* = 53/47 ratio we attributed to the formation of a weak hydrogen bond between the hydrogen on nitrogen and the oxygen of the cycle.¹ For thienylimine **1a**, this *Z/E* ratio of 1/9 is much smaller, even smaller than

[‡]The synthesis of complex **5a** by a similar approach had already been reported.²⁷



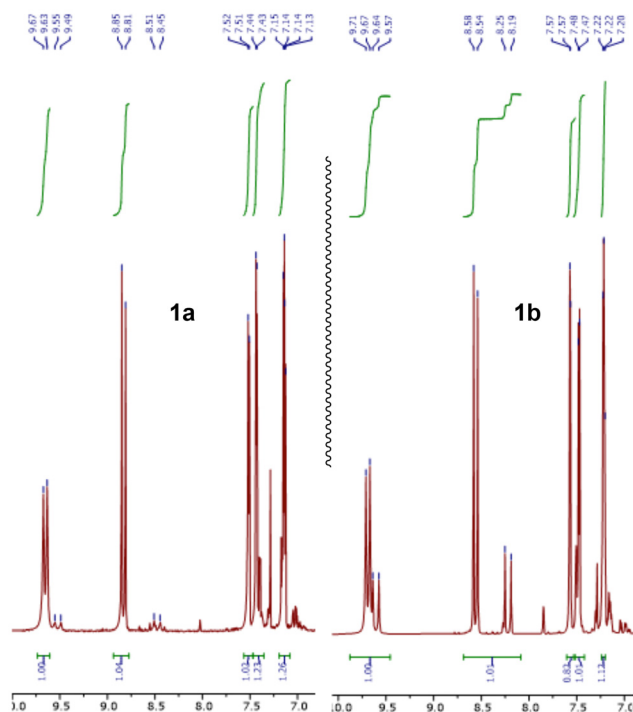


Fig. 1 ^1H NMR spectra from 7.0–10.0 ppm of 2-thiophenemethanimine **1a** (left) and 3-thiophenemethanimine **1b** (right). *E/Z* ratio and chemical shifts show differences.

that of alkylaldimines.¹⁵ That could be explained by a repulsive effect between the N–H and the sulphur atom for thiophenaldimine **1a** in which the proton on the nitrogen of the (*E*) isomer is at downfield than that of the (*Z*) isomer unlike the corresponding chemical shifts of the furanimine which are an exception (Fig. 2). The same effect was observed on imines **1c** with a similar 1/9 ratio for *Z/E*. The main difference between thienylimines and furanimines is the higher aromaticity of thiophenes and the nature of the heteroatom, which has a much lower electronegativity than oxygen. However, a role attributed to the cycle based or not on its greater aromaticity can be excluded since this effect was not observed for 3-thiophenimines **1b**, **1d**.

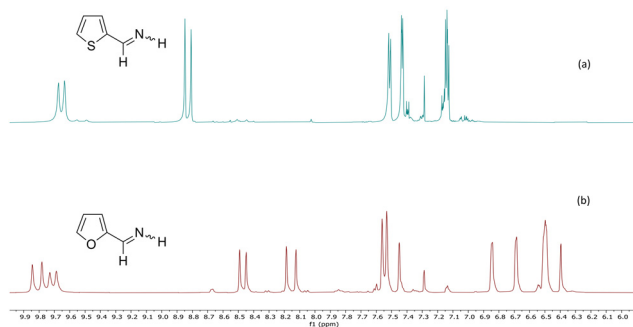


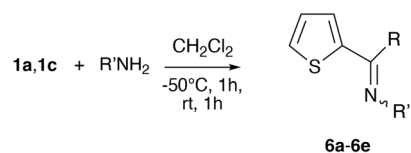
Fig. 2 Comparison between 6–10 ppm ^1H NMR spectra of 2-thiophenemethanimine **1a** (a) and 2-furanemethanimine (b).

