JOC The Journal of Organic Chemistry

Cite This: J. Org. Chem. XXXX, XXX, XXX−XXX

Note

pubs.acs.org/joc

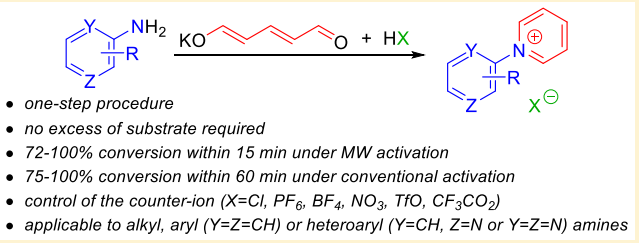
Glutaconaldehyde as an Alternative Reagent to the Zincke Salt for the Transformation of Primary Amines into Pyridinium Salts

Ghada Asskar, Michael Rivard,* and Thierry Martens

ICMPE (UMR 7182), CNRS, UPEC, Université Paris Est, 94320 Thiais, France

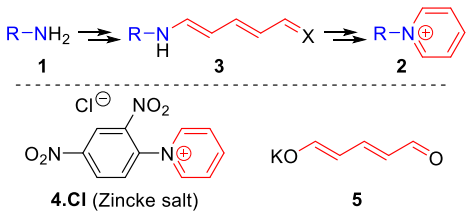
Supporting Information

ABSTRACT: In the presence of amines, the degradation of glutaconaldehyde in acidic medium can be prevented. By exploitation of this behavior, primary amines are transformed into their corresponding pyridinium salts, including those substrates that remain unreactive toward the Zincke salt, which is the reagent typically used to perform this transformation. The use of glutaconaldehyde also allows control of the nature of the counterion of the pyridinium with no need for additional salt metathesis reaction.



The transformation of primary amines **1** into pyridiniums **2** follows a multistep S_N(ANRORC) process that includes the formation of open-chain intermediates of type **3** (Scheme 1). This transformation is typically performed either with pyryliums,[1−4] thiopyryliums,[5,6] or with reagents resulting from the electrophilic activation of pyridines. A common method for the latter is the one originally described by Zincke[7] and using the Zincke salt **4·Cl** (Scheme 1).[8] The quaternization of primary amines by **4·Cl** or its derivatives is commonly used in materials science,[9] supramolecular chemistry,[10,11] and also for the synthesis of compounds of natural origin[12,13] or biological interest.[14,15] Viologens, compounds also valuable in materials science[16,17] and supramolecular chemistry,[18−20] are typically prepared according to the Zincke procedure.

Scheme 1. Transformation of Primary Amines into Pyridinium Salts



Despite its frequent use, the Zincke salt **4·Cl** is associated with various limitations. Using this reagent in excess results in a mixture of salts **4·Cl** and **2·Cl**, inseparable according to traditional chromatographic methods.[21] Consequently, weakly nucleophilic amines need to be engaged in large excess to fully convert the reagent. Even so, reaction times may be long, especially under conventional activation. S_NAr side reactions leading to unwanted diarylamines may also occur with anilines carrying adjacent functions with labile hydrogen.[22] Additionally, to obtain any anion different to the one from the Zincke salt, further steps of salt metathesis are necessary.[23,24] The same limitation occurs with pyrylium salts.

In our search for an alternative reagent to **4·Cl**, we based our idea on Marazano's findings showing the accelerated transformation of primary amines by a Zincke salt in the presence of diethylamine.[25] This result, explained by the in situ formation of intermediate aminopentadiene-imium (**3**, X = NEt_2^+), logically suggested using a reagent that easily generates open-chain species of type **3**. Considering that aminopentadienals (**3**, X = O) lead to pyridiniums after cyclization,[26] glutaconaldehyde salt **5** (Scheme 1) appeared as a promising substitute for the Zincke salt **4·Cl**. It is noteworthy that, although glutaconaldehyde derivatives have already been employed for the quaternization of primary amines, their advantageous use as reagents instead of **4·Cl** has not been demonstrated to date.[27,28]

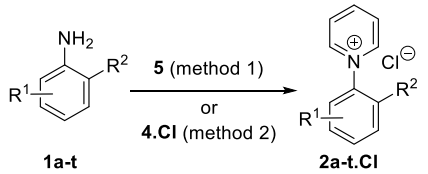
Recently, we showed that the transformation of weakly nucleophilic anilines (typically those with a p*K*a of conjugated acid less than 2.75) requires 12 equiv of substrate to fully convert the Zincke salt **4·Cl**, despite microwave (MW) irradiation at 150 °C and prolonged heating times (60−75 min).[22] In the present study, weakly nucleophilic anilines **1a−e** (0.5 mmol, 1.0 equiv) were engaged with **5** (1.5−2.0 equiv) in an aqueous alcoholic (EtOH or *t*BuOH) solvent and in the presence of HCl. Following these conditions, expected salts **2a−e·Cl** were quantitatively obtained under MW at 130 °C after only 15 min of reaction (Table 1, entries 1−5, method 1).

To compare the efficacy of in situ generated glutaconaldehyde vs **4·Cl**, anilines **1a−e** (1.5−2.0 equiv) were treated with Zincke salt **4·Cl** (1.0 equiv) under MW at 130 °C for 15 min. This returned no or negligible conversions (Table 1, entries 1−5, method 2). In the case of the anilines **1a−d**, unreacted materials were found to be unchanged by ^{1}H NMR and in the

Received: September 18, 2019

DOI: 10.1021/acs.joc.9b02538
J. Org. Chem. XXXX, XXX, XXX−XXX

Table 1. Scope of in Situ Generated Glutaconaldehyde and Comparison with Zincke Salt 4-Cl



				conversion (%)[a]	
entry	substrate	R^1	R^2	method 1[b]	method 2[c,d]
1	**1a**	2-CN	H	100 (90)	n.r.
2	**1b**	4-CN	H	100 (100)	n.r.
3	**1c**	4-Ac	H	100 (61)	3
4	**1d**	2-Cl	H	100 (97)	n.r.
5	**1e**	2-CF_3	H	100 (100)	n.r.[f]
6	**1f**	2-OH	H	100 (98)	8[g]
7	**1g**	3-OH	H	100 (100)	12[g]
8	**1h**	4-OH	H	100 (97)	42
9	**1i**	2-CO_2H	H	100 (85)	n.r.
10	**1j**	3-CO_2H	H	100 (61)	9[g]
11	**1k**	4-CO_2H	H	100 (60)	n.r.
12	**1l**	2-$CONH_2$	H	100[e] (38)	2
13	**1m**	3-$CONH_2$	H	100 (55)	24
14	**1n**	4-$CONH_2$	H	100 (54)	8
15	**1o**	2-Me	Me	100 (91)	n.r.[f]
16	**1p**	2-*i*Pr	*i*Pr	100 (100)	2[f]
17	**1q**	2-Cl	Cl	100 (95)	n.r.[f]
18	**1r**	2-CO_2H	Cl	100 (86)	n.r.
19	**1s**	2-CO_2H	CF_3	72 (65)	n.r.
20	**1t**	4-Me	H	100 (89)	100
21	**1u**	benzylamine		100 (83)	83
22	**1v**	3-aminopyridine		100 (80)	45
23	**1w**	2-aminopyrazine		100 (55)	1

[a]Measured by ^{1}H NMR. [b]Method 1: **1** (0.50 mmol, 1.0 equiv), **5** (0.75−1.00 mmol, 1.5−2.0 equiv), HCl (2.0−5.0 equiv), EtOH/H_2O or *t*BuOH/H_2O (see the Experimental Section), MW, 130 °C, 15 min. Isolated yields are given in brackets. [c]Method 2: **1** (0.75−1.00 mmol, 1.5−2.0 equiv), **4·Cl** (0.50 mmol, 1.0 equiv), EtOH/H_2O, MW, 130 °C, 15 min. [d]n.r. = no reaction. [e]Presence of 25% of **2i·Cl** in the crude (^{1}H NMR estimation). [f]Partial loss of substrate **1** observed by ^{1}H NMR. [g]Salt **2·Cl** obtained in complex mixture.

ratio as expected. This result suggests that, compared with Zincke salt **4·Cl**, in situ generated glutaconaldehyde exhibits a significantly higher electrophilicity and provides easier access to intermediates of type **3**. In the case of *o*-trifluoromethyl aniline **1e**, the analysis of the crude by ^{1}H NMR revealed that the absence of the expected salt was associated with a partial loss of substrate, relative to **4·Cl** (entry 5).

