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5-Methoxyfuroxano[3,4-*d*]pyrimidine: a highly reactive neutral electrophile

Grigoriy Ya. Remennikov, Bernhard Kempf, Armin R. Ofial, Kurt Polborn and Herbert Mayr*

Department Chemie, Ludwig-Maximilians-Universität München, Butenandtstrasse 5–13 (Haus F), D-81377 Munich, Germany

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ABSTRACT: 5-Methoxyfuroxano[3,4-*d*]pyrimidine (**3**) reacts with electron-rich arenes and ethylene derivatives **4** at C-7 to yield 7-substituted 6,7-dihydro-5-methoxyfuroxano[3,4-*d*]pyrimidines (**5**). Kinetic investigations of these reactions showed that the rate constants can be described by the correlation equation $\log k(20\,^{\circ}\mathrm{C}) = s(N + E)$. The electrophilicity parameter $E(\mathbf{3}) = -8.37$ derived from the second-order rate constants indicates that **3** reacts with nucleophiles of $N \geq 3$. Copyright © 2003 John Wiley & Sons, Ltd.

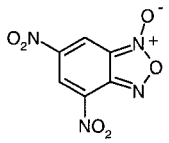
KEYWORDS: furoxanopyrimidine; nucleophilic addition; σ-adducts; kinetics; linear free-energy relationship

INTRODUCTION

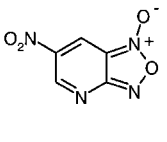
The electron deficiency of aromatic or heteroaromatic rings is significantly increased by annelation of a furoxan ring. There are many examples for the formation of stable anionic σ-complexes in this series.[1] Nitro-substituted benzofuroxans have been recognized to be strong electrophiles. Since 4,6-dinitrobenzofuroxan (**1**) was found to react with heteroarenes faster than the *p*-nitrobenzenediazonium ion and the proton,[2] it has been termed a 'superelectrophile'.[3] Compound **1** reacts with methanol, ethanethiol, L-cysteine, acetone, cyclopentanone and 1,3-diketones, and also with aromatic and heteroaromatic compounds even in the absence of a base. The ability of such compounds to react with intracellular amino and thiol functionalities has been considered to be responsible for their antileukemic activity.[4]

Much attention has been given to aza- and diazabenzofuroxans.[1a,1b,5] Recent investigations have shown that 6-nitro[2,1,3]oxadiazolo[4,5-*b*]pyridine-1-oxide (**2**), an aza analog of **1**, affords an anionic σ-adduct with OH^- which is slightly more stable than the corresponding σ-adduct of **1**.[6] It was thus indicated that the efficiency of an aza group in the aromatic ring in promoting σ-adduct formation is comparable to that of a nitro substituent.

Previously, we reported the formation of σ-adducts when 5-methoxy[1,2,5]oxadiazolo[3,4-*d*]pyrimidine 1-oxide (5-methoxyfuroxano[3,4-*d*]pyrimidine) (**3**) was dissolved in primary, secondary or tertiary alcohols as well as in water.[7] Compound **3** also reacts with carbanions derived from different CH-acids [from $pK_a = 20.0$ (acetone) to 5.21 (dimedone)] to yield the corresponding σ-adducts.[8]



1



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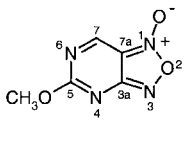

3

We have recently demonstrated that the reactions of carbocations with π-nucleophiles can be described by Eqn. (1),[9–13] and we have recommended a series of benzhydryl cations and π-nucleophiles as reference compounds for characterizing the electrophilic and nucleophilic reactivities of further reagents.[12,13]

$$\log k(20^{\circ}\mathrm{C}) = s(N + E) \qquad (1)$$

where E = electrophilicity parameter, N = nucleophilicity parameter and s = nucleophile-specific parameter. We have now employed this method for determining the electrophilic reactivity of **3** and will demonstrate how to employ the *E*-parameter of **3** for predicting potential reaction partners.

