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Base-Stabilized Nitrilium Ions as Convenient Imine Synthons

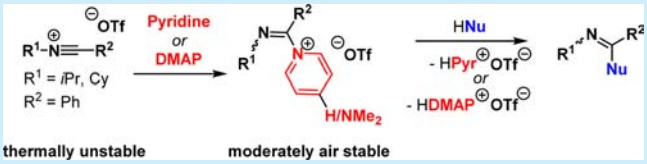
Tom van Dijk,[†] Martijn S. Bakker,[†] Flip Holtrop,[†] Martin Nieger,[‡] J. Chris Slootweg,*[,†] and Koop Lammertsma*[,†]

[†]Department of Chemistry and Pharmaceutical Sciences, VU University Amsterdam, De Boelelaan 1083, 1081 HV Amsterdam, The Netherlands

[‡]Laboratory of Inorganic Chemistry, Department of Chemistry, University of Helsinki, 00014 Helsinki, Finland

Supporting Information

ABSTRACT: A simple and efficient methodology is presented for the synthesis of a wide range of substituted imines. It is based on stabilizing readily available, but thermally labile, *N*-alkylnitrilium triflates with pyridine or DMAP to moderately air-stable adducts. These base-stabilized imine synthons react conveniently with phosphorus- and nitrogen-based nucleophiles to amidines and phosphaamidines.



Nitrilium ions[1] are reactive intermediates in the Beckmann rearrangement[2] and the Ugi,[3] Schmidt,[2b,4] Ritter,[2b,5] Bischler−Napieralski,[2b,6] and von Braun[2b,7] reactions. Isolable, characterizable, and readily synthesizable nitrilium ions (**A**, X = OTf) (Figure 1) were reported by us only recently,[8] but the

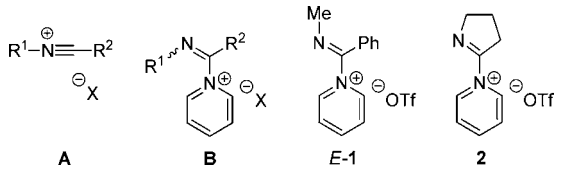
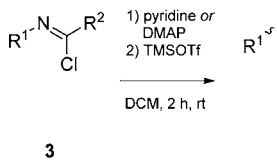


Figure 1. Nitrilium ions and their pyridine adducts.

effective use of these imine synthons in organic synthesis is hampered by their ease of hydrolysis to amides and the thermal lability of the *N*-alkyl derivatives (e.g., R^1 = *i*-Pr or Cy, R^2 = Ph) above −20 °C.[8] We envisioned that increasing the stability, while retaining reactivity, would enhance the synthetic scope of the ions. Toward this end, we focused on the electrophilic *N*-imidoylpyridinium ion **B**.[9] Such pyridine-stabilized nitrilium ions are generated in situ in the synthesis of amidines,[10] esters,[11] thioamides,[12] thiazolines,[13] alkynyl imines,[14] pyridines,[15] and pyrimidines,[16] with the *E*-isomer, such as *E*-**1**, being the key intermediate in the regioselective 1,2-functionalization of pyridines.[17,18] To date, few examples of **B** have been described spectroscopically,[9,16] and only a single X-ray structure has been reported, i.e., for **2**.[19] We now report on the facile synthesis and characterization of base-stabilized nitrilium ions as well as on their use in synthesizing amidines and phosphaamidines.

Imidoyl chlorides **3** reacted at room temperature with pyridine and trimethylsilyl triflate (TMSOTf) to give the pyridine-stabilized nitrilium triflates **4** in good to excellent isolated yields (73−96%; Scheme 1).[20] At room temperature and under an inert atmosphere, both the *N*-aryl and *N*-alkyl derivatives are stable in solution and as solids, which improves their handling

Scheme 1. Formation of Base-Stabilized Nitrilium Ions from Imidoyl Chlorides



	R^1	R^2
a	Mes	*t*Bu
b	Ph	*t*Bu
c	*i*Pr	Ph
d	Cy	Ph

significantly compared to the base-free nitrilium ions.[8] Reacting the imidoyl chlorides **3** instead with 4-(dimethylamino)pyridine (DMAP) gave the corresponding triflates **5** (81−100%; Scheme 1),[20,21] which are still easier to handle because they are stable in air with only 3% decomposition for solid **5a** over a one month period.[22,23]

The molecular structures of **4a** and **5a**, obtained by X-ray crystal structure determinations (Figure 2),[24] reveal *Z*-imine conformations with short C=N double[25] (**4a**: 1.243(2), **5a**: 1.249(5) Å) and average pyridinium C1−N2 single bonds[25] (**4a**: 1.490(2), **5a**: 1.484(5) Å) that are similar in lengths to those reported for **2** (C=N 1.263(7)/1.239(7), C−N 1.442(7)/1.452(7) Å).[19] The ωB97X-D/6-31+G(d,p)[26] calculations confirm a preference for the Z-conformers (ΔG_{E-Z} = 5.2 (**4a**), 2.9 (**5a**) kcal·mol^{-1}), which are also the only ones observed in the ^{1}H and ^{13}C NMR spectra.