Substrates prone to produce S_NAr side reactions with **4·Cl** were also subjected to quaternization. Aminophenols **1f−h** (Table 1, entries 6−8), aminobenzoic acids **1i−k** (entries 9−11), and aminobenzamides **1l−n** (entries 12−14) were treated with **5** in the presence of HCl. This quantitatively led to the expected salts **2f−n·Cl** (method 1) except in the case of **2l·Cl**, which partially hydrolyzed during the reaction. Substrates **1f−n** treated with **4·Cl** (method 2) did not react or returned transformation with low conversion not exceeding 42%. In some cases, method 2 also provided the expected pyridinum salts in complex mixtures (entries 6, 7, and 10).

To our knowledge, there are no descriptions of any transformation of 2,6-disubstituted anilines with **4·Cl** to date, and examples of transformations with other Zincke salts are scarce.[29,30] Consequently, the quaternization of sterically hindered substrates was tested with 2,6-disubstituted anilines **1o−q** (Table 1, entries 15−17). Complete conversions were obtained with in situ generated glutaconaldehyde (method 1), while **4·Cl** provided no or negligible conversions, systematically associated with a partial loss of substrate (method 2).

Challenging substrates with a 2,6-disubstitution and bearing an adjacent function with labile hydrogen were also subjected to quaternization (Table 1, entries 18 and 19). Treating anthranilic acid derivatives **1r** and **1s** with in situ generated glutaconaldehyde yielded the corresponding salts **2r·Cl** and **2s·Cl** with a conversion of 100 and 72%, respectively (method 1), whereas **4·Cl** did not bring about the expected salts (method 2).

To ensure that the acidic medium required to in situ generate glutaconaldehyde from **5** does not prevent the transformation of basic primary amines, *p*-toluidine **1t** and benzylamine **1u** were submitted to quaternization (Table 1, entries 20 and 21). In both cases, quantitative conversions were observed with in situ generated glutaconaldehyde (method 1). The conversions with **4·Cl** were similar or lower (method 2).

The quaternization of primary heteroarylamines was exemplified with 3-aminopyridine **1v** and 2-aminopyrazine **1w** (Table 1, entries 22 and 23). The use of in situ generated glutaconaldehyde returned quantitative conversions, whereas employing **4·Cl** resulted in low or almost no conversion.

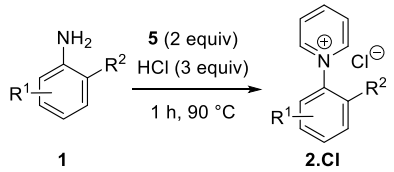
Reactions described above proceeded cleanly in an aqueous-alcoholic mixture, typically in an EtOH/H_2O binary solvent. However, when side reactions were likely to occur, they were alternatively conducted in a *t*BuOH/H_2O mixture (e.g., with substrates prone to esterify **1i−n**, **1r**, and **1s**). Pyridinium salts **2a−w·Cl** prepared according to method 1 were purified by reversed phase chromatography with nonaqueous eluents. Except in the case of salts deriving from aminobenzamides **1l−n** or from 2-aminopyrazine **1w**, expected pyridinium salts were isolated in good to excellent yields (60−100%).

It is established that reactions using **4·Cl** may require prolonged heating times to reach completion when conducted under conventional activation. Trabolsi also demonstrated that the morphology of materials prepared by Zincke reaction may vary depending on the nature of the activation mode employed.[31] Consequently, the transformation of weakly nucleophilic anilines (Table 2, entries 1−3), anilines carrying adjacent functions with labile hydrogen (entries 4−6), and/or sterically hindered (entries 7−11) was carried out in the presence of in situ generated glutaconaldehyde and under conventional activation. Substrates **1** (0.5 mmol) were quantitatively transformed in the presence of **5** (2 equiv) and HCl (3 equiv) at 90 °C after only 1 h of reaction, except for anthranilic acid derivatives **1r** and **1s**. For the latter two, a slightly higher amount of HCl (5 equiv) improved the conversions; in the case of compound **1s**, even dramatically so (entries 10 and 11). Because the conventional heating allows scaling up chemical processes, a reaction with **5** was tested on a multigram scale. Sterically hindered 2,6-dichloraniline **1q** (10 g) was quaternized at 90 °C after 3 h of reaction. The corresponding salt **2q·Cl** was isolated in 97% yield after purification by reversed phase chromatography.

Using **5** also enabled the control of the counterion by simply varying the nature of the acid present in the reaction mixture. For demonstration purposes, *p*-toluidine **1t** (0.5 mmol, 1

DOI: 10.1021/acs.joc.9b02538
J. Org. Chem. XXXX, XXX, XXX−XXX

Table 2. Use of in Situ Generated Glutaconaldehyde under Conventional Activation



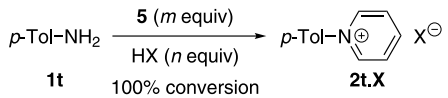
1 2.Cl

entry	substrate[a]	R^1	R^2	conversion (%)[b]
1	**1a**	2-CN	H	100
2	**1d**	2-Cl	H	100
3	**1e**	2-CF_3	H	100
4	**1f**	2-OH	H	100
5	**1i**	2-CO_2H	H	100
6	**1l**	2-$CONH_2$	H	100[c]
7	**1o**	2-Me	Me	100
8	**1p**	2-*i*Pr	*i*Pr	100
9	**1q**	2-Cl	Cl	100
10	**1r**	2-CO_2H	Cl	94 (100)[d]
11	**1s**	2-CO_2H	CF_3	16 (75)[d]

[a]Conditions: **1** (0.50 mmol, 1 equiv), solvent used identical as for method 1 (Table 1). [b]Measured by ^{1}H NMR. [c]Presence of 30% of **2i-Cl** in the crude (^{1}H NMR estimation). [d]HCl (5 equiv).

equiv) was treated with **5** (2 equiv) in the presence of various acids under MW activation at 130 °C for 15 min (Table 3, entries 1−5). In the presence of, respectively, CF_3CO_2H, TfOH, HNO_3, HBF_4, and HPF_6, pyridinium salts **2t·CF_3CO_2**, **2t·TfO**, **2t·NO_3**, **2t·BF_4**, and **2t·PF_6** were quantitatively obtained.

Table 3. Variation of the Counterion[a]



1t 2t.X

entry	X	*m*	*n*	**2t**-X (%)[c]
1	CF_3CO_2	2	5	65
2	CF_3SO_3	2	5	65
3	NO_3	2	3	84
4	BF_4	3	5	60
5	PF_6	3	5	50

[a]Conditions: **1t** (0.50 mmol, 1 equiv), **5** (1.0−1.5 mmol, 2−3 equiv), EtOH/H_2O or *t*BuOH/H_2O (see the Experimental Section), MW, 130 °C, 15 min. [b]Measured by ^{1}H NMR. [c]Isolated yields after reversed phase chromatography.

Again, reactions were conducted in an EtOH/H_2O mixture or alternatively in a *t*BuOH/H_2O mixture when side reactions involving the anion were likely to occur. Reversed phase chromatography produced the expected pyridinium salts in satisfactory yields ranging between 50 and 84%.

It is noteworthy that the generally good conversions observed in this study were obtained despite the instability of glutaconaldehyde, which is known to readily polymerize.[32,33] It has been reported that this compound remains stable for ca. 30 min at −70 °C in a relatively concentrated methanolic solution,[34] and its half-life in Et_2O does not exceed 10 min at room temperature.[35] The propensity of glutaconaldehyde derivatives to dimerize is also well documented.[36] The results presented here therefore suggest that the reaction leading to the formation of intermediates of type **3** is significantly faster than the degradation of **5** in the acidic reaction mixture, even with weakly nucleophilic or sterically hindered substrates.

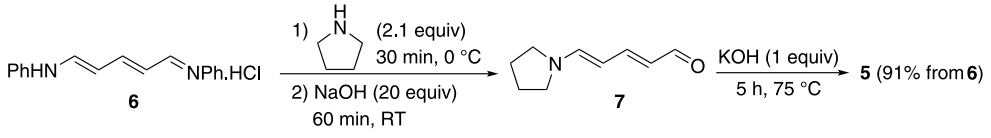
Reagent **5** is classically obtained after basic treatment of activated pyridines.[37,38] For this study, a straightforward access to **5** was developed from the commercially available dianil salt **6** (Scheme 2). Treating **6** (20 g) with a cyclic secondary amine such as pyrrolidine led to the transamination product, which was hydrolyzed under basic conditions. The resulting aminopentadienal **7** was then treated with KOH as previously described. This procedure allowed the obtaining of **5** on multigram scale in only two steps and with an overall yield of 91% from **6**.

