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Direct Synthesis of 3-Aryl-1,2,4,5-tetrazine N-1-Oxides by the Oxidation with Methyl(trifluoromethyl)dioxirane

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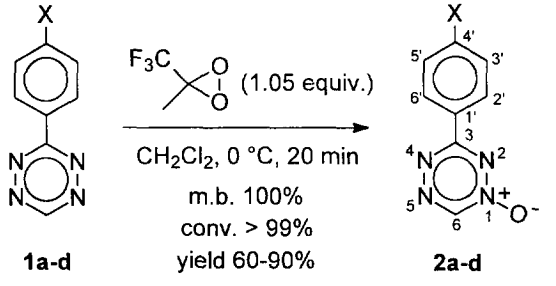
Abstract: 1,2,4,5-Tetrazines are oxidized by methyl(trifluoromethyl)dioxirane (TFD) to their hitherto unknown[1a] *N*-oxides in excellent yields. A detailed NMR study (^1H, ^{13}C, ^{15}N) shows that the N-1 atom of 3-aryl-1,2,4,5-tetrazines **1** is oxidized regioselectively. A Hammett plot ($r^2 = 0.970$) affords a ρ value of -1.53. The correlation of the logarithm of the reaction rates *versus* the ionization potentials, which were calculated by AM1, is much worse for ionization out of the aromatic system (IP_π; $r^2 = 0.804$) than for ionization out of the higher-energy nitrogen lone pairs (IP_N; $r^2 = 0.940$). This implies that an electron transfer mechanism is unlikely and an S_N2 attack by the nitrogen lone pair of the tetrazine on the dioxirane peroxide bond appears to operate.

INTRODUCTION

Efforts have been expended to obtain *N*-oxides from 1,2,4,5-tetrazines by direct oxidation, but standard methods led to other products, e.g. the oxidation of several tetrazines with peracetic acid resulted in oxadiazoles.[2a,b] However, the 1,4-diamino-1,2,4,5-tetrazine has been successfully oxidized to a mixture of its *N*-oxides.[2c] Also a few 1,2,3,4-tetrazine-*N*-oxides are known,[3] but these regioisomers were synthesized by ring closure rather than by oxidation of the corresponding tetrazine. Herein we report the first successful chemo- and regioselective *N*-oxidation of 3-aryl-1,2,4,5-tetrazines directly by isolated methyl(trifluoromethyl)dioxirane (TFD)[4,5] (Scheme 1) as well as by a modified *in situ* method. The latter method is particularly advantageous since it needs only one-tenth of the trifluoroacetone used in the preparation of isolated TFD solutions.

Scheme 1

1-2	X
a	H
b	Me
c	MeO
d	Cl



RESULTS AND DISCUSSION

Tetrazine *N*-oxides **2a-d** have been obtained by the oxidation of the corresponding 3-aryl-1,2,4,5-tetrazines **1** with methyl(trifluoromethyl)dioxirane (TFD) in CH_2Cl_2 at 0 °C within approximately 20 min (Scheme 1). Under these conditions, quantitative conversion of the tetrazines **1** to the corresponding *N*-oxides **2** was achieved in 60-90% yield, isolated as yellow powder after recrystallization from *n*-hexane. The use of the much less reactive dimethyldioxirane (DMD)[6] instead of TFD gave at 25 °C even after five days only 54% conversion, despite the fact that a large excess of DMD (5 equiv.) was employed.

Under appropriately optimized *in situ* conditions, *N*-oxide **2a** was obtained in 47% yield on a preparatively useful (1.5 mmol) scale (cf. Experimental Section). For this purpose a convenient *in situ* method was developed for TFD, in analogy to that for DMD.[7]

The assignment of which regioisomer was formed, was not a trivial task and extensive NMR work was necessary. In Table 1 are collected the ^1H NMR and in Table 2 the ^{13}C NMR chemical shifts of the tetrazine *N*-oxides **2**. Inspection of the literature data[10a-d] reveals the following trends in the changes of the ^1H and ^{13}C NMR chemical shifts [$\Delta\delta$ = δ(*N*-oxide) - δ(amine)] and coupling constants [ΔJ = $^1J_{CH}$(*N*-oxide) - $^1J_{CH}$(amine)] for known pairs of *N*-oxides and their amines (heteroarenes) on *N*-oxidation:

(i) *ortho* and *para* **chemical shift** changes range from -9 to -20 ppm and *meta* changes from -6.5 to +8.3 ppm.