The chemical shift of the carbon corresponding to the imine function carbon lies between δ_{C} 161.9 and 164.7 ppm, a little at downfield than those of furanimines¹ (δ_{C} : 156.9–162.3 ppm) and a lot at upfield than those of arylimines.²⁸ These differences are consistent with those of the aldehydes: $\delta_{\text{C}(\text{CH}=\text{O})}$ of 2-thiophenecarboxaldehyde: 183.1 ppm for $\delta_{\text{C}(\text{CH}=\text{O})}$ of 2-furaldehyde: 177.0 ppm, $\delta_{\text{C}(\text{CH}=\text{O})}$ of 3-thiophenecarboxaldehyde: 185.0 ppm for $\delta_{\text{C}(\text{CH}=\text{O})}$ of 3-furaldehyde: 184.4 ppm while benzaldehyde was observed at $\delta_{\text{C}(\text{CH}=\text{O})}$ 192.3 ppm.

Expected shielding effects were observed in the ^1H and ^{13}C NMR spectra of both complexes **5a**, **5b** with a chemical shift difference of $\Delta\delta_{\text{C}(\text{C}=\text{N})}$ of -7 ppm.^{1,27,28}

The infrared spectra of **1a–1d** showed characteristic $\nu_{\text{C}=\text{N}}$ absorptions at 1616 (**1a**), 1632 (**1b**), 1607 (**1c**) and 1615 cm^{-1} (**1d**), respectively, close to those observed for furanimines¹ or alkylaldimines.¹⁵

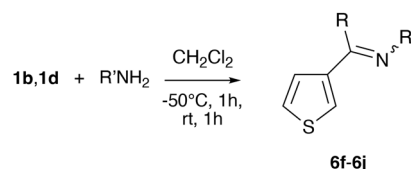
What about the chemistry of *N*-unsubstituted thienylimines? In the aim to confirm that transimination reaction can be involved with kinetically unstable imines in good yields, thienylimines **1a–1d** were readily involved in transimination reactions with propylamine or aniline to give imines **6a**, **6b**, **6d–6g**, **6i**, **6j**. We have extended this study to two transimination reactions using cyanamide with 2-thiophenemethanimine **1a** and hydroxylamine with 3-thiophenemethanimine **1b** to form compounds **6c** and **6h**, respectively (Scheme 7). On the basis of the yields obtained for thienylimines **1a–1d**, the yields of the transimination reaction ranged between 75 and 92%. Compounds **6a–6j** were characterized by ^1H and ^{13}C NMR spectroscopy and compared with the spectra of authentic



6a: R = H, R' = nPr; **6b**: R = H, R' = Ph; **6c**: R = H, R' = CN
6d: R = Me, R' = nPr; **6e**: R = Me, R' = Ph.

Yields from **2a**, **2c**:

6a: 25% yield
6b: 26% yield
6c: 24% yield
6d: 62% yield
6e: 60% yield



6f: R = H, R' = nPr; **6g**: R = H, R' = Ph; **6h**: R = H, R' = OH
6i: R = Me, R' = nPr; **6j**: R = Me, R' = Ph.

Yields from **2b**, **2d**:

6f: 32% yield
6g: 35% yield
6h: 31% yield
6i: 60% yield
6j: 67% yield

Scheme 7 Transimination reactions.

samples.^{23,25} The NMR data of the new compounds are fully consistent with the previous ones.

Conclusions

The parent compounds 2-thiophenemethanimine and 3-thiophenemethanimine and the corresponding *C*-methyl ketimines have been synthesized and spectroscopically characterized. The *C*-methyl derivatives were obtained on a preparative scale by thermolysis of allylamine precursors in a retroene reaction. For the parent compounds, the best purity was achieved by dehydrocyanation of the corresponding α -aminonitriles in a vacuum gas–solid reaction, as thermolysis of the *N*-allyl(thiophenyl)methanamines did not lead to a more efficient synthesis. Due to the boiling point of the *N*-unsubstituted thienylaldimines and their kinetic instability, we are at the limit of species generation in the gas phase. Nevertheless, obtaining these compounds in a gas stream is the key to accessing spectroscopic studies such as millimetre or photoelectron spectroscopy, the determination of molecular structures by gas phase electron diffraction (GED) or mass spectrometry.

Although some differences were observed, the *N*-unsubstituted thiophenimines are differed little from the corresponding furanimines. This can probably be attributed to the presence of an heteroaromatic ring in both series, which reduces the role played by the heteroatom despite the greater aromaticity of thiophenes, whereas a thiol or thiocarbonyl group has properties strongly different from those of the corresponding alcohol or carbonyl group, respectively.