The molecular structure of the *N*-alkyl-substituted pyridinium ion **5c** shows instead an *E*-configurated imine with the expected C1−N1 double and C1−N2 single bonds length of 1.2575(16) and 1.4525(15) Å, respectively (Figure 2);[24] the *E*-conformer is also favored at ωB97X-D/6-31+G(d,p) (ΔG_{E-Z} = −5.4 kcal·mol^{-1}). This is not the only difference in the two base-stabilized nitrilium ions. Namely, the DMAP substituent and the C=N

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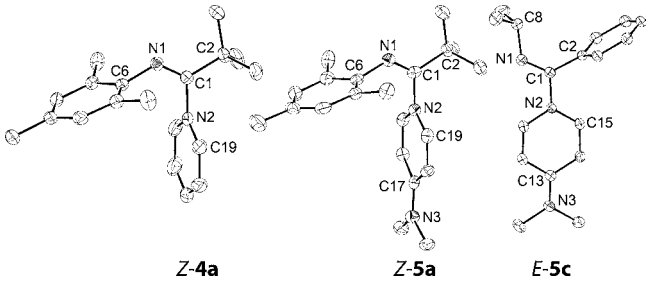
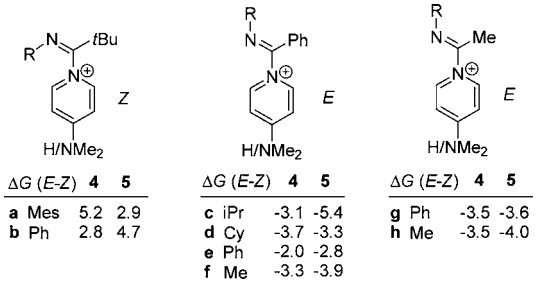


Figure 2. Molecular structures of *Z*-**4a**, *Z*-**5a**, and *E*-**5c** (hydrogen atoms and triflate anions are omitted for clarity, and displacement parameters are drawn at 50% probability level). Selected bond lengths (Å), angles (deg), and torsion angles (deg) for *Z*-**4a**: C1−C2 1.517(2), C1−N1 1.243(2), C1−N2 1.490(2), C6−N1 1.428(2); C2−C1−N2 115.38(14), N1−C1−N2 120.35(14); N1−C1−N2−C19 88.0(2). *Z*-**5a**: C1−C2 1.528(5), C1−N1 1.249(5), C1−N2 1.484(5), C6−N1 1.432(5), C17−N3 1.332(5); C2−C1−N2 115.5(3), N1−C1−N2 121.3(3); N1−C1−N2−C19−86.0(4). *E*-**5c**: C1−C2 1.4928(17), C1−N1 1.2575(16), C1−N2 1.4525(15), C8−N1 1.4660(17), C13−N3 1.3278(16); C2−C1−N1 128.79(12), N1−C1−N2 115.63(11); N1−C1−N2−C15 25.8(12).

bond of *E*-**5c** approach coplanarity (φ = 25.8(12)°), while the pyridine group and the imine bond are orthogonal in *Z*-**4a** (φ = 88.0(2)°) and *Z*-**5a** φ = 86.0(4)°); the corresponding DFT-calculated torsion angles for these three ions are 16.3°, 73.7°, and 70.3°, respectively.

It is evident that the nature of the imine substituents determines the relative stabilities of the *E*/*Z* isomers. This is readily elucidated computationally for the synthesized pyridine- and DMAP-stabilized nitrilium ions **4a−d** and **5a−d**, extended with structures **4e−h** and **5e−h**, respectively (Figure 3).[26] The *E*-



ΔG (*E*-*Z*)	**4**	**5**
a Mes	5.2	2.9
b Ph	2.8	4.7

ΔG (*E*-*Z*)	**4**	**5**
c iPr	-3.1	-5.4
d Cy	-3.7	-3.3
e Ph	-2.0	-2.8
f Me	-3.3	-3.9

