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A High Yield Procedure for the Preparation of 2-Hydroxynitrostyrenes: Synthesis of Imines and Tetracyclic 1,3-Benzoxazines

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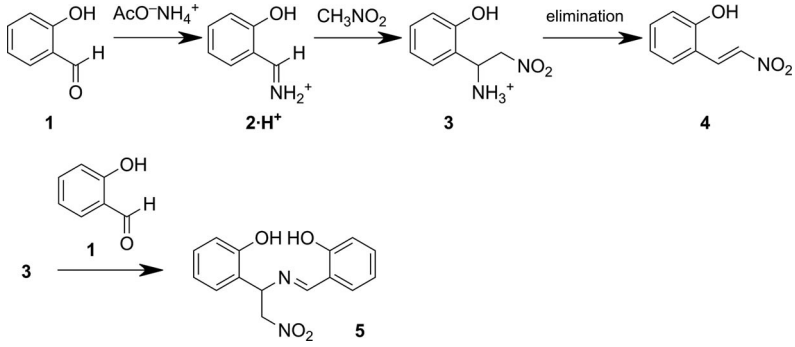
Attempts to synthesize 2-hydroxynitrostyrenes by a Knoevenagel condensation of salicylaldehyde and subsequent elimination were unsuccessful because of the formation of a stable imine. This could be easily prevented by using secondary amines to catalyze the reaction, which then afforded 2-hydroxynitrostyrenes in high yields. In addition, the stable imine that was formed by employing ammonium acetate underwent a reaction with phosgene to allow the preparation of benzoxazines in good yields.

Introduction

Nitrostyrenes are synthetically useful building blocks,[1] and for years their many biological properties have been recognized.[2] They are readily prepared from nitromethane and a suitable aldehyde by ultrasonication under Knoevenagel conditions.[3] Among nitrostyrenes, 2-hydroxynitrostyrenes are of special importance because they are employed as the starting material in the preparation of important pharmacologically active compounds such as Lirinine[4] and amphetamine derivatives.[5] However, the procedure described in the literature for the synthesis of 2-hydroxynitrostyrenes is not completely satisfactory, and poor yields have been reported.[6] Indeed, unlike other aromatic aldehydes, salicylaldehyde requires high temperatures (95 °C)[7] to react with nitromethane. Under these conditions, a dark brown solid is obtained, which is indicative of the presence of tarry materials. High temperatures facilitate side reactions and, therefore, reduce the final yield.



Scheme 1. Preparation of 2-hydroxynitrostyrenes from salicylaldehyde and nitromethane in the presence of ammonium acetate.

The conventional mechanism of the reaction between salicylaldehyde and nitromethane to afford 2-hydroxynitrostyrenes involves the formation of Knoevenagel adduct **3**, which is followed by an elimination reaction (see Scheme 1). However, in our case, the Knoevenagel adduct undergoes further reaction with another salicylaldehyde molecule to furnish imine **5**. The stability of this compound decreases the rate of formation of 2-hydroxynitrostyrene (**4**), which strongly reduces its final yield. Herein, we offer some solutions to overcome these drawbacks, and we report

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a new procedure for the preparation of 2-hydroxynitrostyrenes. In addition, imines **5** have been isolated and transformed into benzoxazines.[8]

Results and Discussion

Preparation of Nitrostyrenes

Under conventional conditions,[3] the reaction between salicylaldehyde and ammonium acetate in nitromethane yields imine **5**. This compound is formed because the Knoevenagel adduct between aldimine **2** and nitromethane is trapped by another aldehyde molecule (even with a low concentration of salicylaldehyde), which reduces the rate of formation of 2-hydroxynitrostyrene. Furthermore, imine **5** can presumably form through secondary reaction pathways, such as further Knoevenagel condensations with additional nitromethane molecules or polymerization reactions by electrophilic attack of the phenolic rings. Modeling studies[9] suggest that the stability of this imine could be ascribed, at least partially, to the formation of two strong hydrogen bonds between the phenolic OH groups and the imine nitrogen atom as shown in Figure 1. The formation of imine **5** reduces the yield of 2-hydroxynitrostyrene.

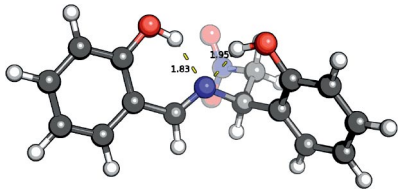


Figure 1. Model for imine **5** generated from salicylaldehyde, nitromethane, and ammonium acetate under Knoevenagel conditions, in which two intramolecular hydrogen bonds are shown.

