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A Photochemical One-Pot Three-Component Synthesis of Tetrasubstituted Imidazoles

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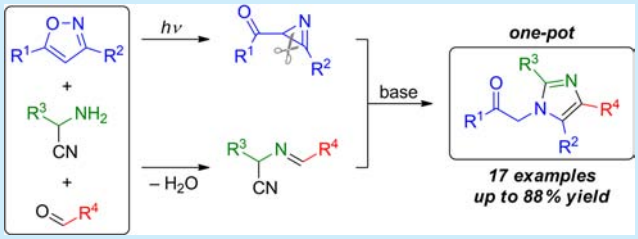
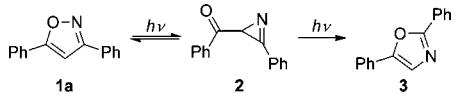
Supporting Information

ABSTRACT: Tetrasubstituted imidazoles can be formed in a photochemical one-pot synthesis from aldehydes, α-aminonitriles, and isoxazoles. Condensation of the first two components produces α-(alkylideneamino)nitriles which react under basic conditions with the acylazirines formed in situ by photochemical ring transformation of the isoxazole component. This process includes an unusual cleavage of the C^2–C^3 bond of the acylazirine. The reaction mechanism was studied by DFT calculations.



Imidazole rings are common structural motifs in biologically active molecules, including both natural products and synthetic pharmaceuticals. In particular, imidazoles containing an arylethanone side chain linked to N-1 have recently been shown to be potent inhibitors of the neuronal nitric oxide synthase (nNOS).[1] An attractive concept for the synthesis of imidazoles is the utilization of the ring strain of azirines. To this end, imidazoles have been prepared from azirinyl acrylates and amidines[2] as well as from azirines and parabanic acid[3] or from azirines and imines.[4] The azirines themselves are frequently synthesized by the Neber rearrangement.[5] However, we chose the photochemical isomerization of isoxazoles **1** to acylazirines of type **2** (Scheme 1) to generate the three-membered ring.[6] It

Scheme 1. Photochemical Isomerization of an Isoxazole to an Azirine and an Oxazole

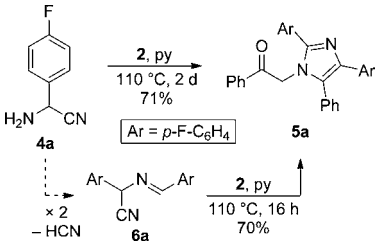


is known that the efficiency of this reaction can be enhanced by triplet sensitizers.[7] Nevertheless, the isolated yields of azirine **2** were limited to around 50% in our hands under all tested conditions due to the competing irreversible formation of the oxazole **3** (see Supporting Information for NMR-based reaction kinetics).

Our investigation on the synthesis of imidazoles from acylazirines was initiated by the finding that azirine **2** reacted with α-aminonitrile[8] **4a** to give the imidazole[9] **5a** upon heating in pyridine (Scheme 2). The structure of the product was elucidated based on NMR data, especially a 2D ^{13}C–^{13}C INADEQUATE contact between atoms C^4 and C^5 of the imidazole ring and could finally be supported by a crystal structure (Figure 1).

This reaction includes an unusual ring opening of the C^2–C^3 bond of the azirine, and only two of the three azirine ring atoms

Scheme 2. Azirine-Based Imidazole Synthesis



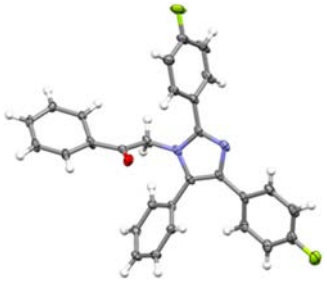


Figure 1. Molecular structure of compound **5a** in the solid state at 173 K (ORTEP-ellipsoids drawn at 30% probability).

are incorporated into the imidazole ring. The structure of imidazole **5a** led to the hypothesis that the α-(alkylideneamino)nitrile **6a** may be formed as an intermediate in the reaction from two molecules **4a** under elimination of HCN. This assumption was supported by the fact that, after the heating of compound **4a** in pyridine-d_5 for 1 h, the formation of imine **6a** (approximately 14%) could be detected. Furthermore, preformed imine **6a** and azirine **2a** produced the imidazole **5a** in a comparable yield under the same reaction conditions.

