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N-Trifluoromethylation

A Ritter-Type Reaction: Direct Electrophilic Trifluoromethylation at Nitrogen Atoms Using Hypervalent Iodine Reagents**

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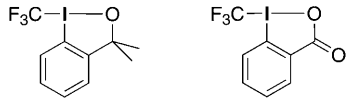
The unique features the trifluoromethyl group imparts to pharmaceuticals, crop-protection agents, and functional materials emphasize the necessity to design and develop new reagents and methods for the direct trifluoromethylation of a wide range of organic substrates. Electrophilic trifluoromethylation, that is, the reaction of a suitable reagent capable of formally transferring an intact CF_3^+ unit, has been shown to be one of these methods.[1] However, despite the availability of several such effective reagents, the electrophilic trifluoromethylation of hard nucleophiles, for example, oxygen- or nitrogen-centered ones, remains challenging. In particular, the formation of a N–CF_3 bond by such a reaction is still extremely rare. In fact, the NCF_3 unit is usually constructed by the interconversion of suitable functional groups. Thus, fluorination of *N*-formylamines,[2] thiuram sulfides,[3] isocyanates,[4] and trichloromethylamines,[5] the reaction of secondary amines with CBr_2F_2 and tetrakis(dimethylamino)ethylene,[6] and the electrochemical fluorination of alkylamines[7] constitute the still relatively modest set of methods. Of these, the most frequently used approach is the oxidative desulfurization–fluorination of dithiocarbamates first described for the generation of NCF_3 groups by Hiyama and Kuroboshi.[8] The single, still very recent report of a direct trifluoromethylation at nitrogen is due to Umemoto and co-workers.[9] They describe the direct N-trifluoromethylation of amines, anilines, and pyridines under very mild conditions achieved with in situ generated and thermally unstable *O*-(trifluoromethyl)dibenzofuranium salts (corresponding reactions of alcohols and phenols are also known). However, this type of reagent suffers from several shortcomings. The active CF_3 source is obtained by photochemical decomposition of diazonium salts at very low temperature, and the synthesis requires several steps including the construction of a CF_3O–aryl moiety. It is therefore likely that this methodology will not replace the corresponding functional-group interconversions in the near future.

We have shown that a new generation of readily accessible trifluoromethylation reagents based on hypervalent iodine, such as compounds **1** and **2** (Scheme 1), display the desired

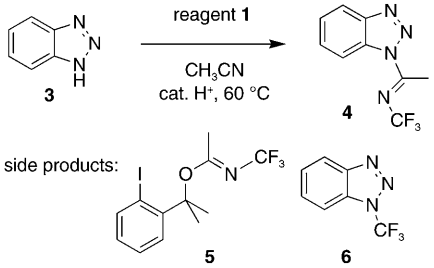


1 2

Scheme 1. Trifluoromethylation reagents based on hypervalent iodine.

reactivity towards a number of C-, S-, P-, and O-centered nucleophiles. Despite their purported soft nature, reagents **1** and **2** do trifluoromethylate alcohols and sulfonic acids upon activation with Lewis[10] and Brønsted acids,[11] respectively, thus significantly expanding their application range.

During a recent investigation of the direct electrophilic trifluoromethylation of heteroarenes[12] using reagent **1** and catalytic amounts of bis(trifluoromethanesulfonyl)imide ($HNTf_2$) in acetonitrile, we surprisingly found that benzotriazole (**3**) is converted to the corresponding N-substituted *N*-trifluoroimidoyl derivative **4**, as shown in Scheme 2. The generation of compound **4** corresponds to a novel Ritter-type[13] reaction during which a new N–CF_3 bond is formed.



3 4 5 6

Scheme 2. Formation of *N*-(trifluoromethyl)imine **4** by a new Ritter-type reaction.

Subsequent substrate screening showed that other azoles such as indazole and substituted pyrazoles also undergo this reaction (see below). Encouraged by these results, we used benzotriazole (**3**) as a model substrate to optimize the reaction conditions. Reactions were carried out at 60 °C in the presence of a Brønsted acid (see Table 1). At higher temperatures the formation of HCF_3 ($\delta_F = -79.9$ ppm, d,

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Table 1: Formation of **4** at various acid concentrations. Conversion and yield after 3.5 h reaction time at 60 °C.