The most obvious way to preclude the formation of the imine is to replace ammonia with a catalyst that contains an alkyl-substituted nitrogen atom, because the *N*-alkyliminium ion that is formed under these conditions should be less stable than the imine formed from ammonia. Both primary and secondary amines were tested in this reaction, and the results are shown in Table 1.

A primary amine such as butylamine (see Table 1, Entry 2) yielded the desired product **4** in a higher yield (65%) than ammonia (see Table 1, Entry 1), but the reaction rate was slow. An explanation for this is that salicylaldehyde can undergo a reaction with a primary amine such as butylamine to yield the imine, which is stabilized by the presence of a strong intramolecular hydrogen bond (see Figure 2).

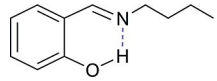


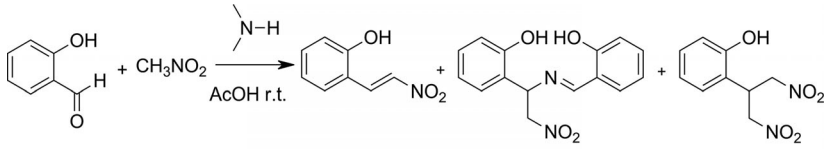
Figure 2. Imine formed between salicylaldehyde and butylamine with the intramolecular hydrogen bond shown.

The reaction of a secondary amine and salicylaldehyde does not produce an imine, and the iminium salt that is formed can, therefore, undergo reaction faster with nitromethane. Indeed, the best results were obtained with pyrrolidine (see Table 1, Entry 3), from which 2-hydroxynitrostyrene (**4**) was obtained almost quantitatively (97% yield) in only 1.5 h at room temperature. However, diethylamine afforded known molecule **6** (see Table 1, Entry 4), as a result of the fast Michael addition between nitromethane and 2-hydroxynitrostyrene.

Because pyrrolidine offered the best results for the preparation of 2-hydroxynitrostyrene, the reaction conditions were optimized with this amine by using different ratios of pyrrolidine/acetic acid to accelerate the reaction. As shown in Table 2, the best results at room temperature were obtained by employing a 2:1 molar ratio of AcOH/pyrrolidine. However, the reaction at room temperature afforded a dark colored product. To reduce the extent of side reactions, the reaction temperature was lowered to 0 °C, which improved the product appearance and increased the yield (see Supporting Information, Figure S36). At this temperature, the AcOH/pyrrolidine molar ratio was adjusted to 1.2:1 to obtain suitable reaction rates.

Additionally, these mild reaction conditions are compatible with many substituted 2-hydroxybenzaldehydes, and all the substrates that were tested (see Table 3) afforded consistently high yields. This reaction was also applicable on a multigram scale (see Table 3, Entry 4).

Table 1. Results of the reaction between salicylaldehyde and nitromethane catalyzed with different amines at room temperature.

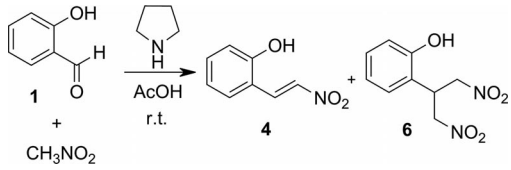


1 **4** **5** **6**

Entry	R^1	R^2	Product	Time [h]	Yield [%]
1	H	H	**4** + **5** (1:3)[a]	4	85
2	Bu	H	**4**	120	65
3	–$(CH_2)_4$–		**4**	1.5	97
4	Et	Et	**6**	120	88

[a] Ratio determined by spectroscopic analysis.

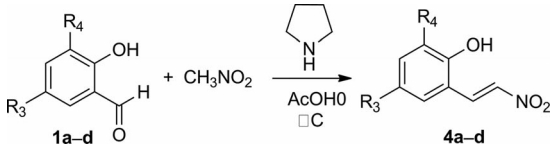
Table 2. Results of the reaction between salicylaldehyde and nitromethane catalyzed by pyrrolidine with different molar amounts of AcOH/pyrrolidine.



Entry	AcOH/ pyrrolidine	Product	Time [min]	Yield [%]
1	1.5:1	**4** + **6** (7:3)[a]	5	80
2	2:1	**4**	45	90
3	2.5:1	**4**	180	85
4	4.8:1	**4**	2880	no reaction
5[b]	1.2:1	**4**	180	99

[a] Ratio determined by spectroscopic analysis. [b] Reaction carried out at 0 °C.

Table 3. Results of the reaction of salicylaldehydes **1a**–**1e** and nitromethane catalyzed by pyrrolidine at 0 °C.