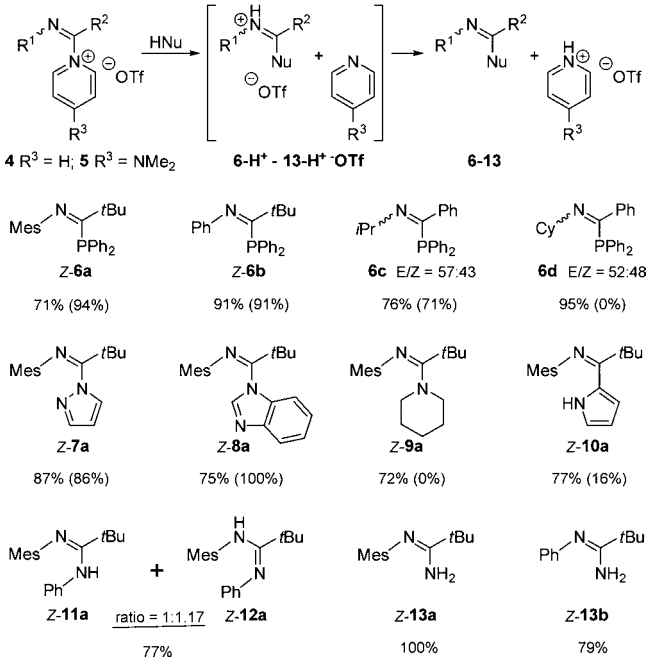
ΔG (*E*-*Z*)	**4**	**5**
g Ph	-3.5	-3.6
h Me	-3.5	-4.0

Figure 3. Relative free energies (ωB97X-D/6-31+G(d,p), kcal·mol^{-1}) for the *E*/*Z*-isomers of **4** and **5**, depicting the most stable ones.

conformer is clearly favored when the imine C atom carries a methyl or phenyl substituent, both of which allow for near coplanarity of the pyridine unit (φ < 31°). Such a coplanar arrangement is impeded with the bulkier *tert*-butyl group giving a more orthogonal orientation of the pyridine unit (φ > 65°), therefore breaking resonance and freeing up space for a *Z*-conformation of the imine and thus rendering this as the most stable conformer. This behavior also underpins that the reported regioselective 1,2-functionalization of pyridines via *E*-configurated imines is tunable by the C-substituent.[18a]

The nitrilium ion reactivity toward *P*- and *N*-nucleophiles[27] was addressed next with a focus on the easier to handle DMAP-stabilized **5** (Scheme 2).[28] We start by reporting on phosphaamidines, which are valuable 1,3-P,N-ligands in coordination chemistry.[8,30] Reacting the *N*-aryl derivative (**5a**) with diphenylphosphane ($HPPh_2$) for 30 min in refluxing toluene caused displacement of the DMAP group to afford

Scheme 2. Reaction of Base-Stabilized Nitrilium Ions with P- and N-Nucleophiles[a]



[a]The yields of **6−13** are for the reaction with **5** and with those for **4** in parentheses.

iminophosphane **6a** in 71% yield after deprotonation, isolation, and crystallization.[20,29] ^{31}P NMR monitoring of the reaction revealed full conversion to only *Z*-**6a** (δ^{31}P = 1.1 ppm), which is also computationally the favored isomer (ΔG_{E-Z} = 2.7 kcal·mol^{-1}). The *N*-phenyl (**5b**) and *N*-isopropyl (**5c**) derivatives reacted likewise with $HPPh_2$ to give after workup the corresponding 1,3-P,N-ligands **6b** (91%) and **9c** (76%).[30] The less stabilized pyridine analogues **4a−c** reacted already at room temperature in DCM to afford **6a−c** in 71−94% yield (Scheme 2), but the *N*-cyclohexyl derivative (**4d**) converted only to a 1.0:1.4 *E*/*Z*-mixture of ion **6d-H**$^+$,[30] which could not be deprotonated by the liberated pyridine (Scheme 2). The importance of the basicity of the pyridine moiety is illustrated by the corresponding reaction of DMAP-stabilized **6d** with $HPPh_2$ that rendered iminophosphane **6d**[30] in 95% isolated yield. This more robust methodology is a welcome extension to the recently reported synthesis of phosphaamidines from nonstabilized nitrilium ions and phosphanes.[8,30]

Next, we explored the scope of the reaction of **5a** with different types of *N*-nucleophiles. Treatment with pyrazole and benzimidazole for 1.5 h in refluxing toluene afforded after workup amidines **7a**[31,32] (87%) and **8a** (75%),[33] respectively, both as a single isomer (Scheme 2), illustrating that also *N*-nucleophiles conveniently displace DMAP. A single-crystal X-ray diffraction analysis of **8a** revealed expectedly a *Z*-configured imine (C1−N1 1.262(4), C1−N2 1.456(4) Å; Figure 4),[24] which concurs with the DFT calculations (ΔG_{E-Z} = 3.5 (**7a**), 4.3 (**8a**) kcal·mol^{-1}). Piperidine and pyrrole[34] reacted likewise with **5a** to give as only observed product the *Z*-isomer of, respectively, *Z*-amidine **9a** (72%)[35,36] and *Z*-iminopyrrole **10a**,[37,38] the assignments of which are supported by the calculated *E*/*Z*-energy differences (ΔG_{E-Z} = 2.4 (**9a**), 8.2 (**10a**) kcal·mol^{-1}). Conducting these reactions instead with **4a** (3 h, room temperature, DCM) gave in each case the same *Z*-products in