Entry[a]	Acid	mol %	Conv.[b] [%]	Yield[b] [%]
1	–		0	0
2	$HNTf_2$	5	69	44
3	$HNTf_2$	10	99	68
4	$HNTf_2$	15	quant.	70
5	$(CF_3)_3COH$	10	quant.	68[c]
6	TFA	10	quant.	60

[a] Reaction conditions: Reagent **1** and benzotriazole (**3**) (1.5 equiv) in CH_3CN were stirred after addition of acid (0.1 M in CH_2Cl_2) at 60 °C for 3.5 h. [b] Calculated based on ^{19}F NMR spectroscopic analysis using $C_6H_5CF_3$ as an internal standard. [c] Yield after completion (1 day).

$^2J(F,H) = 79.5$ Hz) was observed by ^{19}F NMR spectroscopy, indicating reagent decomposition. $HNTf_2$, a strong Brønsted acid with an innocent conjugate base,[14] acts as a catalyst, (Table 1, entries 2–4), while in its absence no reaction is observed (Table 1, entry 1). Though higher catalyst loadings accelerate the reaction, only a minor effect on the yield is observed. The reactions can also be performed using 10 mol % of TFA or $(CF_3)_3COH$. However, TFA leads to slightly lower yields, whereas $(CF_3)_3COH$ is much less efficient in promoting the reaction, presumably because of its weaker acidity (Table 1, entries 5 and 6).

As depicted in Scheme 2, the side products **5** and **6** are also formed. The former is a *N*-(trifluoromethyl)acetimidate corresponding to the Ritter addition product of reagent **1** to acetonitrile. The second, *N*1(trifluoromethyl)benzotriazole (**6**), is the product of the direct trifluoromethylation of benzotriazole. Their formation is influenced by the ratio between substrate and reagent as shown in Table 2. When reagent **1** is used in excess, more side product **5** is formed, whereas an excess of substrate **3** leads to benzotriazole **6** to a greater extent. The best results in terms of product yield and suppression of side products are obtained using reagent **1** as the limiting species and 1.5 equiv of benzotriazole (**3**) (Table 2, entry 3).

Table 2: Distribution of product and side products depending on the starting ratio of benzotriazole (**3**) and reagent **1**.

Entry[a]	**1** [equiv]	**3** [equiv]	Yield **4**[b] [%]	Yield **5**[b] [%]	Yield **6**[b] [%]
1	1.5	1	65	28	5
2	1	1	55	11	5
3	1	1.5	68	8	7
4	1	2	67	5	11
5	1	3	64	3	16

[a] Reaction conditions: reagent **1** and benzotriazole (**3**) were stirred after addition of $HNTf_2$ (10 mol % based on **1**, 0.1 M in CH_2Cl_2) at 60 °C for 3.5 h. [b] Calculated based on ^{19}F NMR spectroscopic analysis using $C_6H_5CF_3$ as an internal standard.

We monitored the reaction of 1.5 equiv of benzotriazole (**3**), 6.8 mol % $HNTf_2$ as a 0.1 M solution in CH_2Cl_2, and reagent **1** in CD_3CN (0.1 M) by ^{19}F NMR spectroscopy. The corresponding reaction profile is shown in Figure 1. Thus, nearly constant rates of both consumption of **1** and formation of **4** were observed, implying that substrate **3** is not involved in the rate-determining step of the reaction. If this were not the case and since the concentration of **3** changes over time, one would expect an exponential decrease of the concentration of **1** as well as an exponential rise to a maximum concentration of **4**. Additionally, under the reaction conditions, the concentrations of CD_3CN and of the Brønsted acid are essentially constant. Therefore, it is reasonable to assume that the rate-determining step of the reaction involves the protonated form of reagent **1** and CD_3CN. This is in line with our previous observations concerning the trifluoromethylation of THF[15] and toluenesulfonic acid.[11]