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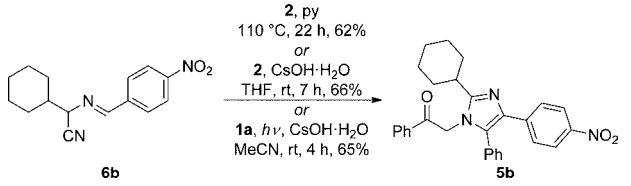
A reaction screening with HPLC-ESI-MS monitoring and preformed α-(alkylideneamino)nitriles showed that an electron-withdrawing substituent is required in the alkylidene portion. Using the preformed α-(alkylideneamino)nitrile **6b**, imidazole **5b** was obtained by refluxing the reactants in pyridine (Scheme 3). An extensive screening proved that the same

Scheme 3. Improvement of the Reaction Conditions



transformation can also be effected at room temperature by cesium hydroxide monohydrate, potassium *tert*-butoxide, or DBU as bases in THF. Gratifyingly, imidazole **5b** could also be obtained when azirine **2** was replaced by isoxazole **1a** and the reaction mixture was irradiated with UV light (300 nm). In this case, the yield-limiting formation of the undesired oxazole byproduct (see Scheme 1) and the tedious chromatographic separation of the isoxazole/azirine/oxazole mixture could be circumvented by an in situ formation of the azirine. The α-(alkylideneamino)nitrile component did not interfere with the photochemical generation of **2**. For this photochemical two-step process, the solvent was switched from THF to MeCN as the latter gives better yields and cannot form peroxides during the irradiation. Triplet sensitizers such as benzophenone did not improve the yield.

Based on this finding, we attempted to develop a one-pot three-component procedure which also includes the formation of the α-(alkylideneamino)nitriles without prior isolation (Table 1). Although the photochemical generation of strained intermediates has already been employed in photoreactions of pyridinium salts,[10] the area of organic one-pot photoreactions is still largely underdeveloped.

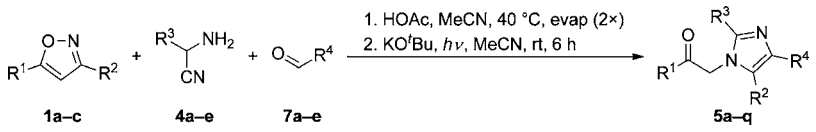
Stirring of aldehydes **7** with α-aminonitriles **4** in dry acetonitrile in the presence of molecular sieves and an acid catalyst proved to be inefficient and slow as judged by NMR reaction monitoring (CD_3CN as the solvent). However, simple evaporation of an aldehyde/α-aminonitrile mixture in acetonitrile containing catalytic amounts of acetic acid at 40 °C on a rotary evaporator resulted in almost quantitative conversion to the desired α-(alkylideneamino)nitriles **6**. These compounds turned out to be sufficiently pure for all further transformations. The isoxazole is added from the beginning and does not react until its light-induced activation. In the final three-component procedure, potassium *tert*-butoxide turned out to be the optimal base for the imidazole formation.

We never observed the formation of regioisomeric mixtures as judged by HPLC-ESI-MS of the crude reaction mixtures. The substitution pattern of the imidazoles was carefully deduced from 2D NMR experiments, in particular from NOESY correlations. For all reactions except one case (Table 1, entry 12), the same regioselectivity was observed.

The cause for the inverted regioselectivity in the reaction of **1a** with **4e** and **7a** remains unclear but might be attributed to the mixed +M/−I nature of the fluorine substituent in R^4, whereas all other substituents in the table are either of the −I or the −M/−I type. The unusual substitution pattern of **5l** could finally be supported by X-ray crystallography (Figure 2).

If the phenacyl-type N-substituent is not desired in the final product, a dephenacylation can be easily performed under reducing conditions.[11] This can also be combined with a preceding alkylation of N-3 allowing the regioselective introduction of alkyl substituents.[12] By this method, compounds **8** and **9** were obtained from the parent imidazoles (Scheme 4).

Table 1. One-Pot Three-Component Imidazole Synthesis from Isoxazoles, α-Aminonitriles, and Aldehydes