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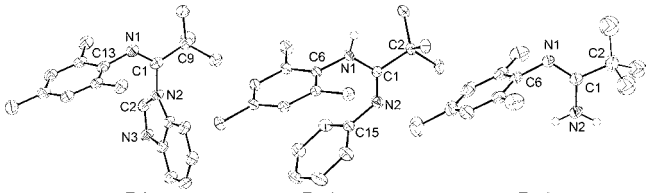

Z-**8a** *Z*-**12a** *Z*-**13a**

Figure 4. Molecular structures of *Z*-**8a**, *Z*-**12a**, and *Z*-**13a** (non-N-bound hydrogen atoms and minor disorder part of the *t*Bu-group of *Z*-**13a** are omitted for clarity, and displacement parameters are drawn at 50% probability level). Selected bond lengths (Å), angles (deg), and torsion angles (deg) for *Z*-**8a**: C1−C9 1.526(4), C1−N1 1.262(4), C1−N2 1.456(4), C2−N2 1.381(4), C2−N3 1.298(4), C13−N1 1.427(4); C9−C1−N2 116.4(2), N1−C1−N2 122.2(3); N1−C1−N2−C2−76.7(4). *Z*-**12a**: C1−C2 1.5406(15), C1−N1 1.3736(14), C1−N2 1.2732(15), C6−N1 1.4348(14), C15−N2 1.4108(15); C1−N2−C15 126.44(10), C2−C1−N2 118.25(10). *Z*-**13a**: C1−C2 1.525 (5), C1−N1 1.287 (4), C1−N2 1.349 (4), C6−N1 1.427 (4); C1−N1−C6 116.5 (2).

similar satisfying yields, except that pyridine was unable to deprotonate the **9a**-H^+ intermediate, just like **6d**-H^+.

The methodology is also suitable for primary amines. For example, aniline reacted with **5a** even at room temperature within 4 h to afford in 77% isolated yield amidines **11a** and **12a** in a 1.0:1.2 ratio (Scheme 2). A single-crystal X-ray diffraction analysis of crystals obtained from the mixture (pentane, −20 °C) revealed the molecular structure of the major product to be *Z*-**12a** (Figure 4).[24] DFT calculations confirmed it to be more stable than the minor product *Z*-**11a** ($\Delta G_{Z\text{-}12a-Z\text{-}11a}$ = 1.6 kcal·mol^{-1}) and that both amidines favor a *Z*-conformation (ΔG_{E-Z} = 0.3 (**11a**), 3.6 (**12a**) kcal·mol^{-1}). Given the small energy difference between *Z*-**11a** and *Z*-**12a** it is not surprising that tautomerism occurs. Finally, the normally challenging to synthesize *C*-alkyl amidines bearing an NH_2 moiety are easily obtained with the outlined methodology.[39] Exemplary are the reactions of the DMAP-stabilized nitrilium ions **5a** and **5b** with ammonia in THF that afforded at room temperature after workup pivalimidamide *Z*-**13a** (quant) and *Z*-**13b** (79%), respectively, as single isomers (Scheme 2). The molecular structure of **13a** confirms a *Z*-conformation (Figure 4),[24] which is also the most stable one for **13b** (ΔG_{E-Z} = 6.8 (**13a**), 6.6 (**13b**) kcal·mol^{-1}). Tautomerism is not observed in either case.

In conclusion, we have demonstrated nitrilium triflates to be stabilized by pyridine and DMAP to thermally and even moderately air-stable imine synthons that react smoothly with a variety of *N*- and *P*-nucleophiles to amidines and phosphaamidines. In these syntheses, the stabilizing (substituted) pyridine ligand also functions as a base to deprotonate the reactive iminium intermediates. The outlined simple synthetic methodology is a highly efficient strategy for generating a wide range of substituted imines.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, computational details, characterization data for all new compounds, and X-ray crystallographic data for *Z*-**4a** (CCDC-1044261), *Z*-**5a** (CCDC-1044262), *E*-**5c** (CCDC-1044263), *Z*-**8a** (CCDC-1044264), *Z*-**12a** (CCDC-1044265) and *Z*-**13a** (CCDC-1044266). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: j.c.slootweg@vu.nl.
*E-mail: k.lammertsma@vu.nl.

Notes

The authors declare no competing financial interest.

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