Entry	AcOH/ pyrrolidine	R^3	R^4	Product	Time [min]	Yield [%]
1	1.2:1	H	H	**4a**	180	99
2	1.2:1	Br	H	**4b**	120	95
3	1.2:1	H	OH	**4c**	300	92
4[a]	1.2:1	Cl	H	**4d**	270	90

[a] Reaction carried out at 50 g scale.

Preparation of Imines and Benzoxazines

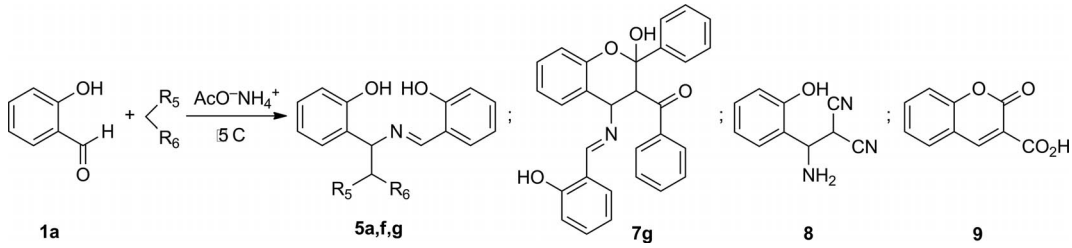
Imine **5** is an interesting molecule, as it is a potential source of benzoxazines, which are attractive to the development of new materials[10] and also exhibit several interesting biological activities.[11] To improve the yield of imine **5**, methanol was added to the reaction mixture to increase the solubility of ammonium acetate, which was otherwise only sparingly soluble in nitromethane. Lowering the reaction temperature to 5 °C was also essential, as low temperatures hinder the elimination reaction that leads to the 2-hydroxynitrostyrene. Under these latter conditions, imine **5** can be obtained in excellent yields by simply pouring the reaction over water and then filtering the mixture.

Nucleophiles other than nitromethane were also tested under these reaction conditions. The results are summarized in Table 4. Surprisingly, not all of the nucleophiles examined successfully led to the corresponding imine, and other products were identified.

Dimethyl malonate (see Table 4, Entry 2) yielded similar results as those of nitromethane (see Table 4, Entry 1) and afforded a clean crystalline adduct after pouring the reaction mixture over water. However, dibenzoyl methane (see Table 4, Entry 3) led to a 1:1 mixture of the expected compound **5g** and a lactol that was obtained by its intramolecular condensation. Malononitrile (see Table 4, Entry 4) failed to produce the expected imine and instead yielded simple Knoevenagel adduct **8**. Meldrum's acid (see Table 4, Entry 5) provided known chromene **9**, which is of technical interest as a rat poison[12] and was obtained with this procedure under especially mild conditions.

By using imines **5a**, **5f**, and **5g**, we attempted to obtain the corresponding benzoxazines by following the procedure described by Betti[8] but, surprisingly, these experiments failed. A modeling study (see Figure 3)[9] showed that because of the double hydrogen-bond stabilization, imine **5** is 5.6 kcal mol^{-1} more stable than benzoxazine **10**. The imine is the more stable compound, and this explains why the isomerization from imine **5** to benzoxazine **10** does not take place under the employed thermodynamic conditions. However, the σ-bonds that are present in the benzoxazine should be stronger than the imine π-bonds, and, therefore, the benzoxazine could be the most stable product if the forma-

Table 4. Products of the reaction between salicylaldehyde and different nucleophiles using ammonium acetate at 5 °C.



Entry	R^5	R^6	Product	Time [h]	Yield [%]
1	H	NO_2	**5a**	8	82
2	CO_2Me	CO_2Me	**5f**	1.5	80
3	COPh	COPh	**5g** + **7g** (1:1)[a]	3	75
4	CN	CN	**8**	1.1	82
5	–(CO)-O-C(Me)$_2$-O-(CO)–		**9**	270	90

[a] Ratio determined by spectroscopic analysis.

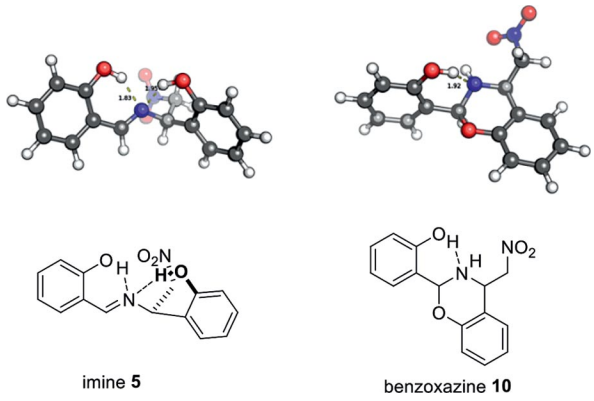


Figure 3. Modeling study of imine **5** versus benzoxazine **10**.

tion of the two intramolecular hydrogen bonds of the imine were prevented.