We are continuing these studies by seeking to isolate *N*-unsubstituted pyrrolaldimines and pyridinaldimines, compounds that are even less volatile than the thienylimines studied here, with the aim of providing tools for understanding the role played by the nature of the aromatic substituent on the unsubstituted imino group and its physicochemical consequences.

Experimental

Route A: general procedure for the synthesis of imines (1a–1d) by dehydrocyanation (see ESI† for the picture of the apparatus).

A reactor ($\phi = 2.0$ cm, $L = 40$ cm) half-filled with KOH powder (39 g, 0.7 mol) was placed in a vacuum line (0.1 mbar) between a reagent inlet on one side and a solvent inlet, a nitrogen gas inlet and a cold finger on the other. KOH was heated to 90 °C by a circulating bath, the cold finger was filled with liquid nitrogen and α -aminonitrile **2a–2d** (2.0 mmol) was slowly vaporised in the reactor. The products formed were condensed on the cold finger and a solvent can be added at this stage. At the end of the addition, the pump was disconnected, the assembly was filled with dry nitrogen and the liquid nitrogen in the cold finger was expelled with compressed air. The

imine formed and the solvent drained rapidly as soon as they melted in the NMR tube or in the flask immersed in a liquid nitrogen bath.

This approach, extended to 5 mmol of precursor, leads to yields around half as high.

Route B: general procedure for the synthesis of imines by retro-ene reaction (see ESI† for the picture of the apparatus).

The reactor used in route A was replaced by an oven. Compound **4a–4d** (2.0 mmol) was vaporized under vacuum (0.1 mbar) in a quartz tube ($L = 35$ cm, $\phi = 25$ mm) heated in an oven to 800 °C. The thermolyzed products were condensed on a cold finger cooled with liquid nitrogen. CDCl_3 (700 μl) was added. At the end of the reaction, the cold finger was isolated from the vacuum line by stopcocks and compounds were isolated by the way reported above for route A.

A very slight decrease in yield was observed from 10 mmol for the synthesis of ketimines **1c**, **1d**, but this approach is only analytical for imines **1a**, **1b**.

In the case of ketimines **1c**, **1d**, the cold finger can be replaced by a U-tube fitted with stopcocks and immersed in a cold bath cooled to -35 °C, enabling the product to be isolated in its pure state.

2-Thiophenemethanimine (1a)

Yield: 33% (route A) (73 mg, 0.66 mmol), 18% (route B), (40 mg, 0.36 mmol). $E/Z = 9/1$. $\tau_{1/2}$ (5% in CDCl_3 or CD_2Cl_2 , 20 °C): 60 min. (*E*) ^1H NMR (400 MHz, CDCl_3 , 223 K) δ 9.65 (d, $^3J = 16.0$ Hz, 1H), 8.83 (d, $^3J = 16.0$ Hz, 1H), 7.51 (d, $^3J = 5.0$ Hz, 1H), 7.43 (d, $^3J = 3.7$ Hz, 1H), 7.14 (dd, $^3J = 5.0$, 3.7 Hz, 1H) ppm. ^{13}C NMR (100 Hz, CDCl_3 , 223 K) δ 163.6, 143.2, 132.9, 130.0, 127.9 ppm. (*Z*) ^1H NMR (400 MHz, CDCl_3 , 223 K) δ 9.52 (d, $^3J = 24.8$ Hz, 1H), 8.48 (d, $^3J = 24.8$ Hz, 1H); 7.51 (d, $^3J = 5.0$ Hz, 1H), 7.43 (d, $^3J = 3.7$ Hz, 1H), 7.14 (dd, $^3J = 5.0$, 3.7 Hz, 1H) ppm. ^{13}C NMR (100 Hz, CDCl_3 , 223 K) δ 162.0, 146.3, 132.9, 130.7, 128.5 ppm. IR (film, 77 K, ν cm^{-1}): 3292 (m), 1616 (s, $\nu_{\text{C=N}}$), 1431 (m), 1261 (m).