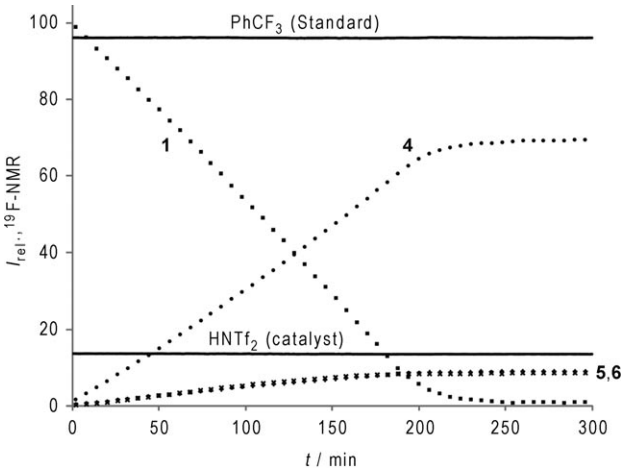
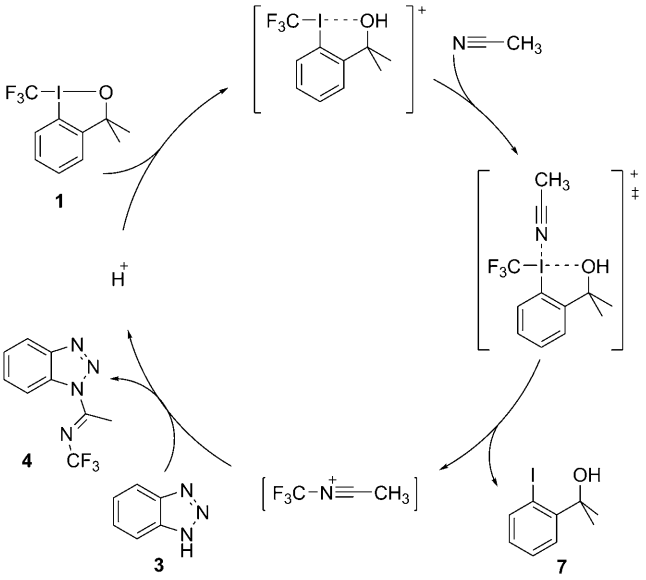


Figure 1. Profile for the reaction of 0.1 M **1** with 0.15 M **2** and 6.8 mM $HNTf_2$ in CD_3CN as monitored by ^{19}F NMR spectroscopy ($C_6H_5CF_3$ internal standard). ■ **1**, ● **4**, ◆ **5**, × **6**.

On the basis of these rate studies and our previous experience with these systems, we propose the mechanism shown in Scheme 3. The protonated form of reagent **1** is the reactive species. That such a protonation is indeed taking

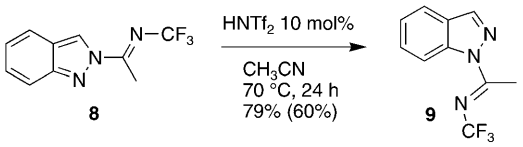


Scheme 3. Proposed reaction mechanism for the acid-catalyzed Ritter-type reaction of reagent **1** with benzotriazole.

place is also indicated by a significant shift of the corresponding CF_3 signal in the ^{19}F NMR spectrum to higher frequency. Thus, whereas the resonance of the free reagent appears at $\delta = -40$ ppm in $CDCl_3$, the addition of 1 equiv of a strong Brønsted acid shifts the signal to $\delta = -20$ ppm. This activation is likely to weaken the I–O bond, thus making the iodine atom more electrophilic (iodonium character); this is analogous to the activation of reagent **2** by Zn^{2+}, as previously reported.[10] A coordinated acetonitrile subsequently undergoes the formation of a *N*-trifluoromethyl nitrilium ion[16] by a reductive-elimination process, as the rate-determining step. The nitrilium ion is then rapidly trapped by benzotriazole (**3**) to form product **4**, thus releasing a proton and completing the catalytic cycle.

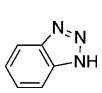
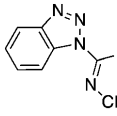
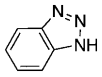
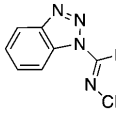
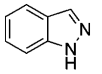
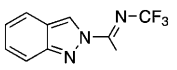
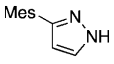
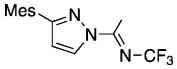
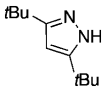
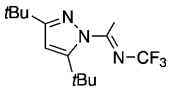
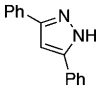
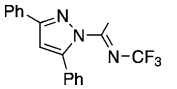
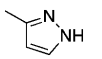
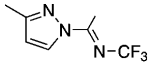
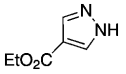
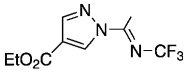
The optimized reaction conditions were subsequently applied to other azoles such as indazole and substituted pyrazoles. The results of these reactions are shown in Table 3. The trifluoromethylated products can easily be separated from the much more polar azoles by simple flash column chromatography. In the reaction using ethyl 4-pyrazolecarboxylate (Table 3, entry 8) the desired product is formed in 68% yield after complete conversion according to NMR analysis. However, the product slowly decomposes under the reaction conditions and, hence, longer reaction times lead to a significantly lower yield. Unfortunately, as the resulting product and alcohol **7** are not separable using flash column chromatography, the Burgess reagent[17] must be added after the reaction is complete in order to dehydrate alcohol **7**. This allows the desired product to be isolated in 38% yield in pure form after flash column chromatography.