In summary, glutaconaldehyde salt **5** in the presence of acid appears as the reagent of choice as a substitute for the Zincke salt to perform the efficient transformation of primary amines into pyridinium salts. Reagent **5** allowed to reverse the stoichiometric ratio in favor of the substrate but also to significantly reduce the excess of material involved when the substrate is a weak nucleophile. Unlike **4·Cl**, it prevented S_NAr side reactions and allowed control of the counterion of the pyridinium with no need for additional steps of salt metathesis. All in all, using **5** in the presence of acid allowed overcoming the limitations associated with **4·Cl** and broadening the scope of the pyridinium salts accessible by quaternization of primary amines. Importantly, all of these advantages have been established in an acidic medium that should induce (according to literature) the fast decomposition of the glutaconaldehyde. As demonstrated in this study, this degradation is prevented in the presence of amines, and this behavior can be used to perform the transformation of primary amines into their corresponding pyridinium salts from milli- to multigram scale.

EXPERIMENTAL SECTION

General Information. All chemicals and solvents were purchased from commercial suppliers (glutaconaldehyde dianil hydrochloride **6** was purchased from TCI) and were used as received; H_2O used as solvent was distillated. Zincke salt **4·Cl** was prepared according to the reported procedure.[21] MW-assisted reactions were carried out with an Anton Paar Monowave 300 reactor, provided with an IR temperature sensor. The automated purification of pyridinum salts was performed on a C18 reversed-phase instrument (40 g cartridges). NMR spectra were recorded at 20 °C at 400 MHz for the ^{1}H NMR spectra, 100 MHz for ^{13}C NMR spectra, and 376 MHz for ^{19}F spectra. Chemical shifts (δ) are reported in part per million (ppm) relative to the residual nondeuterated solvent signal: $\delta_{1H}(CD_3OD)$ = 3.31 ppm, $\delta_{13C}(CD_3OD)$ = 49.00 ppm, $\delta_{1H}(CDCl_3)$ = 7.26 ppm, δ_{1H}(DMSO-d_6) = 2.50 ppm, δ_{13C}(DMSO-d_6) = 39.52 ppm. Coupling constant values (J) are given in hertz (Hz) and refer to apparent multiplicities

Scheme 2. Preparation of Reagent 5



DOI: 10.1021/acs.joc.9b02538
J. Org. Chem. XXXX, XXX, XXX−XXX

indicated as follows: s (singlet), d (doublet), t (triplet), q (quadruplet), hept (heptuplet), m (multiplet), dd (doublet of doublets), td (triplet of doublets), tt (triplet of triplets). IR spectra were recorded on a spectrometer equipped with a diamond ATR unit between 400 and 4000 cm^{-1}. Wavenumbers (ν) are expressed in cm^{-1} at their maximum intensity. LC-MS analyses were performed with a reversed-phase chromatographic system (MeOH was used as eluent in isocratic mode) coupled with a single-quadrupole mass spectrometer (ESI^+ mode, 50 V, 400 °C). CHN analyses were performed by the elemental analysis service of the "Institut de Chimie des Substances Naturelles", Gif-sur-Yvette (France). HRMS spectra were measured in ESI^+ mode by the mass spectrometry service of the "Institut de Chimie Organique et Analytique", Orléans (France).

Preparation of Pyridinum Salts 2a−w·Cl by Action of Glutaconaldehyde Salt 5. Prior to being used in the reaction, a stock-solution of HCl (2.5 N) was prepared either in H_2O or in a *t*BuOH/H_2O mixture. Aqueous solution **S1** was prepared by diluting 2.08 mL of HCl_{aq} (12 N) in 7.92 mL of H_2O; aqueous-alcoholic solution **S2** was prepared by diluting 2.08 mL of HCl_{aq} (12 N) in 7.92 mL of a *t*BuOH/H_2O (50/50) mixture.

Preparation under MW Activation (General Procedure A). Into a MW vial (10 mL) equipped with a stirring bar were successively added the potassium salt **5** (0.75−1.00 mmol, 1.5−2.0 equiv), the aniline derivative **1a−w** (0.50 mmol, 1.0 equiv), and the specified acidic aqueous alcoholic solvent (2 mL). The reaction was performed at 130 °C in a closed vial for 15 min. After completion of the reaction, the solvent was removed under reduced pressure. After addition of MeCN (90 mL), the resulting mixture was sonicated (2 min) and then filtrated over Celite. The salt was obtained after concentration under reduced pressure and purification by reversed phase chromatography according to the specified method (see general procedure B).

Preparation under Conventional Activation. Into a Schlenk tube (10 mL) equipped with a stirring bar were successively added the potassium salt **5** (1.00 mmol, 2.0 equiv), the aniline derivative **1** (0.50 mmol, 1.0 equiv), and the acidic aqueous alcoholic solvent (2 mL). The solvent system used was the same as for the corresponding transformation performed under MW, and it was prepared as follows: 0.6 mL (3.0 equiv of HCl) of **S1** (alternatively, **S2**) and 1.4 mL of EtOH (alternatively, of a *t*BuOH/H_2O (50/50) mixture).

Preparation of Pyridinum Salts 2a−w·Cl by Action of Zincke Salt 4·Cl. Into a MW vial (10 mL) equipped with a stirring bar, were successively added Zincke salt **4·Cl** (141 mg, 0.5 mmol, 1.0 equiv) and the aniline derivative **1a−w** (0.75−1.00 mmol, 1.5−2.0 equiv). For this set of experiments, the aniline was introduced in such amount so that the molar ratio of **1**/**4·Cl** equaled the molar ratio of **5**/**1** used for the equivalent transformation engaged with **5** under MW. The solvent (2 mL) consisted of an EtOH/H_2O (60/40) mixture, except in the case of the aniline derivative **1e**, where an EtOH/H_2O (80/20) mixture was used. The reaction was performed at 130 °C in a closed vial, for 15 min.

Purification of Pyridinium Salts (General Procedure B). The purification was performed by reversed phase chromatography using a CyH/EtOAc/EtOH ternary system as an eluent. The elution gradient was obtained by adding an increasing proportion of EtOH to a solution **S3** consisting of a CyH/EtOAc (50/50) mixture.

Method P1. Impurities were eluted with EtOH/**S3** (10/90) for 4 column-volume (CV), and the salt was eluted with EtOH/**S3** (50/50, 5 CV).

Method P2. Impurities were eluted with EtOH/**S3** (5/95, 4 CV), and the salt was eluted with EtOH/**S3** (50/50, 5 CV).

Method P3. Impurities were eluted with EtOH/**S3** (10/90, 4 CV and then 30/70, 4 CV), and the salt was eluted with EtOH/**S3** (50/50, 5 CV).

Synthesis and Characterization of Pyridinium Salts. Unless specified, the synthesis of pyridinium salts **2a−w·Cl** described hereafter followed the general procedure A. The indicated purification method refers to one of the methods described in the general procedure B. ^1H and ^{13}C NMR spectra of compounds already described were in accordance with data previously reported.

*1-(2-Cyanophenyl)pyridin-1-ium Chloride (**2a-Cl**).*[22] The reaction was performed on a mixture of **1a** (59.1 mg) and **5** (102 mg, 0.75 mmol, 1.5 equiv) in 1.0 mL of **S1** (5.0 equiv of HCl) and 1.0 mL of EtOH. Purification of the crude according to Method P1 gave **2a-Cl** as a light brown powder (98 mg, 90%).

*1-(4-Cyanophenyl)pyridin-1-ium Chloride (**2b·Cl**).*[22] The reaction was performed on a mixture of **1b** (59.1 mg) and **5** (136 mg, 1.00 mmol, 2.0 equiv) in 1.0 mL of **S1** (5.0 equiv of HCl) and 1.0 mL of EtOH. Purification of the crude according to Method P1 gave **2b-Cl** as a beige powder (108 mg, 100%).

*1-(4-Acetylphenyl)pyridin-1-ium Chloride (**2c·Cl**).*[22] The reaction was performed on a mixture of **1c** (67.6 mg) and **5** (136 mg, 1.00 mmol, 2.0 equiv) in 0.6 mL of **S2** (3.0 equiv of HCl) and 1.4 mL of *t*BuOH/H_2O (50/50). Purification of the crude according to Method P1 gave **2c·Cl** as a brown solid (72 mg, 62%).