entry	isoxazole	R^1	R^2	α-aminonitrile	R^3	aldehyde	R^4	imidazole	yield[a,b]
1	**1a**	Ph	Ph	**4a**	*p*-F-C_6H_4	**7a**	*p*-F-C_6H_4	**5a**	40%
2	**1a**	Ph	Ph	**4a**	*p*-F-C_6H_4	**7b**	*p*-O_2N-C_6H_4	**5c**	83%
3	**1a**	Ph	Ph	**4a**	*p*-F-C_6H_4	**7c**	*p*-NC-C_6H_4	**5d**	70%
4	**1a**	Ph	Ph	**4a**	*p*-F-C_6H_4	**7d**	*p*-F_3C-C_6H_4	**5e**	38%
5	**1a**	Ph	Ph	**4b**[c]	Me	**7c**	*p*-NC-C_6H_4	**5f**	32%
6	**1a**	Ph	Ph	**4c**	Cy	**7b**	*p*-O_2N-C_6H_4	**5b**	82%
7	**1a**	Ph	Ph	**4c**	Cy	**7c**	*p*-NC-C_6H_4	**5g**	88%
8	**1a**	Ph	Ph	**4c**	Cy	**7d**	*p*-F_3C-C_6H_4	**5h**	55%
9	**1a**	Ph	Ph	**4d**	Ph	**7b**	*p*-O_2N-C_6H_4	**5i**	85%
10	**1a**	Ph	Ph	**4d**	Ph	**7c**	*p*-NC-C_6H_4	**5j**	66%
11	**1a**	Ph	Ph	**4d**	Ph	**7e**	4-pyridyl	**5k**	56%
12[d]	**1a**	Ph	Ph	**4e**	Bn	**7a**	*p*-F-C_6H_4	**5l**	56%
13	**1a**	Ph	Ph	**4e**	Bn	**7c**	*p*-NC-C_6H_4	**5m**	56%
14	**1b**	Ph	Me	**4a**	*p*-F-C_6H_4	**7b**	*p*-O_2N-C_6H_4	**5n**	24%
15	**1b**	Ph	Me	**4c**	Cy	**7c**	*p*-NC-C_6H_4	**5o**	68%
16	**1c**	*p*-F-C_6H_4	*p*-^{i}Pr-C_6H_4	**4c**	Cy	**7c**	*p*-NC-C_6H_4	**5p**	50%
17	**1c**	*p*-F-C_6H_4	*p*-^{i}Pr-C_6H_4	**4d**	Ph	**7b**	*p*-O_2N-C_6H_4	**5q**	50%

[a]Isolated yields after chromatography. [b]Reaction conditions: 1.0 equiv of isoxazole, 2.0 equiv of α-aminonitrile, 1.5 equiv of aldehyde, 5.0 equiv of base. [c]As hydrochloride. [d]Inverted regiochemistry in the imidazole (R^3/R^4 interchanged); see main text.

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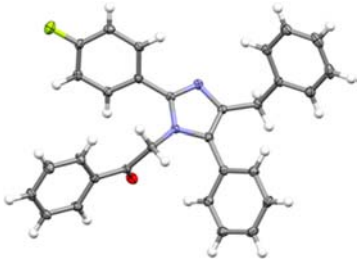
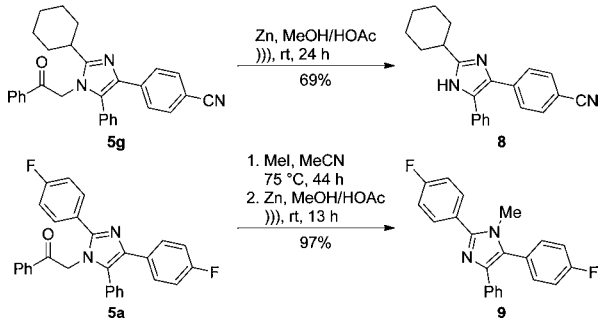


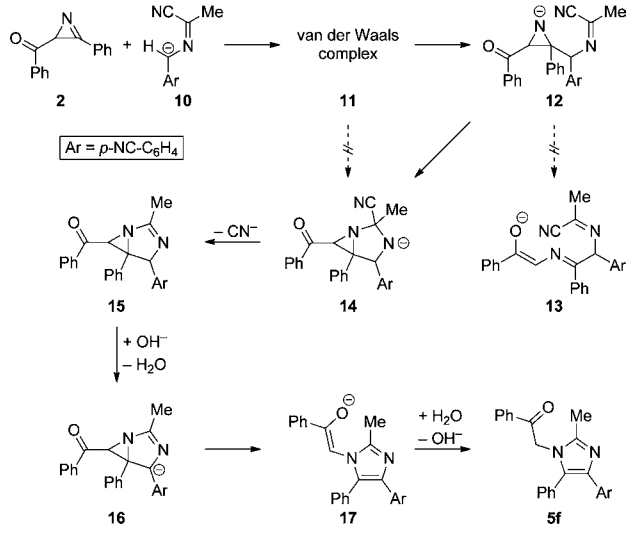
Figure 2. Molecular structure of compound **5l** in the solid state at 173 K (ORTEP-ellipsoids drawn at 30% probability).