Indazole reacts under the same reaction conditions to afford N2-substituted product **8** in 57% NMR yield. The formation of the N1-substituted product **9** accounts for less than 5% yield. Derivative **8** is smoothly converted to its regioisomer **9** in 79% yield (according to NMR analysis) upon heating in acetonitrile and in the presence of a catalytic amount of $HNTf_2$, as shown in Scheme 4. Compound **8** is the kinetic product of the reaction of indazole with reagent **1**, and slowly isomerizes to the thermodynamic product **9**. This process is likely to involve heterolytic N–C bond cleavage, regenerating a trifluoromethyl nitrilium ion. A comparable reaction concerning *N*-(α-aminoalkyl)tetrazoles has recently been reported by Katritzky and co-workers.[18]



Scheme 4. Isomerization of N2-substituted indazole **8** to N1-substituted derivative **9**.

Table 3: Ritter-type N-trifluoromethylation of nitriles using **1**, azoles, and $HNTf_2$ as catalyst.

Entry[a]	Substrate	Product	Yield[b] [%]
1			68 (63)
2[c]			60 (37)
3			57 (47)[d]
4			51 (45)
5			52 (47)[e]
6			59 (47)
7			62 (53)
8			47 (38)[f]

[a] Reaction conditions: $HNTf_2$ (10 mol%, 0.1 M in CH_2Cl_2) was added to a solution of reagent **1** and azole (1.5 equiv) in CH_3CN (6 mL), and the reaction mixture was stirred for 3.5 h at 60°C. [b] Yields were calculated based on reagent **1** from the integration of the ^{19}F NMR signals using $C_6H_5CF_3$ as internal standard. Yields of isolated products are given in brackets. [c] C_2H_5CN instead of CH_3CN. [d] N2-substituted product **8** was formed and isolated. [e] Reaction time 16 h. [f] Owing to separation problems the Burgess reagent[17] (1.5 equiv in CH_2Cl_2) was added after completion of the reaction, and the mixture was stirred for an additional 30 min at 60°C.

Given that the products of our Ritter-type reaction contain the rather uncommon *N*-(trifluoromethyl)amidine unit, we carried out thorough structural characterization, both in solution and in the solid state. Thus, as an example, the structure of compound **4** in solution was determined by multinuclear NMR methods. Figure 2 shows sections of the corresponding $^{19}F,^{15}N$ and $^{1}H,^{15}N$ HMQC spectra. The $^{19}F,^{15}N$ correlation (Figure 2, left) shows only one correlation between the trifluoromethyl resonance ($\delta_F = -53.5$ ppm) and the imido resonance at $\delta_N = -125.7$ ppm. The splitting in the direct dimension is due to the ^2J(N,F) coupling of 20 Hz. The assigned structure was confirmed by X-ray crystallography (see the Supporting Information). On the other hand, in the $^{1}H,^{15}N$ correlation (Figure 2, right) the methyl resonance ($\delta_H = 3.12$ ppm) shows two crosspeaks to the azole and imido resonances ($\delta_N = -134.9$ ppm and $\delta_N = -125.7$ ppm, respectively).

The structure of the two constitutional isomers **8** and **9** were determined in solution by analogous NMR methods and confirmed by X-ray analysis. Corresponding ORTEP representations and selected geometrical parameters are shown in Figure 3. Both imidoyl groups have an *E* configuration, which is common to all azole derivatives prepared in this study. Both isomers are almost perfectly planar molecules, the imidoyl group being only slightly twisted out of the indazole plane as indicated by the torsion angles N1-N2-C8-N3 of 178.06(17)° and 176.71(15)° for **8** and **9**, respectively. A further, more notable deviation from the expected ideal geometry concerns