*1-(2-Chlorophenyl)pyridin-1-ium Chloride (**2d·Cl**).*[22] The reaction was performed on a mixture of **1d** (63.8 mg) and **5** (136 mg, 1.00 mmol, 2.0 equiv) in 1.0 mL of **S1** (5.0 equiv of HCl) and 1.0 mL of EtOH. Purification of the crude according to Method P1 gave **2d·Cl** as a very hygroscopic brown solid (110 mg, 97%).

*1-(2-(Trifluoromethyl)phenyl)pyridin-1-ium Chloride (**2e·Cl**).*[22] The reaction was performed on a mixture of **1e** (80.6 mg) and **5** (136 mg, 1.00 mmol, 2.0 equiv) in 1.0 mL of **S1** (5.0 equiv of HCl) and 1.0 mL of EtOH. Purification of the crude according to Method P1 gave **2e·Cl** as a very hygroscopic brown solid (130 mg, 100%).

*1-(2-Hydroxyphenyl)pyridin-1-ium Chloride (**2f·Cl**).*[22] The reaction was performed on a mixture of **1f** (54.6 mg) and **5** (102 mg, 0.75 mmol, 1.5 equiv) in 1.0 mL of **S1** (5.0 equiv of HCl) and 1.0 mL of EtOH. Purification of the crude according to Method P1 gave **2f·Cl** as a light brown powder (102 mg, 98%).

*1-(3-Hydroxyphenyl)pyridin-1-ium Chloride (**2g·Cl**).*[22] The reaction was performed on a mixture of **1g** (54.6 mg) and **5** (102 mg, 0.75 mmol, 1.5 equiv) in 1.0 mL of **S1** (5.0 equiv of HCl) and 1.0 mL of EtOH. Purification of the crude according to Method P1 gave **2g·Cl** as a beige powder (103 mg, 99%).

*1-(4-Hydroxyphenyl)pyridin-1-ium Chloride (**2h·Cl**).*[22] The reaction was performed on a mixture of **1h** (54.6 mg) and **5** (136 mg, 1.00 mmol, 2.0 equiv) in 1.0 mL of **S1** (5.0 equiv of HCl) and 1.0 mL of EtOH. Purification of the crude according to Method P1 gave **2h·Cl** as a brown powder (101 mg, 97%).

*1-(2-Carboxyphenyl)pyridin-1-ium Chloride (**2i·Cl**).* The reaction was performed on a mixture of **1i** (68.6 mg) and **5** (102 mg, 0.75 mmol, 1.5 equiv) in 1.0 mL of **S2** (5.0 equiv of HCl) and 1.0 mL of *t*BuOH/H_2O (50/50). The purification according to Method P1 gave **2c·Cl** as an orange-brown solid (100 mg, 85%). ^1H NMR (400 MHz, CD_3OD) δ 9.14 (d, J = 7.0 Hz, 2H), 8.81 (t, J = 7.0 Hz, 1H), 8.37 (d, J = 7.5 Hz, 1H), 8.24 (t, J = 7.0 Hz, 2H), 8.01−7.82 (m, 2H), 7.77 (d, J = 7.5 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD) δ 165.9, 148.4, 147.6, 143.8, 135.5, 133.8, 133.3, 128.8, 128.7, 127.2. IR (neat) ν 3370, 2988, 1690, 1626, 1603, 1486, 1394, 1248, 773. LC-MS m/z (%) 200 (100), 201 (14). HRMS (ESI-TOF) m/z: $[M]^+$ Calcd for $C_{12}H_{10}NO_2$ 200.0706; Found 200.0702.

*1-(3-Carboxyphenyl)pyridin-1-ium Chloride (**2j·Cl**).*[22] The reaction was performed on a mixture of **1j** (68.6 mg) and **5** (136 mg, 1.00 mmol, 2.0 equiv) in 0.5 mL of **S2** (2.5 equiv of HCl) and 1.5 mL of *t*BuOH/H_2O (50/50). Purification of the crude according to Method P1 gave **2j·Cl** as a light-brown powder (72 mg, 61%).

*1-(4-Carboxyphenyl)pyridin-1-ium Chloride (**2k·Cl**).*[22] The reaction was performed on a mixture of **1k** (68.6 mg) and **5** (136 mg, 1.00 mmol, 2.0 equiv) in 1.0 mL of **S2** (5.0 equiv of HCl) and 1.0 mL of *t*BuOH/H_2O (50/50). Purification of the crude according to Method P1 gave **2k·Cl** as an orange powder (71 mg, 60%).

*1-(2-Carbamoylphenyl)pyridin-1-ium Chloride (**2l·Cl**).* The reaction was performed on a mixture of **1l** (68.1 mg) and **5** (136 mg, 1.00 mmol, 2.0 equiv) in 1.0 mL of **S2** (5.0 equiv of HCl) and 1.0 mL of *t*BuOH/H_2O (50/50). Purification of the crude according to Method P3 gave **2l·Cl** as a yellow viscous liquid (45 mg, 38%). ^1H NMR (400 MHz, CD_3OD) δ 9.10 (d, J = 7.0 Hz, 2H), 8.79 (t, J = 7.0z Hz, 1H), 8.24 (t, J = 7.0 Hz, 2H), 8.05−7.96 (m, 1H), 7.86 (m, 2H), 7.79 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD) δ 169.1,

DOI: 10.1021/acs.joc.9b02538
J. Org. Chem. XXXX, XXX, XXX−XXX

148.3, 147.4, 142.5, 133.7, 133.2, 132.1, 130.7, 128.8, 128.4. IR (neat) ν 3369, 3067, 1669, 1621, 1575, 1471, 1209, 767. LC-MS m/z (%) 199 (100), 200 (17). HRMS (ESI-TOF) m/z: $[M]^+$ Calcd for $C_{12}H_{11}N_2O$ 199.0866; Found 199.0862.

*1-(3-Carbamoylphenyl)pyridin-1-ium Chloride (**2m·Cl**).*[22] The reaction was performed on a mixture of **1m** (68.1 mg) and **5** (136 mg, 1.00 mmol, 2.0 equiv) in 0.5 mL of **S2** (2.5 equiv of HCl) and 1.5 mL of *t*BuOH/H_2O (50/50). Purification of the crude according to Method P1 gave **2m·Cl** as a brown powder (65 mg, 55%).

*1-(4-Carbamoylphenyl)pyridin-1-ium Chloride (**2n·Cl**).*[22] The reaction was performed on a mixture of **1n** (68.1 mg) and **5** (136 mg, 1.00 mmol, 2.0 equiv) in 0.6 mL of **S2** (3.0 equiv of HCl) and 1.4 mL of *t*BuOH/H_2O (50/50). Purification of the crude according to Method P1 gave **2n·Cl** as a light-brown powder (49 mg, 42%).

*1-(2,6-Dimethylphenyl)pyridin-1-ium Chloride (**2o·Cl**).* The reaction was performed on a mixture of **1o** (60.6 mg) and **5** (102 mg, 0.75 mmol, 1.5 equiv) in 1.0 mL of **S1** (5.0 equiv of HCl) and 1.0 mL of EtOH. Purification of the crude according to Method P1 gave **2o·Cl** as a light-brown powder (100 mg, 91%). ^{1}H NMR (400 MHz, CD_3OD) δ 9.09 (d, J = 6.9 Hz, 2H), 8.89 (t, J = 6.9 Hz, 1H), 8.39 (t, J = 6.9 Hz, 2H), 7.53 (t, J = 7.7 Hz, 1H), 7.41 (d, J = 7.7 Hz, 2H), 2.08 (s, 6H). ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 148.7, 147.6, 143.2, 134.3, 132.6, 130.7, 130.5, 17.1. IR (neat) ν 3349, 3029, 1621, 1468, 1388, 1338, 783, 761. LC-MS m/z (%) 184 (100), 185 (39), 403 (18). HRMS (ESI-TOF) m/z: $[M]^+$ Calcd for $C_{13}H_{14}N$ 184.1121; Found 184.1118.