To change the thermodynamic preference for imine **5**, an acidic medium was examined (see Table 5, Entry 1). We assumed that the higher basic character of the protonated sp^3-hybridized nitrogen atom of the benzoxazine compared to the sp^2-hybridized nitrogen atom of the initially formed iminium salt should favor the protonation of the benzoxazine. Nevertheless, the treatment of imine **5a** with trifluoroacetic acid yielded the iminium salt, which did not progress to give the desired benzoxazine but gave the corresponding 2-hydroxynitrostyrene after a long reaction time (together with the starting salicylaldehyde as a byproduct). This iminium salt was characterized by ^1H NMR analysis by monitoring the appearance of a broad signal at δ = 12.7 ppm, which corresponds to the iminium proton at the nitrogen atom and is coupled to the imine proton at the carbon atom. The signal of this deshielded proton appeared at δ = 8.6 ppm. Thus, the iminium salt proved to be surprisingly stable, probably because it is stabilized by two intramolecular hydrogen bonds and also its phenolic hydroxy group is far away from the imine carbon (4.1 Å according to modeling studies) as shown in Figure 4.

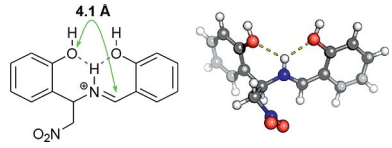


Figure 4. Proposed structure for the iminium salt formed from imine **5a** (left) and energy-minimized model showing the two intramolecular hydrogen bonds and the great distance between the phenolic hydroxy group and the imine carbon atom (right).

As an alternative to the protonation of the imine nitrogen atom, different electrophiles that might acylate this nitrogen were examined. The alkylated or acylated nitrogen atom in the benzoxazine was expected to be more stable than the corresponding alkyl or acyl imine, which should provide the benzoxazine over the imine. The results are summarized in Table 5.

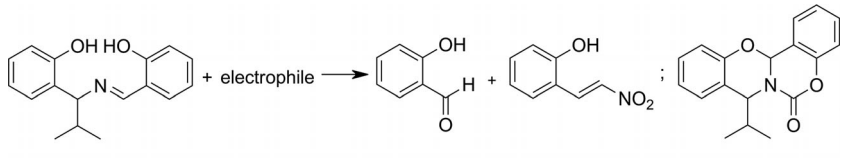
Methyl iodide (see Table 5, Entry 2) only afforded the nitrostyrene product (together with the starting aldehyde as a byproduct), but when phosgene was tested as the electrophile (see Table 5, Entries 3–5), benzoxazines were generated from imines **5a**, **5f**, and **5g** to yield the tetracyclic compounds **10a**, **10f**, and **10g**, respectively. Interestingly, the 1:1 mixture of imines **5g** and **7g**, which were generated from the earlier reaction of salicylaldehyde with dibenzoylmethane, underwent a reaction with phosgene to give a single product (i.e., **10g**; see Table 5, Entry 5) and, thus, confirmed the structure of lactol **7g**.

A final confirmation was obtained by X-ray crystal structure analysis of benzoxazine **10g**. This compound crystallized with a chloroform molecule (see Figure 5) and exhibited all the structural features expected for this compound.

Conclusions

In the present work, a study of the preparation of 2-hydroxynitrostyrenes was carried out. The results provided

Table 5. Products of the reaction of imines **5** with several electrophiles.



Entry	Substrate	R^5	R^6	Electrophile	Product	Time [h]	Yield [%]
1	**5a**	H	NO_2	CF_3CO_2H	**1a** + **4a** (1:1)[a]	0.75	99
2	**5a**	H	NO_2	MeI	**1a** + **4a** (1:1)[a]	16	99
3	**5a**	H	NO_2	$(CO)Cl_2$	**10a**	1	87
4	**5f**	CO_2Me	CO_2Me	$(CO)Cl_2$	**10f**	2.5	80
5	**5g**[b] + **7g** (1:1)	COPh	COPh	$(CO)Cl_2$	**10g**	2	76

[a] Ratio determined by spectroscopic analysis. [b] This imine was employed as a mixture with lactol **7g**, which resulted from the intramolecular condensation of the imine as described in Table 4, Entry 3.