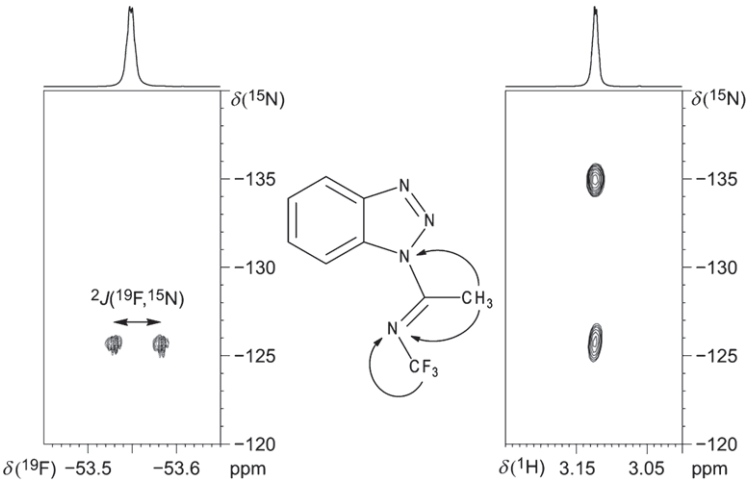


Figure 2. Sections of the $^{19}F,^{15}N$ (left) and $^{1}H,^{15}N$ (right) HMQC spectra of compound **4**. Correlations found are indicated by arrows.

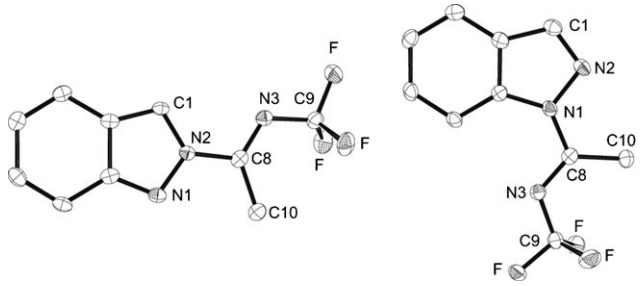
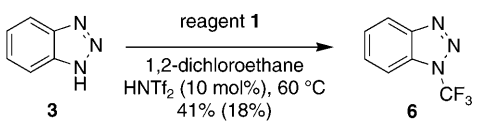


Figure 3. ORTEP representation of compounds **8** (left) and **9** (right). Thermal ellipsoids are drawn at the 50% probability level; hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and angles [°] for **8**: N1–N2 1.363(2), N2–C1 1.360(3), N2–C8 1.408(3), N3–C8 1.276(3), N3–C9 1.389(3), C8–C10 1.488(3), C1-N2-N1 113.52(17), N3-C8-N2 115.38(18), N3-C8-C10 129.9(2), N1-N2-C8-N3 178.06(17). Selected bond lengths [Å] and angles [°] for **9**: N1–N2 1.390(2), N2–C1 1.302(2), N1–C8 1.383(2), N3–C8 1.283(2), N3–C9 1.387(2), C8–C10 1.499(2); C1-N2-N1 105.69(15), N3-C8-N1 115.88(16), N3-C8-C10 128.52(17), N2-N1-C8-N3 176.71(15).

the angle N3-C8-C10, which in both compounds significantly is larger than 120° (129.9(2)° in **8** and 128.52(17)° in **9**), whereas the angle subtended by the two substituents at N3 is in both cases almost unsignificantly below 120°.

Finally, and as already mentioned above, the reaction of benzotriazole in CH_3CN affords the direct N-trifluoromethylation side product **6**. In preliminary experiments the yield of this reaction was increased by using 1,2-dichloroethane as solvent instead of acetonitrile. Thus, the desired product, showing spectroscopic properties identical to those previously reported by Yagupolskii et al.,[19] was formed to an extent of 41% and isolated after flash chromatography in 18% yield (Scheme 5).



Scheme 5. Direct N-trifluoromethylation of benzotriazole.

In conclusion, we have shown that N-substituted *N*-(trifluoromethyl)imidoyl compounds are formed in a Ritter-type reaction using an azole and reagent **1** as the trifluoromethylating agent in a nitrile under $HNTf_2$ catalysis. To the best of our knowledge such a reaction is unprecedented and represents a fundamentally new access to NCF_3 derivatives by formation of the $N{-}CF_3$ bond. Furthermore, it has been shown that benzotriazole (**3**) can be directly N-trifluoromethylated. We are currently improving these new reactions further and also exploring the reactivity and synthetic utility of the newly accessed compounds.

Experimental Section

General procedure: A flame-dried 20 mL Young–Schlenk flask was charged with 1-trifluoromethyl-1,3-dihydro-3,3-dimethyl-1,2-benziodoxole (**1**; 198 mg, 0.60 mmol) and azole (0.90 mmol, 1.5 equiv). CH_3CN (6 mL) and $HNTf_2$ (0.6 mL, 0.1M in CH_2Cl_2, 10 mol%) were added. The mixture was stirred at 60°C for 3.5 h. The mixture was extracted with pentane (3 × 15 mL) and the pentane was removed under reduced pressure.