(ii) *ortho* and *para* changes of the **coupling constants** range from +7 to +11 Hz and *meta* changes from +3 to +4 Hz.

Table 1: ^1H NMR[a] chemical shifts of the tetrazine *N*-oxides **2**

N-Oxide	X	6-H	2′-H	3′-H	4′-X
2a	H	9.21	8.46	7.72 - 7.57 [b]	
2b	CH_3	9.18	8.35	7.41	2.50
2c	OCH_3	9.14	8.42	7.08	3.95
2d	Cl	9.11	8.32	7.50	-

[a] Recorded at 250 MHz in $CDCl_3$ with TMS as reference. [b] A definite assignment of the aryl protons 3′-H to 5′-H was not possible.

Table 2: ^{13}C NMR[a] chemical shifts and $^1J_{CH}$ (Hz) coupling constants (in parentheses) of the tetrazine *N*-oxide **2**

N-Oxide	X	C-3	C-6	C-1′	C-2′	C-3′	C-4′	C-X
2a	H	165.1	145.6 (228)	130.5	129.5 (165)	128.8 (163)	133.9 (161)	-
2b	CH_3	165.1	145.3 (227)	127.7	130.3 (161)	128.9 (163)	144.9	22.0 (127)
2c	OCH_3	165.0	144.8 (229)	122.7	130.9 (167)	115.0 (167)	164.4	55.9 (145)
2d	Cl	164.3	145.6 (226)	129.0	130.1 (164)	129.9 (166)	140.6	-

[a] Recorded at 63 MHz in $CDCl_3$ and TMS as reference.

The proposed regiochemistry of the 1,2,4,5-tetrazines **1** and their *N*-oxides **2** (cf. Tables 1 and 2) are in good agreement with the general trends in the NMR data of reported pairs of related heterocyclic amines and their *N*-oxides. Thus, the carbon atoms *ortho* to the *N*-oxide functionality experience high-field shifts and the corresponding C-H coupling constants are as well higher which speak in favor of the *N*-1-oxide rather than the *N*-2-oxide regioisomer. Furthermore, the resonance structures below for the N-1-oxides suggest a higher electron density in the *ortho* positions. The AM1 calculations (cf. Fig. 1) on the tetrazine *N*-1-oxide **2a** corroborate the higher electron density at the *ortho* position. Moreover, comparison of the observed ^{15}N NMR chemical shift data for the 3-phenyl-1,2,4,5-tetrazine (**1a**) and its *N*-1-oxide **2a** (cf. Experimental Section) with those of reported triazine derivatives[10a] corroborate the regioisomeric assignment. Thus, the changes in the ^{15}N NMR chemical shift of the oxidized nitrogen atom ($\Delta\delta_{ipso}$) as well as those of the *ortho* ($\Delta\delta_{ortho}$) and *para* ($\Delta\delta_{para}$) ones are quite negative in all cases compared to the changes for the *meta* nitrogen atom ($\Delta\delta_{meta}$).

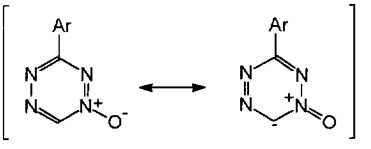
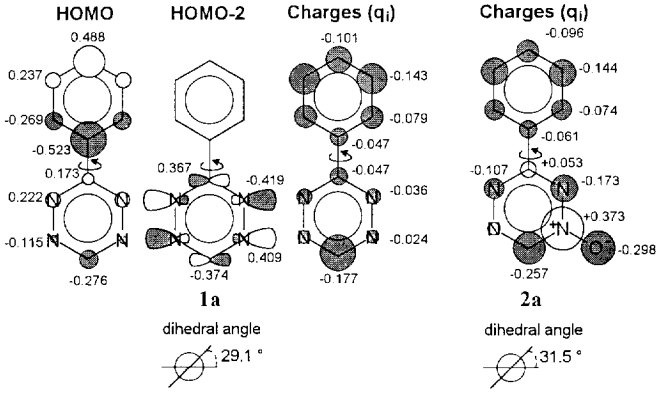
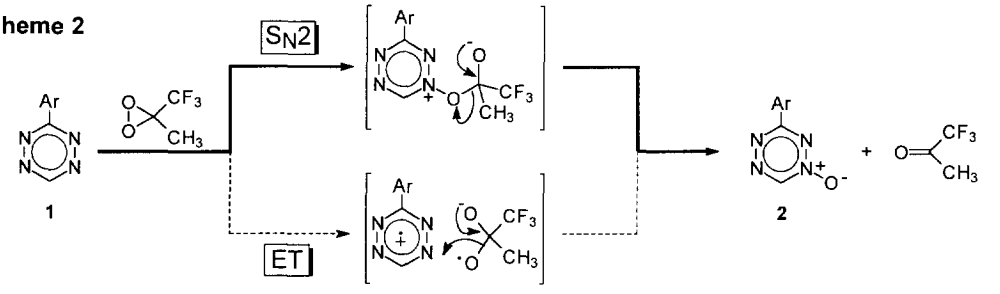