*1-(2,6-Diisopropylphenyl)pyridin-1-ium Chloride (**2p·Cl**).* The reaction was performed on a mixture of **1p** (88.6 mg) and **5** (136 mg, 1.00 mmol, 2.0 equiv) in 1.0 mL of **S1** (5.0 equiv of HCl) and 1.0 mL of EtOH. Purification of the crude according to Method P2 gave **2p·Cl** as a brown solid (138 mg, 100%). ^{1}H NMR (400 MHz, CD_3OD) δ 9.22 (d, J = 6.8 Hz, 2H), 8.92 (t, J = 6.8 Hz, 1H), 8.39 (t, J = 6.8 Hz, 2H), 7.71 (t, J = 7.9 Hz, 1H), 7.54 (d, J = 7.9 Hz, 2H), 2.12 (hept, J = 6.8 Hz, 2H), 1.21 (d, J = 6.8 Hz, 12H). ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 149.0, 148.0, 144.7, 140.3, 133.5, 130.2 126.3, 29.9, 24.2. IR (neat) ν 3362, 3107, 3064, 2934, 2908, 1621, 1464, 789, 695. LC-MS m/z (%) 240 (100), 241 (39), 242 (3). Anal. calcd for $C_{17}H_{22}ClN.2H_2O$: C, 65.48; H, 8.40; N, 4.49; Found C, 65.34; H, 8.31; N, 4.32. HRMS (ESI-TOF) m/z: $[M]^+$ Calcd for $C_{17}H_{22}N$ 240.1747; Found 240.1747.

*1-(2,6-Dichlorophenyl)pyridin-1-ium Chloride (**2q·Cl**).* The reaction was performed on a mixture of **1q** (81.0 mg) and **5** (102 mg, 0.75 mmol, 1.5 equiv) in 1.0 mL of **S1** (5.0 equiv of HCl) and 1.0 mL of EtOH. Purification of the crude according to Method P1 gave **2q·Cl** as a brown powder (124 mg, 95%). The multigram scale preparation of **2q·Cl** was performed in a one-neck round-bottom flask (500 mL) equipped with a stirring bar and containing aniline **1q** (10.0 g, 61.7 mmol, 1.0 equiv) in EtOH (120 mL). Potassium salt **5** (12.6 g, 92.6 mmol, 1.5 equiv) and HCl_{aq} (2.5 N, 123.4 mL, 5.0 equiv) were successively added to this solution. After the flask was capped with a rubber septum, the mixture was heated and kept at 90 °C for 3 h and then concentrated under reduced pressure. The resulting solid was taken up with MeCN (450 mL), and KCl was removed by filtration on a fritted glass. After concentration of the mother liquor, the resulting slurry was purified according to Method P1 (15.65 g, 97%). ^{1}H NMR (400 MHz, CD_3OD) δ 9.29 (d, J = 7.0 Hz, 2H), 9.01 (t, J = 7.0 Hz, 1H), 8.48 (t, J = 7.0 Hz, 2H), 7.86 (d, J = 7.1 Hz, 2H), 7.83−7.76 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 150.6, 148.2, 138.7, 135.2, 132.5, 131.1, 130.6. IR (neat) ν 3382, 3007, 1620, 1577, 1471, 1446, 780, 729, 691. LC-MS m/z (%) 224 (100), 225 (23), 226 (95). Anal. calcd for $C_{11}H_8Cl_3N.H_2O$: C, 47.43; H, 3.62 N, 5.03; Found C, 47.22; H, 3.57; N, 4.94. HRMS (ESI-TOF) m/z: $[M]^+$ Calcd for $C_{11}H_8Cl_2N$ 224.0028; Found 224.0029.

*1-(2-Carboxy-6-chlorophenyl)pyridin-1-ium Chloride (**2r·Cl**).* The reaction was performed on a mixture of **1r** (85.8 mg) and **5** (136 mg, 1.00 mmol, 2.0 equiv) in 1.0 mL of **S2** (5.0 equiv of HCl) and 1.0 mL of *t*BuOH/H_2O (50/50). Purification of the crude according to Method P3 gave **2r·Cl** as a brown powder (116 mg, 86%). ^{1}H NMR (400 MHz, CD_3OD) δ 9.20 (d, J = 6.8 Hz, 2H), 8.92 (t, J = 6.8 Hz, 1H), 8.36 (m, 3H), 8.09 (d, J = 8.2 Hz, 1H), 7.91 (t, J = 8.2 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 165.0, 149.6, 148.1, 140.4, 136.1, 134.4, 132.5, 132.4, 129.8, 129.6. IR (neat) ν 3369, 3024, 2946, 1697, 1631, 1591, 1471, 1356, 1238, 898, 777, 722. LC-MS m/z (%) 234 (100), 235 (15), 236 (37). HRMS (ESI-TOF) m/z $[M]^+$ Calcd for $C_{12}H_9ClNO_2$ 234.0316; Found 234.0314.

*1-(2-Carboxy-6-(trifluoromethyl)phenyl)pyridin-1-ium Chloride (**2s·Cl**).* The reaction was performed on a mixture of **1s** (102.6 mg) and **5** (136 mg, 1.00 mmol, 2.0 equiv) in 1.0 mL of **S2** (5.0 equiv of HCl) and 1.0 mL of *t*BuOH/H_2O (50/50). Purification of the crude according to Method P3 gave **2s·Cl** as a light-brown solid (99 mg, 65%). ^{1}H NMR (400 MHz, CD_3OD) δ 9.30 (d, J = 7.0 Hz, 2H), 8.91 (t, J = 7.0 Hz, 1H), 8.64 (d, J = 7.9 Hz, 1H), 8.32 (m, 3H), 8.11 (t, J = 7.9 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 164.7, 150.1, 148.8, 140.0, 137.8, 134.3, 132.8, 129.8, 128.9, 127.7 (q, J = 32.1 Hz), 123.6 (q, J = 273.8 Hz). ^{19}F{^{1}H} NMR (376 MHz, CD_3OD) δ −59.85. IR (neat) ν 3369, 2978, 1713, 1628, 1607, 1477, 1385, 1314, 1185, 1125, 793, 692. LC-MS m/z (%) 268 (100), 269 (14), 535 (8). HRMS (ESI-TOF) m/z: $[M]^+$ Calcd for $C_{13}H_9F_3NO_2$ 268.0580; Found 268.0576.

*1-(p-Tolyl)pyridin-1-ium Chloride (**2t·Cl**).*[22] The reaction was performed on a mixture of **1t** (53.6 mg) and **5** (136 mg, 1.00 mmol, 2.0 equiv) in 1.0 mL of **S1** (5.0 equiv of HCl) and 1.0 mL of EtOH. Purification of the crude according to Method P1 gave **2t·Cl** as a red-brown powder (92 mg, 89%).

*1-Benzylpyridin-1-ium Chloride (**2u·Cl**).*[39] The reaction was performed on a mixture of **1u** (53.6 mg) and **5** (102 mg, 0.75 mmol, 1.5 equiv) in 0.4 mL of **S1** (2.0 equiv of HCl) and 1.6 mL of EtOH. Purification of the crude according to Method P1 gave **2u·Cl** as a brown viscous liquid (85 mg, 83%).

*[1,3′-Bipyridin]-1-ium Chloride (**2v·Cl**).* The reaction was performed on a mixture of **1v** (47.1 mg) and **5** (102 mg, 0.75 mmol, 1.5 equiv) in 1.0 mL of **S1** (5.0 equiv of HCl) and 1.0 mL of EtOH. Purification of the crude according to Method P1 gave **2v·Cl** as a yellow viscous liquid (77 mg, 80%). ^{1}H NMR (400 MHz, CD_3OD) δ 9.34 (d, J = 7.2 Hz, 2H), 9.11 (s, 1H), 8.96 (d, J = 4.9 Hz, 1H), 8.87 (t, J = 7.2 Hz, 1H), 8.44−8.39 (m, 1H), 8.36 (t, J = 7.2 Hz, 2H), 7.86 (dd, J = 8.4, 4.9 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 152.7, 148.8, 146.4, 145.8, 141.5, 135.1, 129.8, 126.7. IR (neat) ν 3364, 3040, 1626, 1470, 777, 679. LC-MS m/z (%) 157 (100), 158 (12). Anal. calcd for $C_{10}H_9ClN_2.3/8H_2O$: C, 49.90; H, 6.00; N, 11.64; Found C, 50.06; H, 5.60; N, 11.44. HRMS (ESI-TOF) m/z: $[M]^+$ Calcd for $C_{10}H_9N_2$ 157.0760; Found 157.0759.