Scheme 4. Dephenacylations



The reaction mechanism of the imidazole formation was studied using DFT calculations (Scheme 5, Orca program package, PW6B95/ma-def2-SVP level of theory including solvation and dispersion correction; see Supporting Information for details).[13]

Scheme 5. Proposed Reaction Mechanism for the Condensation of an Azirine and a Deprotonated α-(Alkylideneamino)nitrile



After formation of a loose van der Waals complex (**11**) between azirine **2** and the deprotonated α-(alkylideneamino)-nitrile **10**, the addition product **12** is formed. The electrocyclic ring opening of **12** to **13** was found to proceed via a higher-lying transition state than its ring closure to the bicyclic anion **14** (Figure 3). The latter transformation is a 5-*endo-trig* cyclization and formally disfavored according to Baldwin's rules.[14] However, similar observations have been made in other

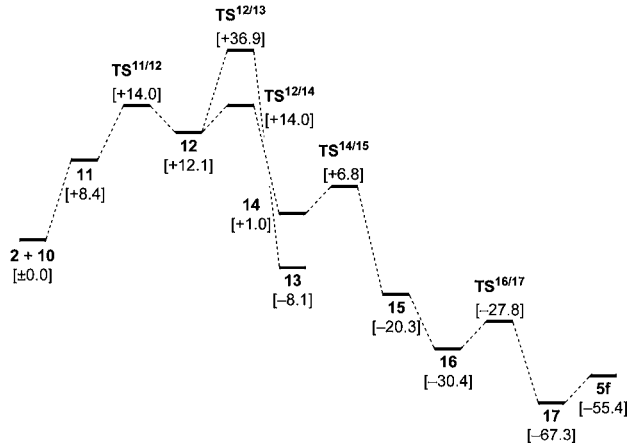


Figure 3. Energy profile for the reaction shown in Scheme 5 (numbers in square brackets: Gibbs free enthalpy in kcal/mol at 1 atm and 298 K).

syntheses of nitrogen heterocycles,[15] and anionic 5-*endo-trig* cyclizations have recently been interpreted as aborted [2,3]-sigmatropic shifts.[16] A competing direct cycloaddition of **12** to **14** could be ruled out based on a scan of the potential energy surface (Figure 4). However, the activation energy for the

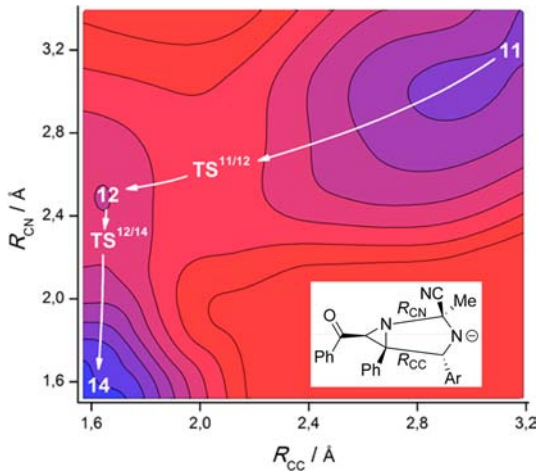


Figure 4. Contour plot showing the potential energy surface near compounds **11**/**12**/**14** (blue and red represent regions of low and high electronic energy, respectively).

cyclization is very low and the **12** → **14** transformation seems to be almost at the border between a stepwise addition/ring closure and a concerted cycloaddition mechanism. Accordingly, the isosurface of the HOMO of the **11** → **12** transition state not only resembles the formation of the C–C bond but also shows C/N secondary orbital interactions (Figure 5).

From **14** on, the reaction proceeds in an all-exergonic manner via elimination of cyanide (to **15**), deprotonation (to **16**), and ring opening to give enolate **17**. This anion is then protonated to the final product **5f**.

In summary, a simple photochemical one-pot three-component synthesis of tetrasubstituted imidazoles from disubstituted isoxazoles, α-aminonitriles, and aldehydes has been developed. The isoxazoles are readily available from enones by cyclocondensation with hydroxylamine and oxidation,[17] from 1,3-diketones and hydroxylamine,[7,18] by 1,3-dipolar cycloaddition of nitrile oxides to terminal alkynes[19] or

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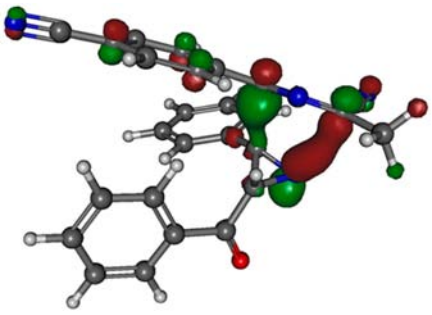

Figure 5. HOMO isosurface plot of $\mathbf{TS}^{11/12}$.

via three-component syntheses.[20] The imidazole products carry a phenacyl-type N-substituent which can be removed or replaced by an *N*-alkyl group under transposition.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, analytical data, 1D/2D NMR spectra, crystal structures, computational chemistry. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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