Figure 1: HOMO and HOMO-2 coefficients (c_i) of tetrazine **1a** and heavy atom charges (the deficit in the positive charges are at the hydrogen atoms) for tetrazine **1a** and its *N*-1-oxide **2a**, calculated by the AM1 method.[8,9]



To elucidate the mechanism (Scheme 2) of the oxygen transfer, i.e. nucleophilic substitution (S_N2) *versus* electron transfer (ET), the dependence of the reaction rate on the substituent X was determined for this TFD *N*-oxidation. The results are collected in Table 3. From a Hammett plot of these rate data the reaction constant was found to be $\rho = -1.53$ ($r^2 = 0.970$). The negative sign suggests that the tetrazine serves as the nucleophile, despite its electron poor nature, and the dioxirane TFD as the electrophile. This *N*-oxidation constitutes apparently the first nucleophilic reaction of tetrazines.[12]

Scheme 2



AM1 calculations[8] (using the software package VAMP 5.0[9]) on both the tetrazines **1** and the *N*-oxides **2** were carried out to gain further insight into the S_N2 *versus* ET reactivity of the tetrazines towards the dioxirane (Table 3). The HOMO of tetrazine **1a** proved to be a π-type orbital with an orbital energy of E_{HOMO} = -9.785 eV, which is a measure of the ionization potential of the aromatic system (IP_π). Thus, an electron transfer mechanism should involve ionization out of π HOMO; however, a plot of the IP_π *versus* log k_{rel} gave a poor correlation (r^2 = 0.804), for which particularly the chloro substituent deviates. Additionally and as expected, the π HOMO is spread over the whole molecule, but has its highest electron densities in the phenyl rather than in the electron-poor tetrazine ring (Fig. 1). Therefore, oxidation at the phenyl moiety should have been observed rather than at the tetrazine nitrogen atoms.

Table 3: Rate data for of the *N*-oxidation of tetrazines **1** by TFD

	X	k_{rel} [a]	IP_π [b]	$IP_{N:}$ [c]	σ_p [d]
1a	H	1.00	9.785	10.748	0.00
1b	CH_3	1.78	9.519	10.697	-0.17
1c	OCH_3	3.34	9.230	10.659	-0.27
1d	Cl	0.534	9.721	10.860	0.23
		r^2 [e]	0.804	0.940	0.970

[a] Relative to X = H; determined by competition kinetics (cf. Experimental Section); error ± 2% of the stated values. [b] Orbital energy of the π HOMO (AM1 calculation [8] using the software package VAMP 5.0[9]). [c] Orbital energy (AM1 calculation) of the HOMO-2. [d] Hammett substituent constants.[11] [e] Statistical analysis of the log k_{rel} *versus* the IP_π, $IP_{N:}$ and σ_p plots.

The AM1 calculations reveal that the third highest occupied MO, i.e. HOMO-2, represents the nitrogen lone pairs of the tetrazine ring (Fig. 1), which should be involved in the oxidation process. Indeed, the orbital energies of the HOMO-2 for the 1,2,4,5-tetrazines **1** (Table 3), which are taken as a measure of the ionization potential for the nitrogen lone pair, correlate quite well (r^2 = 0.940) when plotted against log k_{rel}. This correlation is only slightly worse than that of the Hammett plot (0.970), but much better (0.804) than for

IP_π *versus* log k_{rel} (Table 3). Therefore, in view of the significantly higher IP_N *versus* IP_π values, i.e. by ca. 1 eV (Table 3), if the dioxirane TFD were to oxidize the 1,2,4,5-tetrazines **1** by an electron transfer process, it would be unreasonable to ionize out of the nitrogen lone pair rather than the π system. Therefore, analogous to the more nucleophilic pyridine-type heteroarenes,[13] we propose that the tetrazine *N*-oxidation also proceeds by an S_N2 mechanism. It should be kept in mind that a correlation with ionization potentials is not necessarily a criterion for electron transfer since nucleophilicity also depends on ionization potentials[14] and, thus, is consistent with the proposed S_N2 reactivity.