RESULTS

Synthesis

5-Methoxyfuroxano[3,4-*d*]pyrimidine (**3**) reacts with the electron-rich aromatic and non-aromatic CC double-

**Correspondence to:* H. Mayr, Department Chemie, Ludwig-Maximilians-Universität München, Butenandtstrasse 5–13 (Haus F), D-81377 Munich, Germany.
E-mail: herbert.mayr@cup.uni-muenchen.de
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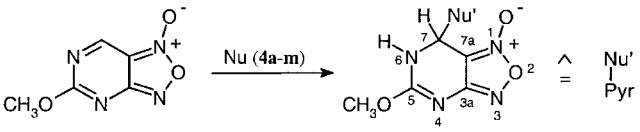
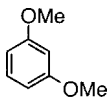
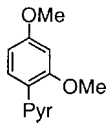
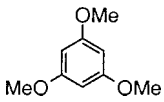
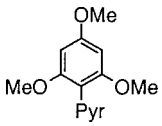
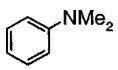
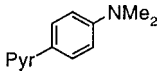
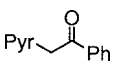
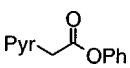
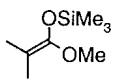
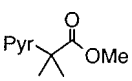
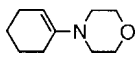
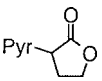
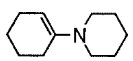
Contract/grant sponsor: Fonds der Chemischen Industrie.

Table 1. 7-Substituted 5-methoxyfuroxano[3,4-*d*]-6,7-dihydropyrimidines **5a–k** from **3** and the nucleophiles **4a–m**



3 **5a-k**

Nucleophile		*N*-Parameter[a]	Solvent	Product		Yield, %
	**4a**	2.48	DMSO		**5a**	23
	**4b**	—	DMSO		**5b**	29
	**4c**	5.21	CH_2Cl_2		**5c**	30
	**4d**	5.41	CH_2Cl_2		**5d**	47
	**4e**	≈ 5.5	DMSO		**5e**	45
	**4f**	5.85	DMSO		**5f**	47
	**4g**	6.22	CH_2Cl_2		**5g**	55
	**4h**	6.57	CH_2Cl_2		**5h**	62
	**4i**	8.23	CH_2Cl_2		**5i**	63
	**4j**	9.00	CH_2Cl_2		**5j**	79
	**4k**	11.40	CH_2Cl_2		**5c**	26
	**4l**	12.56	CH_2Cl_2		**5k**	58
	**4m**	13.36	CH_2Cl_2		**5c**	24

[a] From Ref. 12.

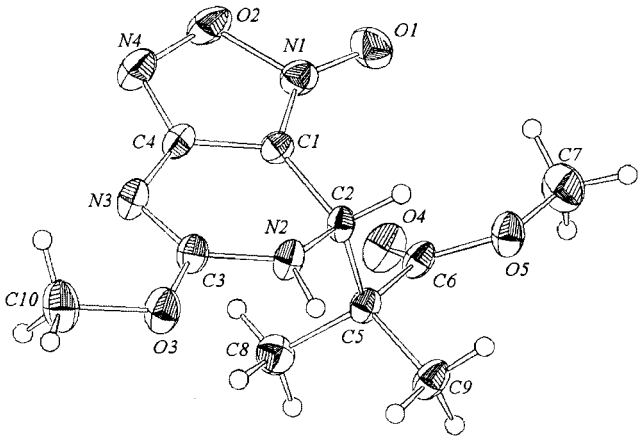


Figure 1. Crystallographic structure (ZORTEP projection) of **5j**

bonded systems **4a**–**m** in DMSO or CH_2Cl_2 at room temperature to give the 7-substituted 5-methoxyfuroxano[3,4-*d*]-6,7-dihydropyrimidines **5a**–**k**, respectively (Table 1).

Compounds **5a**–**k** show ^{1}H NMR spectra with a signal at δ 4.95–6.75 (7-H). The strong upfield shift of this signal compared with δ(H7) of **3** (9.41 ppm) and the ^{13}C NMR signal of the sp^3-carbon C-7 at δ 41.4–53.7 are in accord with the 6,7-dihydropyrimidine structure of **5a**–**k**. Moreover, the ^{13}C resonances at δ 104–107 and 158–162 for C-7a and C-3a, respectively, and the presence of the characteristic 'furoxan' absorption band at 1600–1640 cm^{-1} in the IR spectra[14] indicate that the pyrimido[3,4-*d*]furoxan ring has been retained. Additional structural evidence comes from the x-ray crystal structure of **5j**, which unequivocally proves the position of the exocyclic NO-group (Fig. 1).

Kinetics

The formation of **5a**–**k** proceeds through the intermediacy of the zwitterions **6a**–**k**, which are generated by the attack of nucleophiles at C-7 of **3** (Scheme 1).