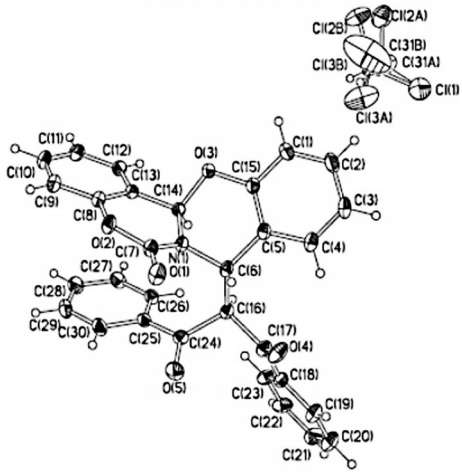


Figure 5. ORTEP diagram of benzoxazine **10g**.

an improvement over the previously described method for their preparation. The reaction mechanism was elucidated to optimize the experimental conditions for the preparation of a series of 2-hydroxynitrostyrenes with high yields and purities. In addition, the corresponding imines were obtained and transformed into new benzoxazine compounds.

Experimental Section

General Methods: Solvents were purified by standard procedures and distilled before use. Reagents and starting materials from commercial suppliers were used without further purification IR spectra were recorded as neat films, and the frequencies are given in cm^{-1}. Melting points are reported in °C. The ^1H and ^{13} NMR spectroscopic data were recorded with a 200 MHz spectrometer. For ^1H NMR, the chemical shifts are reported in ppm with tetramethylsilane (TMS) as the internal standard, and the data are reported as chemical shift (in ppm), multiplicity [s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br. (broad), coupling constant (in Hz), and number of hydrogen atoms. The splitting patterns that could not be clearly distinguished are designated as multiplets (m). For ^{13}C NMR, the chemical shifts are reported in ppm, and the number of attached hydrogen atoms is provided. High resolution mass spectrometry was performed using ESI ionization and a quadrupole TOF (QTOF) mass analyzer. Flash chromatography was performed with 70–200 mesh silica gel. The starting salicylaldehydes were either commercially available or synthesized according to published methods.[13]

General Procedure for the Preparation of 2-Hydroxynitrostyrenes: The corresponding aldehyde (1.0 mmol), nitromethane (2.4 g, 5.0 mmol), and acetic acid (1.7 mL, 3.4 mmol) were added dropwise into a two-necked round-bottomed flask that was equipped with a thermometer and cooled with an ice bath. The resulting mixture was stirred at 0 °C, and then pyrrolidine (0.6 mL, 2.9 mmol) was added dropwise by an addition funnel. The progress of the reaction was monitored by ^1H NMR analysis of aliquots of the reaction mixture. Upon completion, the crude mixture was poured over water, and the solid product that precipitated was filtered and then purified by recrystallization (methanol/diethyl ether mixture). The physical and spectroscopic data of all the 2-hydroxynitrostyrenes were identical to those reported.[6,13]

(*E*)-2-(2-Nitrovinyl)phenol (4a): Following the general procedure and using salicylaldehyde (5.0 g, 41 mmol) for 3 h gave **4a** (6.7 g, 99% yield).

(*E*)-4-Bromo-2-(2-nitrovinyl)phenol (4b): Following the general procedure and using 5-bromosalicylaldehyde (1.0 g, 5 mmol) for 2 h gave **4b** (1.2 g, 95% yield).

(*E*)-3-(2-Nitrovinyl)benzene-1,2-diol (4c): Following the general procedure and using 2,3-dihydroxybenzaldehyde (690 mg, 5 mmol) for 5 h gave **4c** (830 mg, 92% yield).

(*E*)-4-Chloro-2-(2-nitrovinyl)phenol (4d): Following the general procedure and using 5-chlorosalicylaldehyde (50.0 g, 0.3 mol) for 4.5 h gave **4d** (57.4 g, 90% yield).

2-(1,3-Dinitropropan-2-yl)phenol (6): This compound was prepared from salicylaldehyde by following a variation of the general procedure. Salicylaldehyde (0.5 mL, 1.0 mmol), nitromethane (2.4 g, 5.0 mmol), and acetic acid (1.7 mL, 3.4 mmol) were added to a two-necked round-bottomed flask that was equipped with a thermometer and cooled with an ice bath. Diethylamine (2.5 mL, 2.9 mmol) was added dropwise by an addition funnel. The resulting mixture was stirred at 0 °C for 12 h, and then it was warmed to room temperature and stirred for an additional 108 h. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (CH_2Cl_2/AcOEt) to give **6** (1.6 g, 86% yield) as a yellow oil. The physical and spectroscopic properties were identical to those described in the literature.[14]

General Procedure for the Preparation of Imines: The corresponding aldehyde (1.0 mmol), nucleophile (5.0 mmol), ammonium acetate (2.0 mmol), acetic acid (1.0 mmol), and methanol (6.0 mL g^{-1} of ammonium acetate) were added to a two-necked round-bottomed flask, and the resulting mixture was stirred at room temperature for 1.5–8.0 h. (When nitromethane was used as the nucleophile, the reaction was conducted at 5 °C, instead of at room temperature.) The reaction progress was monitored by ^1H NMR analysis of aliquots from the reaction mixture. Upon completion, the crude mixture was poured over water at 0 °C, and the yellow solid product that precipitated was filtered and used in the next reaction step without further purification.