As to the regioselectivity, i.e. exclusive oxygen transfer to the N-1 position, this can hardly be electronic control because the AM1 calculation gives essentially identical orbital coefficients for the N-1 (0.409) and N-2 (0.419) sites (Fig. 1); at best one would expect equal amounts of both regioisomers. Thus, steric factors must be at play. The calculated minimum energy geometry of the tetrazine **1a** (Fig. 1) reveals a significant dihedral angle of 29.1 ° [15a] between the two aryl rings (compared to 37.3 ° for biphenyl[15b]) due to steric repulsion between the *ortho* hydrogen atoms of the phenyl and the *ortho* electron pairs of the tetrazine rings. Consequently, the N-2 position is sterically sufficiently hindered that dioxirane attack takes place exclusively at the N-1 site. This stereoselectivity is analogous to 3-phenyl-substituted pyridazines, which give exclusively 1-*N*-oxides on *N*-oxidation with peracids.[1b] The latter is a well established[16] S_N2 mechanism.

Our present results confirm that methyl(trifluoromethyl)dioxirane (TFD) is much more reactive[5] than dimethyldioxirane, since the latter oxidizes 1,2,4,5-tetrazines **1** only sluggishly. Nevertheless, despite the significantly lower reduction potential of TFD,[17a] like DMD it transfers an oxygen atom by an S_N2 rather than ET mechanism to afford with the rather weak tetrazine nucleophiles regioselectively the hitherto unknown *N*-1-oxides.

EXPERIMENTAL SECTION

Equipment. Melting points were determined by differential thermal analysis (DTA) with an DuPont 9000 Differential Scanning Calorimeter under a nitrogen atmosphere and a temperature program of 10 °C/min. IR spectra were recorded on a *Perkin-Elmer* 1420 Ratio Recording Infrared Spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a spectrometer AC 250 (Bruker) and the ^{15}N NMR spectra on a WM 400 (Bruker). The C-H coupling constants were measured on a Bruker AC 200 NMR spectrometer ("GATEDEC.AU" program). UV spectra were recorded on a Hitachi U3200 spectrometer. CHN analyses were carried out by the Microanalytical Division of the Institute of Inorganic Chemistry of the University of Würzburg.

Materials. All oxidations with DMD and TFD were run in distilled (over P_2O_5) methylene chloride. For the preparation of TFD and for the *in situ* method distilled water (over EDTA) was used. The concentration of TFD in the 1,1,1-trifluoroacetone solution was determined iodometrically. The Caroate for the synthesis of DMD[6] and TFD[4,5] was obtained from the Peroxid Chemie (D-82049 Pullach, Germany). 1,1,1-Trifluoroacetone was obtained from Fluka, which was usually not contamined by ether.[17b]

The *para*-substituted benzonitriles, obtained as described in the literature,[18] were converted to the corresponding iminoester hydrochlorides with HCl in methanol according to the reported method.[19]

Preparation of Methyl(trifluoromethyl)dioxirane[4,5]. A 500-mL, four-necked, round-bottomed flask, was equipped with an efficient mechanical stirrer, an addition funnel for low-boiling liquids, i.e. for trifluoroacetone (TFA), an addition funnel for solids, i.e. for Caroate, and a gas-inlet tube. The exit of the gas-inlet tube was connected to the top entry of a high-efficiency, double-jacketed spiral condenser, supplied with ethanol coolant (-80 °C) from a LAUDA RLS 6-D cryostat (2.1 kW). The bottom exit of the high-efficiency condenser was attached to a 50-mL, pear-shaped receiving flask, cooled at -60 to -50 °C by an ethanol bath with liquid air. A sidearm at the condenser allowed application of a slightly reduced pressure with a water aspirator, which was controlled automatically at the desired pressure.