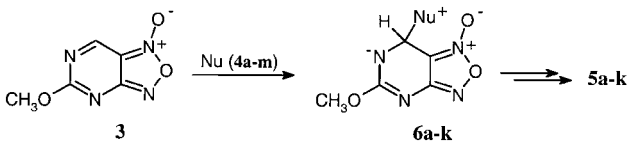
Since the change of hybridization of C-7 changes the nature of the conjugated π-system, the reaction described in Scheme 1 is associated with a hypsochromic shift in the UV spectrum (see Experimental).

When the nucleophiles **4** are used in high excess over **3**, their concentrations remain almost constant throughout the reactions, and the operation of pseudo-first-order rate laws is indicated by the exponential decay of the absorbance of **3** at $\lambda = 301$ nm in dichloromethane. Division of the pseudo-first-order rate constant $k_{1\psi}$ by the concentration of the nucleophiles gave the second-order rate constants k_2 for the reactions of **3** with **4k**, **4l** and **4m** (Table 2).

^{1}H NMR spectroscopy was used to follow the kinetics of the reaction of **3** with *N*-methylpyrrole (**4f**). The disappearance of 7-H of **3** (δ 9.41) occurred with equal rate to the appearance of the resonances of **5**, indicating that the proton shift in the intermediate **6** is a fast process (Fig. 2).

Equation (1) can now be used to calculate E(**3**) from the rate constants given in Table 2 and the *N*- and *s*-parameters of the nucleophiles **4f**,**k**–**m** published previously.[12,13] Table 2 shows that closely similar values of E are derived from the reactions of **3** with different nucleophiles, indicating that Eqn. (1) is suitable for describing the reactions under consideration.

The good agreement of the E-values derived from reactions in dichloromethane (entries 2–4, Table 2) with the E-value derived from a reaction in DMSO solution (entry 1) cannot *a priori* be expected since the rates of reactions of neutral nucleophiles with neutral electrophiles yielding zwitterionic intermediates may show considerable solvent dependence.[15,16] Possibly because of the high polarity of the reactant **3**, the solvent dependence of the rate constant is small in these reactions.



Scheme 1

DISCUSSION

With an electrophilicity parameter $E = -8.37$, 5-methoxyfuroxano[3,4-*d*]pyrimidine (**3**) ranks among the strongest noncharged electrophiles, comparable in its reactivity to stabilized carbocations and cationic metal π-complexes as shown in Fig. 3.

At typical concentrations (1 M), second-order reactions with $k_2 = 1 \times 10^{-4}$ M^{-1} s^{-1} proceed slowly with a half-life of 3 h. Since the slope parameters s of nucleophiles as defined by Eqn. (1) are typically in the range $0.7 < s < 1.2$, we have derived the rule of thumb that reactions of electrophiles with nucleophiles will take place at room temperature, when $E + N \geq -5$.[9,12]

As a consequence of the electrophilicity parameter E(**3**) = −8.37 derived above, the furoxanopyrimidine **3** can be expected to react with nucleophiles of $N > 3$–4. Table 1 shows that with the exception of **4a**, all nucleophiles **4** which were found to react with **3** fall into this category. From the reactivity parameters of **4a** ($N = 2.48$, $s = 1.09$) and **3** ($E = -8.37$) one would derive a second-order rate constant of 4×10^{-7} M^{-1} s^{-1}, corresponding to a half-life of 1 month at room temperature for 1 M solutions. The isolation of 23% of **5a** after 12 h at

Table 2. Rate constants for the reactions of **3** with the nucleophiles **4f** and **4k–m**, and determination of the electrophilicity parameter *E* of **3**

Nucleophile	k(20 °C) (M^{-1} s^{-1})	N[a]	s[a]	E
4f	$(2.628 \pm 0.128) \times 10^{-3}$	5.85	1.03	−8.36
4k	$(2.634 \pm 0.045) \times 10^{2}$	11.40	0.83	−8.48
4l	$(5.907 \pm 0.044) \times 10^{2}$	12.56	0.70	−8.60
4m	$(1.801 \pm 0.037) \times 10^{4}$	13.36	0.81	−8.10
				E(**3**) = −8.37[b]

[a] Data from Ref. 12.
[b] By minimization of $\Delta^2 = \Sigma[\log k_i - s_i (N_i + E)]^2$ as described in Ref. 12. The calculations were actually performed with more decimal places for log *k*, *N*, and *s* than indicated in the table. The use of log *k*, *N*, and *s* given in the table leads to slightly deviating results.

room temperature indicates that the reaction between **3** and **4a** proceeds faster than expected.