*1-(Pyrazin-2-yl)pyridin-1-ium Chloride (**2w·Cl**).* The reaction was performed on a mixture of **1w** (47.6 mg) and **5** (136 mg, 1.00 mmol, 2.0 equiv) in 1.0 mL of **S1** (5.0 equiv of HCl) and 1.0 mL of EtOH. Purification of the crude according to Method P1 gave **2w·Cl** as a light-brown powder (53 mg, 55%). ^{1}H NMR (400 MHz, CD_3OD) δ 9.69 (d, J = 7.0 Hz, 2H), 9.44 (s, 1H), 9.07 (d, J = 1.9 Hz, 1H), 8.92 (t, J = 7.0 Hz, 1H), 8.85 (d, J = 1.9 Hz, 1H), 8.40 (t, J = 7.0 Hz, 2H).^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 150.2 (overlap of two signals), 149.1, 145.1, 144.2, 140.5, 129.7. IR (neat) ν 3420, 3029, 1621, 1612, 1484, 797, 679. LC-MS m/z (%) 158 (100), 159 (12). HRMS (ESI-TOF) m/z: $[M]^+$ Calcd for $C_9H_8N_3$ 158.0713; Found 158.0711.

*1-(p-Tolyl)pyridin-1-ium 2,2,2-trifluoroacetate (**2t·CF$_3$CO$_2$**).* The reaction was performed in a closed MW vial (10 mL) equipped with a stirring bar and containing **1t** (53.6 mg, 0.50 mmol, 1.0 equiv), **5** (136 mg, 1.00 mmol, 2.0 equiv), 1.0 mL (5 equiv) of CF_3CO_2H (2.5 N) in H_2O and 1.0 mL of EtOH. After 15 min of reaction at 130 °C, the solvent was removed under reduced pressure. EtOAc (90 mL) was added to the crude, and the resulting solution was successively sonicated (2 min), filtrated over Celite, and concentrated under reduced pressure. Purification by reversed phase chromatography according to Method P2 gave **2t·CF$_3$CO$_2$** as a brown viscous liquid (92 mg, 65%). ^{1}H NMR (400 MHz, CD_3OD) δ 9.22 (d, J = 7.1 Hz, 2H), 8.77 (t, J = 7.1 Hz, 1H), 8.27 (t, J = 7.1 Hz, 2H), 7.70 (d, J = 8.1 Hz, 2H), 7.56 (d, J = 8.1 Hz, 2H), 2.51 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 162.6 (q, J = 34.0 Hz), 147.62, 145.0, 143.7, 142.2, 132.2, 129.5, 125.2, 118.0 (q, J = 292.3 Hz), 21.1. ^{19}F{^{1}H} NMR (376 MHz, CD_3OD) δ −76.86. IR (neat) ν 3427, 3070, 1672, 1629, 1509,

DOI: 10.1021/acs.joc.9b02538
J. Org. Chem. XXXX, XXX, XXX−XXX

1476, 1415, 1198, 1171, 1120, 799. LC-MS *m/z* (%) 170 (100), 171 (13). HRMS (ESI-TOF) *m/z*: $[M]^+$ Calcd for $C_{12}H_{12}N$ 170.0964; Found 170.0962.

*1-(p-Tolyl)pyridin-1-ium Trifluoromethanesulfonate (**2t·CF$_3$SO$_3$**).* The reaction was performed in a closed MW vial (10 mL) equipped with a stirring bar and containing **1t** (53.6 mg, 0.50 mmol, 1.0 equiv), **5** (136 mg, 1.00 mmol, 2.0 equiv), 1.0 mL (5 equiv) of CF_3SO_3H (2.5 N) in EtOH and 1.0 mL of H_2O. After 15 min of reaction at 130 °C, the solvent was removed under reduced pressure. EtOAc (90 mL) was added to the crude, and the resulting solution was successively sonicated (2 min), filtrated over Celite, and concentrated under reduced pressure. Purification by reversed phase chromatography according to Method P2 gave **2t·CF$_3$SO$_3$** as a brown viscous liquid (104 mg, 65%). ^{1}H NMR (400 MHz, CD_3OD) δ 9.21 (d, J = 7.0 Hz, 2H), 8.76 (t, J = 7.0 Hz, 1H), 8.26 (t, J = 7.0 Hz, 2H), 7.69 (d, J = 8.0 Hz, 2H), 7.56 (d, J = 8.0 Hz, 2H), 2.51 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD) δ 147.5, 145.8, 143.6, 142.1, 132.1, 129.5, 125.1, 121.75 (q, J = 318.7 Hz), 21.1. $^{19}F\{^1H\}$ NMR (376 MHz, CD_3OD) δ −79.94. IR (neat) ν 3444, 3075, 1630, 1509, 1476, 1447, 1155, 1027, 778. LC-MS *m/z* (%) 170 (100), 171 (15), 489 (6). Anal. calcd for $C_{13}H_{12}F_3NO_3S$: C, 48.90; H, 3.79; N, 4.39; Found C, 48.74; H, 3.75; N, 4.05. HRMS (ESI-TOF) *m/z*: $[M]^+$ Calcd for $C_{12}H_{12}N$ 170.0964; Found 170.0961.

*1-(p-Tolyl)pyridin-1-ium Nitrate (**2t·NO$_3$**).* The reaction was performed in a closed MW vial (10 mL) equipped with a stirring bar and containing **1t** (53.6 mg, 0.50 mmol, 1.0 equiv), **5** (136 mg, 1.00 mmol, 2.0 equiv), 0.6 mL (3 equiv) of HNO_3 (2.5 N) in *t*BuOH/H_2O (50/50) and 1.4 mL of *t*BuOH/H_2O (50/50). After 15 min of reaction at 130 °C, the solvent was removed under reduced pressure. EtOH (90 mL) was added to the crude, and the resulting solution was successively sonicated (2 min), filtrated over Celite, and concentrated under reduced pressure. Purification by reversed phase chromatography according to Method P1 gave **2t·NO$_3$** as a brown viscous liquid (98 mg, 84%). ^{1}H NMR (400 MHz, CD_3OD) δ 9.22 (d, J = 7.0 Hz, 2H), 8.76 (t, J = 7.0 Hz, 1H), 8.26 (t, J = 7.0 Hz, 2H), 7.70 (d, J = 8.2 Hz, 2H), 7.56 (d, J = 8.2 Hz, 2H), 2.51 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD) δ 147.6, 146.0, 143.7, 142.2, 132.1, 129.5, 125.2, 21.1. IR (neat) ν 3119, 3062, 1629, 1511, 1475, 1339, 827. LC-MS *m/z* (%) 170 (100), 171 (13). HRMS (ESI-TOF) *m/z*: $[M]^+$ Calcd for $C_{12}H_{12}N$ 170.0964; Found 170.0959.

*1-(p-Tolyl)pyridin-1-ium Tetrafluoroborate (**2t·BF$_4$**).* The reaction was performed in a closed MW vial (10 mL) equipped with a stirring bar and containing **1t** (53.6 mg, 0.50 mmol, 1.0 equiv), **5** (204 mg, 1.50 mmol, 3.0 equiv), 1.0 mL (5 equiv) of HBF_4 (2.5 N) in *t*BuOH/H_2O (50/50) and 1.0 mL of *t*BuOH/H_2O (50/50). After 15 min of reaction at 130 °C, the solvent was removed under reduced pressure. EtOH (90 mL) was added to the crude, and the resulting solution was successively sonicated (2 min), filtrated over Celite, and concentrated under reduced pressure. Purification by reversed phase chromatography according to Method P2 gave **2t·BF$_4$** as an orange powder (77 mg, 60%). ^{1}H NMR (400 MHz, CD_3OD) δ 9.19 (d, J = 6.9 Hz, 2H), 8.76 (t, J = 6.9 Hz, 1H), 8.26 (t, J = 6.9 Hz, 2H), 7.70 (d, J = 8.2 Hz, 2H), 7.56 (d, J = 8.2 Hz, 2H), 2.51 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD) δ 147.6 (s), 146.0, 143.7, 142.2, 132.1, 129.5, 125.2, 21.1. $^{19}F\{^1H\}$ NMR (376 MHz, CD_3OD) δ −154.2. IR (neat) ν 3132, 3082, 1633, 1515, 1488, 1415, 781. LC-MS *m/z* (%) 170 (100), 171 (14). Anal. calcd for $C_{12}H_{12}BF_4N.1/4H_2O$: C, 55.11; H, 4.82; N, 5.36; Found C, 55.45; H, 4.64; N, 5.29. HRMS (ESI-TOF) *m/z*: $[M]^+$ Calcd for $C_{12}H_{12}N$ 170.0964; Found 170.0963.