The four-necked flask was charged with a slurry of $NaHCO_3$ (13.0 g; 155 mmol) in water (13 mL) and while cooling with an icebath, from the addition funnel for solids the Caroate (24.0 g; 39.1 mmol) was added to the vigorously stirred slurry of $NaHCO_3$, while much CO_2 gas evolved. The pre-cooled (0 °C) addition funnel for liquids was quickly charged with TFA (12.0 mL; density of 1.252 g cm^{-3}; 15.0 g, 134 mmol) and after ca. 80 s of CO_2 evolution, the TFA was added within ca. 1 min. After further 20 s, the water aspirator was adjusted to a slight vacuum (715 Torr) and the pale yellow solution of the methyl(trifluoromethyl)dioxirane (TFD) in trifluoroacetone was collected in the cooled (-60 to -50 °C) receiving flask. After 8 min, a new batch of Caroate (8.00 g; 13.0 mmol) was added, and the reaction mixture was stirred for an additional 8 min. The water aspirator was disconnected and the receiving flask was allowed to warm up to -25 °C (to allow the frozen CO_2 to evolve), removed after ca. 5 min from the high-efficiency condenser, tightly closed with a plastic stopper, and wrapped with aluminum foil to protect the TFD from light.

The TFD yield was 2.0 ± 0.5% (relative to TFA) and was determined iodometrically (1 mL H_2O, 3 mL glacial acetic acid, 0.5 mL saturated KI solution; addition of 0.200 mL of the TFD solution at 0 °C; titration with a freshly standardized 0.05 N $Na_2S_2O_3$ solution). The concentration of TFD in TFA ranged typically from 0.4 to 0.6 M and the volume from 4 to 6 mL (determined by a balance; a density of 1.252 g cm^{-3} was assumed).

The solution can be stored for several months at -20 °C with only minor loss of peroxide titer (ca. 5% loss per month). To administer conveniently and reproducibly (± 5% error) quantitative amounts of the TFD solution for the oxidations, a calibrated pipette was employed, which had been cooled briefly with liquid air to handle the volatile TFA (b.p. 21 °C).

General Procedure for the Synthesis of Tetrazines.[19] The *para*-substituted iminoester hydrochlorides (25.0 mmol) and formamidine acetate (80.0 mmol) were well mixed, 17.5 mL hydrazine hydrate (100%) were added and allowed to reflux for 15 min. On addition of 70 mL water, a yellow solid precipitated, which was collected by filtration. The latter was dissolved in 20-40 mL of acetic acid and oxidized with sodium nitrite (2.50 g; 36.2 mmol). After adding 50 mL of water, a red solid precipitated, which was collected on a Büchner funnel. The powder was dissolved in CH_2Cl_2 and dried over $MgSO_4$ to give sufficiently pure 3-aryl-1,2,4,5-tetrazine for further use. Only the chloro isomer had to be purified by silica gel column chromatography with CH_2Cl_2 as eluent [to dissolve the crude compound, 2 mL of CH_2Cl_2 / MeOH (1:1) were used]. The yields varied from 6 to 37% based on the iminoester hydrochlorides.

General Procedures for the Synthesis of Tetrazine *N*-Oxides with Isolated TFD. To a solution of ca. 0.3 mmol tetrazine **1** in 5-10 mL of dry CH_2Cl_2 was added at 0 °C TFD (1.05 equiv.) in trifluoroacetone solution (0.4 - 0.6 M). After stirring for 20 min, the solvent was evaporated (25 °C / 12 Torr) and ^1H NMR analysis of the residue showed that the *N*-oxides **2** had been formed essentially quantitatively (98%). For further purification, recrystallization from *n*-hexane gave the pure *N*-oxides **2** which were isolated in 68-90% yields.

3-Phenyl-1,2,4,5-tetrazine *N*-Oxide (2a) was obtained in 68% yield as yellow powder (small prisms) from 81.6 mg of tetrazine **1a** after recrystallization from *n*-hexane; mp 126 °C, decomp. >201 °C (exothermic); UV (CCl_4): λ (lg ε) = 264.6 nm (4.327), 349.6 (3.488); IR (CCl_4) 1510, 1440, 1395, 1350, 1170, 1100, 690 cm^{-1}; Anal. Calcd for $C_8H_6N_4O$: C, 55.17; H, 3.47; N, 32.17; Found: C, 55.07; H, 3.51; N,

31.82. The ^{1}H and ^{13}C NMR data are given in Tables 1 and 2. ^{15}N NMR ($CDCl_3$, 40.5 MHz) δ -60.8 (br. s, N-2), -51.4 (d, $^{2}J_{NH}$ = 5.1 Hz, N-1), -46.6 (d, $^{3}J_{NH}$ = 2.4 Hz, N-4), 6.72 (d, $^{2}J_{NH}$ = 13.5 Hz, N-5).