In agreement with their *N*-parameters, allyltrimethylsilane ($N = 1.79$) and 3-methylanisole ($N = 0.13$) did not react with **3** at room temperature. With $N = 3.61$, 2-methylfuran is a borderline case. Although we have so far not isolated a product from **3** and 2-methylfuran, it is likely that a reaction should be observed when prolonged reaction times are employed.

CONCLUSION

Annelation of a furoxan ring significantly increases the electron deficiency of the pyrimidine ring with the consequence that non-catalyzed reactions of 5-methoxyfuroxano[3,4-*d*]pyrimidine (**3**) with electron-rich arenes and alkenes become possible. Additions of π-nucleophiles to **3** follow Eqn. (1) and, therefore, allow one to characterize **3** by an electrophilicity parameter.

Since the rate-determining step of the reaction sequence shown in Scheme 1 resembles that of nucleophilic aromatic substitutions, it is likely that this important class of reactions can also be described by Eqn. (1). Preliminary results corroborate this indication.

EXPERIMENTAL

The proton and carbon NMR spectra were obtained by using Bruker ARX 300 (300 MHz) and Varian INOVA 400 (400 MHz) spectrometers. ^{1}H NMR chemical shifts refer to tetramethylsilane (δ_H 0.00) and ^{13}C NMR chemical shifts refer to the solvent as internal standard (DMSO-d_6 δ_C 39.5). DEPT experiments were used to obtain information about the multiplicities of ^{13}C resonances. Signal assignments were based on gHSQC experiments. The IR spectra were recorded on a Perkin-Elmer 325 instrument. A Perkin-Elmer λ 16 spectrometer was used for measuring the UV–visible spectra. Melting-points (uncorrected) were determined on a Reichert Thermovar.

All reactions were performed under an atmosphere of dry nitrogen. Dichloromethane and DMSO were freshly distilled from CaH_2 before use.

X-ray diffraction analysis of ***5j*** *(see Figure 1).* Monoclinic, space group $P2_1/c$, No. 14. Unit cell dimensions: $a = 12.129(4)$, $b = 6.477(2)$, $c = 15.596(5)$ Å, $\beta = 95.96(3)°$, volume 1218.5(7) Å^3, $Z = 4$, $D_c = 1.473$ mg m^{-3}, $F(000) = 568$, $T = 293(2)$ K, μ(Mo Kα) = 0.120 mm^{-1}. Data collection: Nonius MACH3

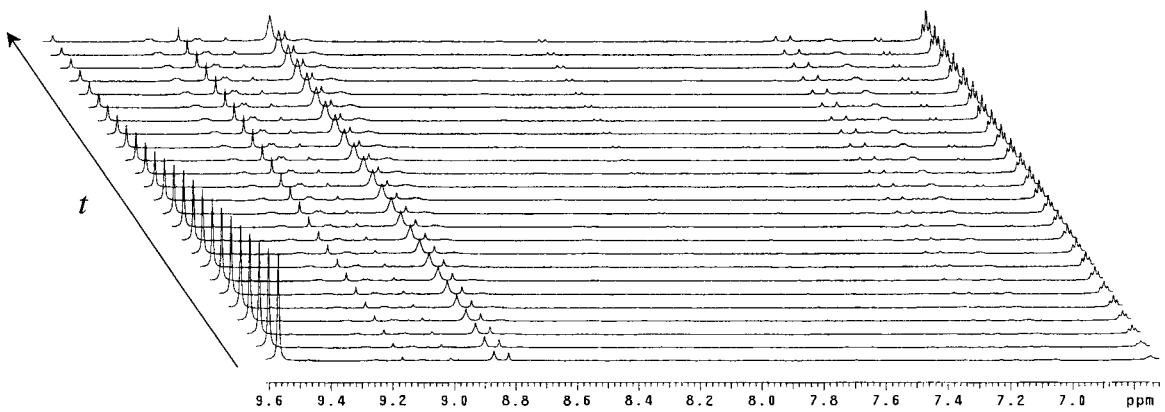


Figure 2. ^{1}H NMR spectra during the reaction of 5-methoxyfuroxano[3,4-*d*]pyrimidine (**3**) with *N*-methylpyrrole (**4f**) in DMSO-d_6 at 20 °C