*1-(p-Tolyl)pyridin-1-ium Hexafluorophosphate (**2t·PF$_6$**).* The reaction was performed in a closed MW vial (10 mL) equipped with a stirring bar and containing **1t** (53.6 mg, 0.50 mmol, 1.0 equiv), **5** (204 mg, 1.50 mmol, 3.0 equiv), 1.0 mL (5 equiv) of HPF_6 (2.5 N) in *t*BuOH/H_2O (50/50) and 1.0 mL of *t*BuOH/H_2O (50/50). After 15 min of reaction at 130 °C, the solvent was removed under reduced pressure. EtOH (90 mL) was added to the crude, and the resulting solution was successively sonicated (2 min), filtrated over Celite, and concentrated under reduced pressure. Purification by reversed phase chromatography according to Method P2 gave **2t·PF$_6$** as a brown viscous liquid (55 mg, 35%). ^{1}H NMR (400 MHz, CD_3OD) δ 9.22 (d, J = 7.1 Hz, 2H), 8.77 (t, J = 7.1 Hz, 1H), 8.27 (t, J = 7.1 Hz, 2H), 7.70 (d, J = 8.1 Hz, 2H), 7.56 (d, J = 8.1 Hz, 2H), 2.51 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD) δ 147.6, 146.0, 143.8, 142.2, 132.2, 129.5, 125.2, 21.1. IR (neat) ν 3288, 2940, 2874, 1634, 1524, 1455, 882. ν LC-MS *m/z* (%) 170 (100), 171 (14). HRMS (ESI-TOF) *m/z*: $[M]^+$ Calcd for $C_{12}H_{12}N$ 170.0964; Found 170.0960.

Preparation of Glutaconaldehyde Salt 5. *(2E,4E)-5-(Pyrrolidin-1-yl)penta-2,4-dienal (**7**).* A solution of pyrrolidine (12.1 mL, 147.4 mmol, 2.1 equiv) in MeOH (250 mL) was prepared in a one-neck round-bottom flask (500 mL) equipped with a stirring bar and cooled at 0 °C. Glutaconaldehyde dianil hydrochloride **6** (20 g, 70.2 mmol, 1.0 equiv) was added portionwise to the solution, and the mixture was maintained at 0 °C under agitation. After 45 min, the solvent was removed under reduced pressure. To the resulting solid, THF (200 mL) was added. After trituration, the mixture was filtrated on a fritted glass, and the solid was first washed with THF (3 × 100 mL), then with Et_2O (200 mL). After dissolution of the solid in H_2O (300 mL), the resulting aqueous solution was washed with Et_2O (4 × 100 mL) and then poured in an Erlenmeyer (1 L) equipped with a stirring bar. Under stirring, the aqueous solution was cooled down to 0 °C and then basified by adding NaOH (56 g, 1.4 mol, 20.0 equiv). CH_2Cl_2 (400 mL) was added to this solution, and the biphasic mixture was stirred for a further 60 min at room temperature. After separation, the organic layer was dried over Na_2SO_4, filtrated, and concentrated under reduced pressure. Aminopentadienal **7** was obtained as a brown solid (10.2 g) and engaged in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (d, J = 8.5 Hz, 1H), 7.09 (t, J = 14.0 Hz, 1H), 7.01 (d, J = 12.5 Hz, 1H), 5.83 (dd, J = 14.0, 8.5 Hz, 1H), 5.24 (t, J = 12.5 Hz, 1H), 3.53- 3.04 (m, 4H), 2.07−1.81 (m, 4H).

*Glutaconaldehyde Potassium Salt (**5**).*[40] In a one-neck round-bottom flask (500 mL) equipped with a stirring bar, KOH (99.98% purity, 3.77 g, 67.4 mmol, 1.0 equiv) was dissolved in MeOH (18 mL). After addition of THF (160 mL) and aminopentadienal **7** (10.2 g, 67.4 mmol, 1.0 equiv), the mixture was refluxed for 5 h. The mixture was cooled to 0 °C, and the expected salt was precipitated by addition of Et_2O (300 mL). After filtration on a fritted glass, the solid was washed with CH_2Cl_2 (70 mL) and then dissolved in a MeOH/EtOH (90/10) mixture (880 mL). The alcoholic solution was filtered over a pad of Celite and concentrated under reduced pressure. Glutaconaldehyde potassium salt **5** was obtained as a brown powder, stored in a desiccator, and used without further purification (8.7 g, 91% from dianil hydrochloride **6**).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.9b02538.

NMR and IR spectra of purified compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: rivard@icmpe.cnrs.fr.

ORCID

Michael Rivard: 0000-0002-5487-1595

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

G.A. thanks the MENESR and the Ecole Doctorale SIE (Université Paris Est) for a PhD fellowship. G.A. also thanks the team "Systèmes Polymères Complexes" for financial support. Tanya Farthing is gratefully acknowledged for proofreading this article.

DOI: 10.1021/acs.joc.9b02538
J. Org. Chem. XXXX, XXX, XXX−XXX

DEDICATION

In memory of Dr. Christian Marazano, who passed away on November 12, 2008.

REFERENCES

(1) Klauck, F. J. R.; James, M. J.; Glorius, F. Deaminative strategy for the visible-light-mediated generation of alkyl radicals. *Angew. Chem., Int. Ed.* **2017**, *56* (40), 12336−12339.

(2) Moser, D.; Duan, Y.; Wang, F.; Ma, Y.; O'Neill, M. J.; Cornella, J. Selective functionalization of aminoheterocycles by a pyrylium salt. *Angew. Chem., Int. Ed.* **2018**, *57* (34), 11035−11039.

(3) Wu, J.; He, L.; Noble, A.; Aggarwal, V. K. Photoinduced deaminative borylation of alkylamines. *J. Am. Chem. Soc.* **2018**, *140* (34), 10700−10704.

(4) Plunkett, S.; Basch, C. H.; Santana, S. O.; Watson, M. P. Harnessing alkylpyridinium salts as electrophiles in deaminative alkyl−alkyl cross-couplings. *J. Am. Chem. Soc.* **2019**, *141* (6), 2257−2262.

(5) Yoshida, Z.; Sugimoto, H.; Sugimoto, T.; Yoneda, S. Reactions of thiopyrylium cations with amines. *J. Org. Chem.* **1973**, *38* (23), 3990−3993.

(6) Graphakos, B. J.; Katritzky, A. R.; Lhommet, G.; Reynolds, K. Heterocycles in organic synthesis. Part 13. The reaction of 2,4-diphenylthiopyrylium perchlorate with amines. *J. Chem. Soc., Perkin Trans. 1* **1980**, No. 7, 1345−1346.

(7) Zincke, T. On dinitrophenylpyridinium chloride and its conversion products. *Justus Liebigs Ann. Chem.* **1904**, *330*, 361−374.

(8) Cheng, W.-C.; Kurth, M. J. The Zincke reaction. A review. *Org. Prep. Proced. Int.* **2002**, *34* (6), 585−608.

(9) Han, Z.; Kortlever, R.; Chen, H.-Y.; Peters, J. C.; Agapie, T. CO_2 reduction selective for C ≥ 2 products on polycrystalline copper with *N*-substituted pyridinium additives. *ACS Cent. Sci.* **2017**, *3* (8), 853−859.

(10) Chen, S.; Polen, S. M.; Wang, L.; Yamasaki, M.; Hadad, C. M.; Badjic, J. D. Two-dimensional supramolecular polymers embodying large unilamellar vesicles in water. *J. Am. Chem. Soc.* **2016**, *138* (35), 11312−11317.

(11) Yin, H.; Rosas, R.; Gigmes, D.; Ouari, O.; Wang, R.; Kermagoret, A.; Bardelang, D. Metal actuated ring translocation switches in water. *Org. Lett.* **2018**, *20* (11), 3187−3191.

(12) Vu, V. H.; Jouanno, L.-A.; Cheignon, A.; Roisnel, T.; Dorcet, V.; Sinbandhit, S.; Hurvois, J.-P. Modified Fry cyanation of a chiral pyridinium salt: asymmetric syntheses of (−)-coniine and (−)-solenopsin A. *Eur. J. Org. Chem.* **2013**, *2013* (24), 5464−5474.

(13) Kaiser, A.; Billot, X.; Gateau-Olesker, A.; Marazano, C.; Das, B. C. Selective entry to the dimeric or oligomeric pyridinium sponge macrocycles via aminopentadienal derivatives. Possible biogenetic relevance with manzamine alkaloids. *J. Am. Chem. Soc.* **1998**, *120* (32), 8026−8034.