(*E*)-2-[1-(2-Hydroxybenzylideneamino)-2-nitroethyl]phenol (5a): Following the general procedure and using salicylaldehyde (610 mg, 5 mmol) and nitromethane (1.8 mL, 25 mmol) for a reaction time of 8 h gave imine **5a** (586 mg, 82% yield); m.p. 135–138 °C (CH_2Cl_2/MeOH). ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 4.89–4.93 (m, 2 H), 5.46 (dd, J = 4, 8 Hz, 1 H), 6.80–6.96 (m, 4 H), 7.25–7.31 (m, 4 H), 8.44 (s, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 66.0 (CH), 79.0 (CH_2), 115.9 (CH), 117.2 (CH), 118.6 (C), 119.3 (CH), 120.5 (CH), 123.5 (C), 128.3 (CH), 129.8 (CH), 132.4 (CH), 133.3 (CH), 154.2 (C), 160.9 (C), 162.7 (CH) ppm. IR (Nujol): $\tilde{\nu}$ = 762, 1158, 1554, 1638 cm^{-1}. HRMS (ESI-QTOF): calcd. for $C_{15}H_{14}N_2O_4Na$ $[M + Na]^+$ 309.0846; found 309.0853.

(*E*)-Dimethyl 2-[(2-Hydroxybenzylideneamino)(2-hydroxyphenyl)-methyl]malonate (5f): Following the general procedure and using salicylaldehyde (610 mg, 5 mmol) and dimethyl malonate (3.3 g, 25 mmol) for a reaction time of 1.5 h gave compound **5f** (714 mg, 80% yield); m.p. 182–185 °C (CH_2Cl_2/MeOH). ^1H NMR (200 MHz, CD_3OD, 25 °C): δ = 3.61 (s, 3 H), 3.73 (s, 3 H), 4.48 (d, J = 10 Hz, 1 H), 5.36 (d, J = 10 Hz, 1 H), 6.75–6.99 (m, 5 H), 7.09–7.40 (m, 3 H), 8.41 (s, 1 H) ppm. ^{13}C NMR (50 MHz, CD_3OD, 25 °C): δ = 52.8 (CH_3), 53.1 (CH_3), 57.4 (CH), 67.0 (CH), 117.4 (CH), 117.8 (CH), 118.5 (CH), 118.7 (CH), 121.1 (CH), 125.5 (C), 129.3 (CH), 129.8 (CH), 132.4 (CH), 133.5 (CH), 154.1 (C), 162.5 (C), 167.2 (CH), 168.3 (C), 168.4 (C) ppm. IR (Nujol): $\tilde{\nu}$ =

1612, 1729 cm^{-1}. HRMS (ESI-QTOF): calcd. for $C_{19}H_{20}NO_6$ $[M + H]^+$ 358.1285; found 358.1285.

(*E*)-2-[(2-Hydroxybenzylideneamino)(2-hydroxyphenyl)methyl]-1,3-diphenylpropane-1,3-dione (5g): Following the general procedure but reducing the molar ratio of nucleophile/aldehyde from 5:1 to 2:1 and using salicylaldehyde (610 mg, 5 mmol) and dibenzoyl methane (2.2 g, 10 mmol) for a reaction time of 3 h gave imine **5g** (842 mg, 75% yield); m.p. 145–147 °C (diethyl ether/MeOH). ^1H NMR (200 MHz, [D$_6$]DMSO, 25 °C): δ = 5.75 (d, J = 10 Hz, 1 H), 6.58–7.11 (m, 6 H), 7.11–7.66 (m, 9 H), 7.94 (d, J = 8 Hz, 2 H), 8.07 (d, J = 8 Hz, 2 H), 8.52 (s, 1 H), 9.88 (s, 1 H), 12.97 (s, 1 H) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO, 25 °C): δ = 59.4 (CH), 69.0 (CH), 116.3 (CH), 117.0 (CH), 119.2 (2 CH), 119.7 (CH), 126.3 (CH), 129.0 (2 CH), 129.4 (3 CH), 129.5 (2 CH), 129.6 (2 CH), 129.9 (CH), 132.6 (CH), 133.2 (CH), 134.4 (CH), 134.5 (CH), 136.7 (C), 137.3 (C), 155.6 (C), 160.8 (C), 166.4 (CH), 193.7 (C), 195.6 (C) ppm. IR (Nujol): $\tilde{\nu}$ = 762, 1015, 1638, 1690 cm^{-1}. HRMS (ESI-QTOF): calcd. for $C_{29}H_{24}NO_4$ $[M + H]^+$ 450.1700; found 450.1704.