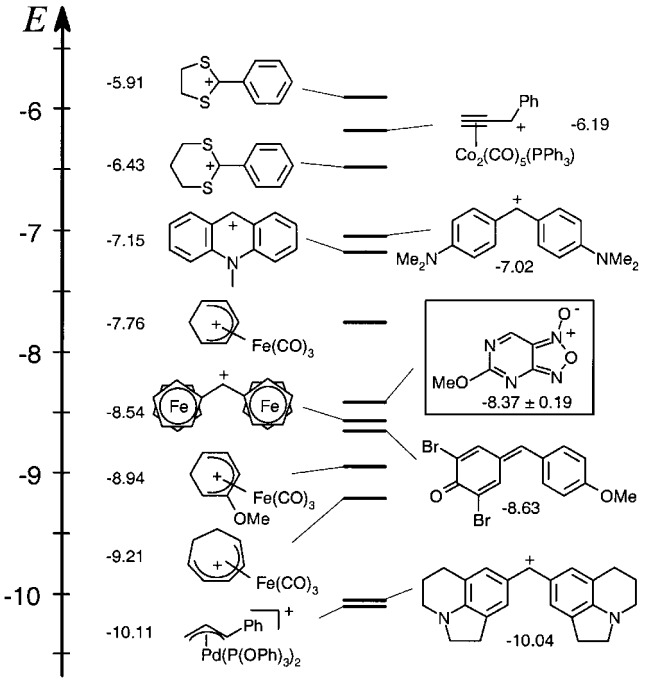


Figure 3. Comparison of the electrophilicity *E* of **3** with that of related charged and non-charged electrophiles

diffractometer, colourless plate ($0.13 \times 0.23 \times 0.53$ mm), mounted in a glass capillary, cell constants from 25 centered reflections. Mo Kα radiation, $\lambda =$ 0.71073 Å, graphite monochromator, $\omega - 2\theta$ scan, scan width $(0.98 + 0.55 \tan\theta)°$, maximum measuring time 60 s, intensity of three standard reflections checked every 2 h, θ range 2.63–23.99° for all $\pm h$, $+k$, $-l$ reflections, 1998 reflections measured, 1915 unique and 1449 reflections with $I > 2\sigma(I)$. Lorentz, polarization and absorption correction (T_{min}/T_{max} 0.9057 and 0.9972). Structure solution with SHELXS-86 and refinement with SHELXL-93 (G. M. Sheldrick, SHELXS-86 and SHELXL-93 programs for the solution and the refinement of X-ray structures, University of Göttingen, 1986 and 1993). Final $R1 = 0.0536$ and $wR2 = 0.1358$ for 1449 reflections with $I > 2\sigma(I)$ and 177 variables. $R1 = 0.0726$ and $wR2 = 0.1561$ for all data. Weight: SHELXL-93. Extinction coefficient 0.0175(36). Maximum and minimum of the final difference Fourier synthesis 0.262 and −0.268 e Å^{-3}. ZORTEP plot (L. Zsolnai and G. Huttner, ZORTEP, University of Heidelberg, 1994). CCDC-193388 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Center, Cambridge, UK).

*5-Methoxyfuroxano[3,4-d]pyrimidine (**3**).* **CAUTION**: 5-Methoxyfuroxano[3,4-*d*]pyrimidine (**3**) has an irritating effect on the respiratory system and the skin! Avoid inhalation and skin contact! Compound **3** was prepared as described.[7] A solution of $NaNO_2$ (3.2 g, 46 mmol) in 25 ml of water was added dropwise with stirring to a solution of 4-hydrazino-2-methoxy-5-nitropyrimidine[17] (5.0 g, 27 mmol) in 87 ml of 0.75 M HCl at − 2 to 0 °C (20 min). The mixture was then allowed to warm to room temperature and stirring was continued for 2 h. The yellow precipitate was filtered, washed with water and dried *in vacuo*. Purification by column chromatography (silica gel, absolute $CHCl_3$) and heating in absolute $CHCl_3$ (60 °C, 6 h) yielded **3** (3.54 g, 78%), m.p. 85–87 °C (n-hexane) (lit.[7] m.p. 85–87 °C). ^{1}H NMR (DMSO-d_6), δ 4.05 (s, 3H, OCH_3), 9.41 (s, 1H, 7-H); ^{13}C NMR (DMSO-d_6), δ 56.5 (OCH_3), 105.8 (C-7a), 156.8 (C-7), 159.9 (C-3a), 166.4 (C-5); UV (CH_2Cl_2), λ_{max} 301, 314, 333 (sh) nm.