CCDC 792179 (compound **4**), 792180 (compound **8**), 7928181 (compound **9**), and 792182 ((*E*)-*N*-(1-(3,5-diphenyl-1*H*-pyrazol-1-yl)ethylidene)-1,1,1-trifluoromethanamine) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Keywords: electrophilic addition · hypervalent compounds · nitrogen heterocycles · synthetic methods · trifluoromethylation

[1] For a recent review, see: N. Shibata, A. Matsnev, D. Cahard, *Beilstein J. Org. Chem.* **2010**, *6*, No. 65, DOI: 10.3762/bjoc.6.65.
[2] W. Dmowski, M. Kaminski, *J. Fluorine Chem.* **1983**, *23*, 207–218.
[3] a) R. J. Harder, W. C. Smith, *J. Am. Chem. Soc.* **1961**, *83*, 3422–3424; b) L. N. Markovskij, V. E. Pashinnik, A. V. Kirsanov, *Synthesis* **1973**, 787–789.
[4] E. Klauke, *Angew. Chem.* **1966**, *78*, 829; *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 848.
[5] L. M. Yagupolskii, N. V. Kondratenko, G. N. Timofeeva, M. I. Dronkina, Y. L. Yagupolskii, *Zh. Org. Khim.* **1980**, *16*, 2508–2513.
[6] G. Pawelke, *J. Fluorine Chem.* **1991**, *52*, 229–234.
[7] T. Abe, E. Hayashi, H. Baba, H. Fukaya, *J. Fluorine Chem.* **1990**, *48*, 257–279.
[8] M. Kuroboshi, T. Hiyama, *Tetrahedron Lett.* **1992**, *33*, 4177–4178.
[9] T. Umemoto, K. Adachi, S. Ishihara, *J. Org. Chem.* **2007**, *72*, 6905–6917.
[10] R. Koller, K. Stanek, D. Stolz, R. Aardoom, K. Niedermann, A. Togni, *Angew. Chem.* **2009**, *121*, 4396–4400; *Angew. Chem. Int. Ed.* **2009**, *48*, 4332–4336.
[11] R. Koller, Q. Huchet, P. Battaglia, J. M. Welch, A. Togni, *Chem. Commun.* **2009**, 5993–5995.
[12] M. S. Wiehn, E. V. Vinogradova, A. Togni, *J. Fluorine Chem.* **2010**, *131*, 951–957.

[13] For a general reference about the Ritter reaction, see: A. R. E. Brewer In *Name Reactions for Functional Group Transformations* (Ed.: J. J. Li), Wiley, New York, **2007**, and references therein.
[14] I. A. Koppel, R. W. Taft, F. Anvia, S.-Z. Zhu, L.-Q. Hu, K.-S. Sung, D. D. DesMarteau, L. M. Yagupolskii, Y. L. Yagupolskii, *J. Am. Chem. Soc.* **1994**, *116*, 3047 – 3057.
[15] S. Fantasia, J. M. Welch, A. Togni, *J. Org. Chem.* **2010**, *75*, 1779 – 1782.
[16] For recent studies concerning the formation and reactivity of nitrilium ions, see, e.g.: a) P. H. Ruane, A. R. Ahmed, R. A. McClelland, *J. Chem. Soc. Perkin Trans. 2* **2002**, 312 – 317; b) R. W. Darbeau, R. S. Pease, E. V. Perez, R. E. Gibble, F. A. Ayo, A. W. Sweeney, *J. Chem. Soc. Perkin Trans. 2* **2002**, 2146 – 2153; c) J. L. Jiménez Blanco, E. M. Rubio, C. Ortiz Mellet, J. M. García Fernández, *Synlett* **2004**, 2230 – 2232.
[17] E. M. Burgess, H. R. Penton, E. A. Taylor, *J. Org. Chem.* **1973**, *38*, 26 – 31.
[18] A. L. Katritzky, B. E. M. El-Gendy, B. Draghici, C. D. Hall, P. J. Steel, *J. Org. Chem.* **2010**, *75*, 6468 – 6476.
[19] L. M. Yagupolskii, D. V. Fedyuk, K. I. Petko, V. I. Troitskaya, V. I. Rudyk, V. V. Rudyuk, *J. Fluorine Chem.* **2000**, *106*, 181 – 187.