For comparison purposes, also the ^{15}N NMR resonances ($CDCl_3$, 40.5 MHz) of 3-phenyl-1,2,4,5-tetrazine (**1a**) are given: δ 4.97 (d, $^{3}J_{NH}$ = 2.1 Hz, N-2), 12.6 (d, $^{2}J_{NH}$ = 14.0 Hz, N-1).

3-(4-Methylphenyl)-1,2,4,5-tetrazine *N*-Oxide (2b) was obtained in 90% yield as yellow powder (small prisms) from 86.6 mg of tetrazine **1b** after recrystallization from *n*-hexane; mp 146 °C, decomp. >155 °C (exothermic); UV (CCl_4): λ_{max} (lg ε) = 226.4 nm (4.013), 273.6 (4.367), 291.8 (4.412), 350.0 (3.513); IR (CCl_4) 1490, 1380, 1350, 1180, 1170, 1090 cm^{-1}; Anal. Calcd for $C_9H_8N_4O$: C, 57.44; H, 4.28; N, 29.77; Found: C, 57.75; H, 4.39; N, 30.08. The ^{1}H and ^{13}C NMR data are given in Tables 1 and 2.

3-(4-Methoxyphenyl)-1,2,4,5-tetrazine *N*-Oxide (2c) was obtained in 73% yield as yellow powder (small prisms) from 60.0 mg of tetrazine **1c** after recrystallization from *n*-hexane; mp 160 °C, decomp. >188 °C (exothermic); UV (CH_2Cl_2): λ_{max} (lg ε) = 230 nm (4.109), 266 (4.068), 313 (4.422), 364 (3.306), 472 (2.195); IR (CCl_4) 1590, 1385, 1345, 1245, 1160, 1025, 835 cm^{-1}; Anal. Calcd for $C_9H_8N_4O_2$: C, 52.94; H, 3.95; N, 27.44; Found: C, 52.70; H, 3.78; N, 27.15. The ^{1}H and ^{13}C NMR data are given in Tables 1 and 2.

3-(4-Chlorophenyl)-1,2,4,5-tetrazine *N*-Oxide (2d) was obtained in 74% yield as yellow powder (small prisms) from 76.2 mg of tetrazine **1d** after recrystallization from *n*-hexane; mp 180 °C, decomp. >196 °C (exothermic); UV (CCl_4): λ_{max} (lg ε) = 272 nm (4.378), 283 (4.376), 349 (3.557); IR (CCl_4) 1580, 1500, 1415, 1380, 1350, 1090, 1005 cm^{-1}; Anal. Calcd for $C_8H_5ClN_4O$: C, 46.06; H, 2.42; N, 26.86; Found: C, 46.27; H, 2.50; N, 26.61. The ^{1}H and ^{13}C NMR data are given in Tables 1 and 2.

Synthesis of 3-Phenyl-1,2,4,5-tetrazine *N*-Oxide (2a) by the *in situ* Method. In a 250-mL, three-necked, round-bottomed flask, equipped with mechanical stirrer, were added to a solution of 500 mg (3.16 mmol) tetrazine **1a** in 30 mL of CH_2Cl_2 at 0 °C 14 mL of water, 7.0 g (0.083 mmol) $NaHCO_3$ and lastly 1 mL (1.25 g; 11.2 mmol) of 1,1,1-trifluoroacetone. Within 3 × 10 min each were added in succession 3 x 7.0 g (11 mmol) Caroate. After 10 min, an additional 14 mL of water, 7.0 g $NaHCO_3$ and 7.0 g Caroate were added, followed by 2 x 7.0 g Caroate, added within 10-min intervals. On complete addition of the Caroate, the mixture was stirred for an additional 10 min, the upper organic layer was removed by decantation. The aqueous layer was washed with CH_2Cl_2 (2 x 30 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was removed by distillation (40 °C / 12 Torr). Two recrystallizations from *n*-hexane gave 260 mg (47%) of the *N*-oxide **2a** as yellow powder (small prisms).

Determination or Relative Reaction Rates (k_{rel}) by Competition Kinetics. To a solution of the parent tetrazine **1a** (2.00 equiv.) and the appropriate derivative **1b-d** (2.00 equiv.) in 5.00 mL of CH_2Cl_2 the TFD solution (1.00 equiv.) was added at 0 °C and stirred for about 30 min. The solvent was evaporated (25 °C / 15 Torr), the residue was taken up in $CDCl_3$ and the product ratio was determined by quantitative ^{1}H NMR analysis. The rate constants relative to tetrazine **1a** were calculated according to the standard formula[20] (Table 3).

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