3-Thiophenemethanimine (1b)

Yield: 38% (route A) (84 mg, 0.76 mmol), 24% (route B), (53 mg, 0.48 mmol). $E/Z = 4/1$. $\tau_{1/2}$ (5% in CDCl_3 or CD_2Cl_2 , 20 °C): 45 min. (*E*) ^1H NMR (400 MHz, CDCl_3 , 223 K) δ 9.69 (d, $^3J = 16.4$ Hz, 1H), 8.56 (d, $^3J = 16.4$ Hz, 1H), 7.57 (d, $J = 2.9$ Hz, 1H), 7.48 (d, $^3J = 5.1$ Hz, 1H), 7.21 (dd, $J = 5.1$, 2.9 Hz, 1H) ppm. ^{13}C NMR (100 Hz, CDCl_3 , 223 K) δ 164.7, 141.2, 131.1, 127.0, 124.4 ppm. (*Z*) ^1H NMR (400 MHz, CDCl_3 , 223 K) δ 9.61 (d, $^3J = 25.4$ Hz, 1H), 8.22 (d, $^3J = 25.4$ Hz, 1H), 7.57 (d, $J = 2.9$ Hz, 1H), 7.48 (d, $^3J = 5.1$ Hz, 1H), 7.21 (dd, $J = 5.1$, 2.9 Hz, 1H) ppm. ^{13}C NMR (100 Hz, CDCl_3 , 223 K) δ 163.3, 139.5, 129.9, 127.6, 122.9 ppm. IR (film, 77 K, ν cm^{-1}): 3368 (m), 1632 (m, $\nu_{\text{C=N}}$), 1465 (s), 1262 (s).

α -Methyl-2-thiophenemethanimine (1c)

Yield: 53% (route A) (132 mg, 1.06 mmol), 70% (route B), (175 mg, 1.40 mmol). $E/Z = 9/1$. $\tau_{1/2}$ (5% in CDCl_3 or CD_2Cl_2 , 20 °C): 30 h. (*E*) ^1H NMR (400 MHz, CDCl_3 , 223 K) δ 8.99 (s, 1H), 7.37 (m, 1H), 7.31 (m, 1H), 7.01 (m, 1H), 2.37 (s, 3H)



ppm. ^{13}C NMR (100 MHz, CDCl_3 , 223 K) δ 169.1, 143.7, 129.4, 129.2, 127.3, 26.0 ppm. (Z) ^1H NMR (400 MHz, CDCl_3 , 223 K) δ 9.26 (s, 1H), 7.35 (m, 1H), 7.28 (m, 1H), 7.00 (m, 1H), 2.53 (s, 3H) ppm. ^{13}C NMR (100 Hz, CDCl_3 , 223 K) δ 168.1, 142.5, 128.0, 126.5, 124.9, 26.6 ppm. IR (film, 77 K, ν cm^{-1}): 3372 (s), 1607 (vs., $\nu_{\text{C}=\text{N}}$), 1430 (s), 1241 (s). HRMS (ASAP) m/z : calculated for $\text{C}_6\text{H}_8\text{NS}^+ [\text{M} + \text{H}]^+$: 126.0372; found: 126.0371.

α -Methyl-3-thiophenemethanimine (1d)

Yield: 56% (route A) (140 mg, 1.12 mmol), 73% (route B), (182 mg, 1.46 mmol). $E/Z = 7/3$. $\tau_{1/2}$ (5% in CDCl_3 or CD_2Cl_2): 30 h. (E) ^1H NMR (400 MHz, CDCl_3) δ 9.17 (s, 1H), 7.73 (m, 1H), 7.63 (m, 1H), 7.36 (m, 1H), 2.42 (s, 3H) ppm. ^{13}C NMR (100 MHz, CDCl_3) δ 170.6, 141.9, 128.0, 126.5, 126.3, 27.9 ppm. (Z) ^1H NMR (400 MHz, CDCl_3) δ 9.39 (s, 1H), 7.73 (m, 1H), 7.63 (m, 1H), 7.36 (m, 1H), 2.56 (s, 3H) ppm. ^{13}C NMR (100 MHz, CDCl_3) δ 167.6, 140.9, 126.9, 126.3, 124.5, 24.9 ppm. IR (film, 77 K, ν cm^{-1}): 3353 (m), 1671 (m, $\nu_{\text{C}=\text{N}}$), 1425 (s), 1259 (m). HRMS (ASAP) m/z : calculated for $\text{C}_6\text{H}_8\text{NS}^+ [\text{M} + \text{H}]^+$: 126.0372; found: 126.0371.

Data availability

The data underlying this study are available in the published article and its ESI.† Synthesis of all compounds, NMR and IR characterization data, NMR spectra of all new compounds.

Conflicts of interest

There are no conflicts to declare.

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