2-[Amino(2-hydroxyphenyl)methyl]malononitrile (8): Following the general procedure but reducing the molar ratio of the nucleophile/aldehyde from 5:1 to 2:1 and using salicylaldehyde (610 mg, 5 mmol) and malononitrile (660 mg, 10 mmol) for a reaction time of 2 h gave compound **8** (768 mg, 82% yield) as a pale brown solid; m.p. 147–150 °C (CH_2Cl_2/MeOH). ^1H NMR (200 MHz, CD_3OD, 25 °C): δ = 4.13 (d, J = 4 Hz, 1 H), 4.25 (d, J = 4 Hz, 1 H), 7.07 (d, J = 8 Hz, 1 H), 7.20 (t, J = 8 Hz, 1 H), 7.34 (d, J = 8 Hz, 1 H), 7.39 (t, J = 8 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, CD_3OD, 25 °C): δ = 38.4 (2 CH), 116.7 (CH), 117.7 (C), 119.3 (C), 125.2 (CH), 128.7 (CH), 130.2 (CH), 150.4 (C), 164.4 (C) ppm. IR (Nujol): $\tilde{\nu}$ = 1268, 1366, 1456, 2196, 3345 3442 cm^{-1}. HRMS (ESI-QTOF): calcd. for $C_{10}H_6N_2O$ $[M - 17]^+$ 171.0553; found 171.0555.

2-Oxo-2*H*-chromene-3-carboxylic Acid (9): Following the general procedure but reducing the molar ratio of the nucleophile/aldehyde from 5:1 to 2:1 and using salicylaldehyde (610 mg, 5 mmol) and Meldrum's acid (1.4 g, 10 mmol) for a reaction time of 2 h gave compound **9** (840 mg, 89% yield) as a brown solid. Its physical and spectroscopic properties were identical to those described in the literature.[15]

General Procedure for the Preparation of Benzoxazines: *Caution!* Because the toxic gas phosgene is employed in this preparation, the reaction should be performed in an efficient hood. The glassware may be coated with a solution of phosgene and should, therefore, be washed with ethanol containing ammonia before removing from the hood. The corresponding imine (1.0 mmol) was dissolved in anhydrous THF (5.0 mL) in a two-necked round-bottomed flask that was equipped with a thermometer, and the solution was cooled to –80 °C. Phosgene [20% solution in toluene, 2.1 mL, 4.0 mmol] was then added, and the reaction mixture was warmed to room temperature. The progress of the reaction was monitored by ^1H NMR analysis of aliquots of the reaction mixture. Upon completion, the solvent was removed under reduced pressure, and the crude product was purified by crystallization.

2′,3-[4-(Nitromethyl)-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazin-2-yl]-phenyl Carbamate (10a): Following the general procedure and using imine **5a** (400 mg, 1.4 mmol) for a reaction time of 1 h gave benzoxazine **10a** (380 mg, 87% yield); m.p. 224–226 °C (CH_2Cl_2/MeOH). ^1H NMR (200 MHz, CD_3OD, 25 °C): δ = 5.23–5.38 (dd, J = 4, 14 Hz, 1 H), 5.38–5.56 (dd, J = 10, 14 Hz, 1 H), 6.16–6.30 (dd, J = 10, 4 Hz, 1 H), 6.80 (s, 1 H), 6.95 (d, J = 8 Hz, 1 H), 7.09 (t, J = 8 Hz, 1 H), 7.23–7.44 (m, 3 H), 7.47–7.67 (m, 3 H) ppm. ^{13}C NMR (50 MHz, CD_3OD, 25 °C): δ = 52.1 (CH), 77.6 (CH + CH_2), 115.9 (C), 116.7 (CH), 118.2 (C), 118.7 (CH), 122.9 (CH), 125.9 (CH), 128.8 (CH), 129.2 (CH), 130.3 (CH), 132.8 (CH), 148.7 (C), 149.6 (C), 153.7 (C) ppm. IR (Nujol): $\tilde{\nu}$ = 749, 982, 1209, 1463, 1560, 1741 cm^{-1}. HRMS (ESI-QTOF): calcd. for $C_{16}H_{13}N_2O_5$ $[M + H]^+$ 313.0819; found 313.0819.