(14) Szczepankiewicz, B. G.; Dai, H.; Koppetsch, K. J.; Qian, D.; Jiang, F.; Mao, C.; Perni, R. B. Synthesis of carba-NAD and the structures of its ternary complexes with SIRT3 and SIRT5. *J. Org. Chem.* **2012**, *77* (17), 7319−7329.

(15) van der Aa, L. J.; Vader, P.; Storm, G.; Schiffelers, R. M.; Engbersen, J. F. J. Intercalating quaternary nicotinamide-based poly(amido amine)s for gene delivery. *J. Controlled Release* **2014**, *195*, 11−20.

(16) Colquhoun, H. M.; Greenland, B. W.; Zhu, Z.; Shaw, J. S.; Cardin, C. J.; Burattini, S.; Elliott, J. M.; Basu, S.; Gasa, T. B.; Stoddart, J. F. A general synthesis of macrocyclic π-electron-acceptor systems. *Org. Lett.* **2009**, *11* (22), 5238−5241.

(17) Coe, B. J.; Foxon, S. P.; Harper, E. C.; Helliwell, M.; Raftery, J.; Swanson, C. A.; Brunschwig, B. S.; Clays, K.; Franz, E.; Garin, J.; Orduna, J.; Horton, P. N.; Hursthouse, M. B. Evolution of linear absorption and nonlinear optical properties in V-shaped ruthenium(II)-based chromophores. *J. Am. Chem. Soc.* **2010**, *132* (5), 1706−1723.

(18) Yazaki, K.; Sei, Y.; Akita, M.; Yoshizawa, M. A polyaromatic molecular tube that binds long hydrocarbons with high selectivity. *Nat. Commun.* **2014**, *5*, 5179.

(19) Kahlfuss, C.; Denis-Quanquin, S.; Calin, N.; Dumont, E.; Garavelli, M.; Royal, G.; Cobo, S.; Saint-Aman, E.; Bucher, C. Electron-triggered metamorphism in porphyrin-based self-assembled coordination polymers. *J. Am. Chem. Soc.* **2016**, *138* (46), 15234−15242.

(20) Wu, G.; Olesinska, M.; Wu, Y.; Matak-Vinkovic, D.; Scherman, O. A. Mining 2:2 complexes from 1:1 stoichiometry: formation of cucurbit[8]uril-diarylviologen quaternary complexes favored by electron-donating substituents. *J. Am. Chem. Soc.* **2017**, *139* (8), 3202−3208.

(21) Lachaise, I.; Zeghbib, N.; Asskar, G.; Rivard, M.; Martens, T. Contribution of the centrifugal partition chromatography (CPC) to the purification of Zincke reaction products. *ChemistrySelect* **2019**, *4* (12), 3538−3541.

(22) Zeghbib, N.; Thelliere, P.; Rivard, M.; Martens, T. Microwaves and aqueous solvents promote the reaction of poorly nucleophilic anilines with a Zincke salt. *J. Org. Chem.* **2016**, *81* (8), 3256−3262.

(23) Wang, R.-T.; Lee, G.-H.; Lai, C. K. Effect of counter ions on the mesogenic ionic *N*-phenylpyridiniums. *CrystEngComm* **2018**, *20* (18), 2593−2607.

(24) Rama, T.; Alvarino, C.; Domarco, O.; Platas-Iglesias, C.; Blanco, V.; Garcia, M. D.; Peinador, C.; Quintela, J. M. Self-assembly of Pd_2L_2 metallacycles owning diversely functionalized racemic ligands. *Inorg. Chem.* **2016**, *55* (5), 2290−2298.

(25) Nguyen, T. M.; Sanchez-Salvatori, M. d. R.; Wypych, J.-C.; Marazano, C. Aminopentadiene imines from Zincke salts of 3-alkylpyridines. Application to a synthesis of pyridinium salts from amino acids. *J. Org. Chem.* **2007**, *72* (15), 5916−5919.

(26) Peixoto, S.; Nguyen, T. M.; Crich, D.; Delpech, B.; Marazano, C. One-pot formation of piperidine- and pyrrolidine-substituted pyridinium salts via addition of 5-alkylaminopenta-2,4-dienals to *N*-acyliminium ions: application to the synthesis of (±)-nicotine and analogs. *Org. Lett.* **2010**, *12* (21), 4760−4763.

(27) Kossmehl, G.; Kabbeckkupijai, D. Synthesis and electrical-conductivity of *N*-arylated pyridinium TCNQ complex salts. *Synth. Met.* **1993**, *53* (3), 347−351.

(28) Tsukamoto, T.; Shimada, T.; Takagi, S. Unique photochemical properties of p-substituted cationic triphenylbenzene derivatives on a clay layer surface. *J. Phys. Chem. C* **2013**, *117* (6), 2774−2779.

(29) Wang, L.; Kong, L.; Li, Y.; Ganguly, R.; Kinjo, R. Anti-Markovnikov hydroimination of terminal alkynes in gold-catalyzed pyridine construction from ammonia. *Chem. Commun.* **2015**, *51* (62), 12419−12422.

(30) Tinnermann, H.; Nicholls, L. D. M.; Johannsen, T.; Wille, C.; Golz, C.; Goddard, R.; Alcarazo, M. *N*-Arylpyridiniophosphines: synthesis, structure, and applications in Au(I) catalysis. *ACS Catal.* **2018**, *8* (11), 10457−10463.

(31) Das, G.; Skorjanc, T.; Sharma, S. K.; Gandara, F.; Lusi, M.; Shankar Rao, D. S.; Vimala, S.; Krishna Prasad, S.; Raya, J.; Han, D. S.; Jagannathan, R.; Olsen, J.-C.; Trabolsi, A. Viologen-based conjugated covalent organic networks via Zincke reaction. *J. Am. Chem. Soc.* **2017**, *139* (28), 9558−9565.

(32) Becher, J. Synthesis and reactions of glutaconaldehyde and 5-amino-2,4-pentadienals. *Synthesis* **1980**, *8*, 589−612.

(33) Klages, F.; Träger, H. Über den Austausch von Pyridin-Stickstoff gegen Oxonium-Sauerstoff (III. Mitteil. über Oxonium-Salze. *Chem. Ber.* **1953**, *86* (10), 1327−1330.

(34) Becher, J.; Christensen, M. C. Derivatives and reactions of glutaconaldehyde. IX. Substitution reactions in the glutaconaldehyde anion. Assignment of structure of a free glutaconaldehyde. *Tetrahedron* **1979**, *35* (12), 1523−1530.

(35) Becher, J.; Haunso, N.; Pedersen, T. Derivatives of glutacondialdehyde. 2. Ring-opening of 3-methylpyridine 3-methoxypyridine. Preparation of 2-substituted and 4-substituted glutacondialdehyde derivatives. The structure of glutacondialdehyde bis-diacetal. *Acta Chem. Scand.* **1975**, *B 29* (1), 124−132.

DOI: 10.1021/acs.joc.9b02538
J. Org. Chem. XXXX, XXX, XXX−XXX

(36) Sanchez-Salvatori, M. d. R.; Lopez-Giral, A.; Ben Abdeljelil, K.; Marazano, C. 3-Substituted pentadienals derivatives from condensation of imines anions to malonaldehyde equivalents. A C-C-C+C-C +N type entry to 3-alkyl substituted pyridinium salts. *Tetrahedron Lett.* **2006**, *47* (31), 5503−5506.
(37) Becher, J. Glutaconaldehyde sodium salt from hydrolysis of pyridinium-1-sulfonate. *Org. Synth.* **1979**, *59*, 79−84.
(38) Hong, A. Y.; Vanderwal, C. D. A synthesis of alsmaphorazine B demonstrates the chemical feasibility of a new biogenetic hypothesis. *J. Am. Chem. Soc.* **2015**, *137* (23), 7306−7309.
(39) Gayet, F.; El Kalamouni, C.; Lavedan, P.; Marty, J.-D.; Brûlet, A.; Lauth-de Viguerie, N. Ionic liquid/oil microemulsions as chemical nanoreactors. *Langmuir* **2009**, *25* (17), 9741−9750.
(40) Nguyen, T. M.; Peixoto, S.; Ouairy, C.; Nguyen, T. D.; Benechie, M.; Marazano, C.; Michel, P. Simple and convenient method for the synthesis of 2-substituted glutaconaldehyde salts and 2-substituted glutaconaldehyde derivatives. *Synthesis* **2010**, *1*, 103−109.

DOI: 10.1021/acs.joc.9b02538
J. Org. Chem. XXXX, XXX, XXX−XXX