Dimethyl 2-(6-Oxo-8,13a-dihydro-6*H*-benzo[*e*]benzo[5,6][1,3]oxazino[4,3-*b*][1,3]oxazin-8-yl)malonate (10f): Following the general procedure and using imine **5f** (410 mg, 1.1 mmol) for a reaction time of 2.5 h gave benzoxazine **10f** (352 mg, 80% yield): m.p. 130–132 °C ($CHCl_3$/diethyl ether). ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 3.69 (s, 3 H), 3.74 (s, 3 H), 4.19 (d, J = 8 Hz, 1 H), 6.27 (d, J = 8 Hz, 1 H), 6.56 (s, 1 H), 6.87–7.04 (m, 2 H), 7.08–7.33 (m, 4 H), 7.41–7.57 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 52.1 (CH), 53.2 (CH_3), 53.3 (CH_3), 57.9 (CH), 78.7 (CH), 115.3 (C), 116.6 (CH), 118.0 (CH), 120.3 (C), 122.5 (CH), 125.2 (CH), 127.3 (CH), 128.2 (CH), 129.7 (CH), 131.9 (CH), 148.4 (C), 149.2 (C), 152.8 (C), 167.1 (C), 167.3 (C) ppm. IR (Nujol): $\tilde{\nu}$ = 755, 970, 1216, 1599, 1748 cm^{-1}. HRMS (ESI-QTOF): calcd. for $C_{20}H_{18}NO_7$ $[M + H]^+$ 384.1078; found 384.1075.

2-(6-Oxo-8,13a-dihydro-6*H*-benzo[*e*]benzo[5,6][1,3]oxazino[4,3-*b*]-[1,3]oxazin-8-yl)-1,3-diphenylpropane-1,3-dione (10g): Following the general procedure and using imine **5g** (400 mg, 0.9 mmol) for a reaction time of 2 h gave benzoxazine **10g** (322 mg, 76% yield); m.p. 120–122 °C ($CHCl_3$/EtOH). ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 6.05 (d, J = 8 Hz, 1 H), 6.52 (s, 1 H), 6.80–7.05 (m, 4 H), 7.13–7.25 (m, 3 H), 7.29–7.62 (m, 8 H), 7.92–8.06 (t, J = 8 Hz, 4 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 52.6 (CH), 64.7 (CH), 79.1 (CH), 115.2 (C), 116.5 (CH), 118.0 (CH), 122.6 (C), 125.0 (CH), 127.5 (CH), 128.0 (CH), 129.0 (5 CH), 129.1 (2 CH), 129.2 (2 CH), 129.4 (CH), 131.7 (CH), 134.2 (CH), 134.3 (CH), 136.1 (C), 136.8 (C), 148.5 (C), 149.2 (C), 152.6 (C), 193.4 (C), 193.7 (C) ppm. IR (Nujol): $\tilde{\nu}$ = 756, 996, 1216, 1599, 1723 cm^{-1}. HRMS (ESI-QTOF): calcd. for $C_{30}H_{21}NO_5Na$ $[M + Na]^+$ 498.1312; found 498.1315.

Supporting Information (see footnote on the first page of this article): ^1H NMR spectra of compounds **4a**–**4d**, **5a**, **5f**, **5g**, **7g** (mixture with **5g**), **8**, **9**, **10a**, **10f**, and **10g**; ^{13}C NMR, IR, and MS spectra of compounds **5a**, **5f**, **5g**, **8**, **10a**, **10f**, and **10g**; Cartesian coordinates of the optimized structures; and details regarding how the temperature affects the appearance of product **4**.

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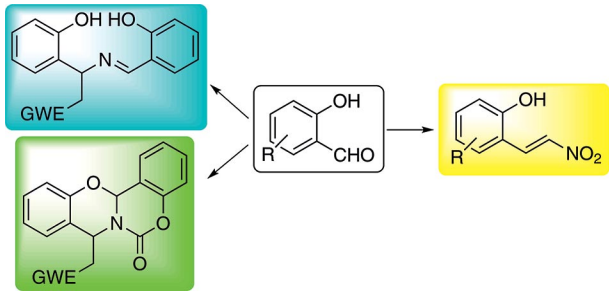

The reaction of salicylaldehyde, nitromethane, and ammonium acetate yields a surprisingly stable imine, which hinders the synthesis of 2-hydroxynitrostyrene. Herein, we present a procedure to overcome this drawback and report the reaction of this stable imine with phosgene to afford benzoxazines in good yields.

Keywords: Synthetic methods / Heterocycles / Schiff bases / Nucleophilic addition / Elimination