*General procedure for the reaction of **3** with the nucleophiles **4**.* Under a nitrogen atmosphere, nucleophile **4** (3.3 mmol) was added to a stirred solution of **3** (500 mg, 2.97 mmol) in 3 ml of dry DMSO (or CH_2Cl_2). After 20 h, the reaction mixture was poured into water (100 ml) and extracted with ethyl acetate or CH_2Cl_2 (3×50 ml). The organic layer was dried ($CaCl_2$) and the solvent was evaporated to give a residue, which was purified by column chromatography (silica gel, chloroform). Crystallization from ethanol yielded pure products **5a**–**k**.

*7-(2′,4′-Dimethoxyphenyl)-5-methoxyfuroxano[3,4-d]-6,7-dihydropyrimidine (**5a**).* M.p. 213–214 °C. ^{1}H NMR (DMSO-d_6), δ 3.69, 3.77, 3.84 (3s, 3×3H, 5-OCH_3, 2′-OCH_3, and 4′-OCH_3), 5.82 (br. s, 1H, 7-H), 6.52 (dd, $J = 8.4$, 2.4 Hz, 1H, ArH), 6.59 (d, $J = 2.3$ Hz, 1H, ArH), 7.16 (d, $J = 8.4$ Hz, 1H, ArH), 8.58 (br. s, 1H, NH); ^{13}C NMR (DMSO-d_6), δ 48.1 (d, C-7), 54.3, 55.3, 55.7 (3q, 5-OCH_3, 2′-OCH_3 and 4′-OCH_3), 99.2 (d, Ar), 104.2 (s, C-7a), 104.9 (d, Ar), 116.9 (s, Ar), 130.7 (d, Ar), 158.5 (2C), 160.7, 161.4 (2s, C-3a, C-5 and Ar); UV (MeOH): λ_{max} 234 nm (log $\epsilon = 4.2$), 282 nm (log $\epsilon = 3.8$). Anal. Calcd for $C_{13}H_{14}N_4O_5$ (306.3): C, 50.98; H, 4.61; N, 18.29. Found: C, 50.90; H, 4.66; N, 18.37%. IR (KBr): 3429, 2951, 2839, 1652, 1612, 1576, 1539, 1508, 1444, 1372, 1342, 1300, 1262 cm^{-1}.

*7-(2,4,6-Trimethoxyphenyl)-5-methoxyfuroxano[3,4-d]-6,7-dihydropyrimidine (**5b**).* M.p. 233–235 °C. ^{1}H NMR (DMSO-d_6), δ 3.71 (s, 6H, $2 \times OCH_3$), 3.79, 3.82 (2s, 2×3H, $2 \times OCH_3$), 6.15 (d, $J = 1.0$ Hz, 1H, 7-H), 6.27 (s, 2H, ArH), 8.39 (br. s, 1H, NH); ^{13}C NMR (DMSO-d_6), δ 41.4 (d, C-7), 54.2, 55.4, 56.0 (3q, OCH_3), 91.4 (d, Ar), 104.7, 105.0 (2s, C-7a and Ar), 159.0, 161.0, 161.7 (3s, C-3a, C-5 and Ar); UV (MeOH), λ_{max} 241 nm (log $\epsilon = 4.2$). Anal. Calcd for $C_{14}H_{16}N_4O_6$ (336.3): C, 50.00; H, 4.80; N, 16.66. Found: C, 49.69; H, 4.51; N, 16.70%. IR (KBr): 3435, 2952, 2845, 1653, 1609, 1575, 1541, 1496, 1449, 1371, 1338, 1302, 1282, 1260, 1230, 1207 cm^{-1}.

*2-(5-Methoxyfuroxano[3,4-d]-6,7-dihydropyrimidin-7-yl)cyclohexanone (**5c**).* M.p. 201–203 °C. ^{1}H NMR (DMSO-d_6), δ 1.46–2.50 (m, 8H, 4 × CH_2), 2.90–3.03 (m, 1H, CH), 3.78 (s, 3H, OCH_3), 5.24 (d, J = 1.8 Hz, 1H, 7-H), 7.97 (br. s, 1H, NH); ^{13}C NMR (DMSO-d_6), δ 23.7, 25.9, 26.8, 41.0 (4 t, 4 × CH_2), 46.8 (d, C-7), 51.6 (d, CH), 54.4 (q, 5-OCH_3), 103.7 (s, C-7a), 158.8, 161.1 (2s, C-3a and C-5), 208.2 (s, CO); UV (MeOH), λ_{max} 241 nm (log ϵ = 3.9). Anal. Calcd. for $C_{11}H_{14}N_4O_4$ (266.3): C, 49.62; H, 5.30; N, 21.04. Found: C, 49.61; H, 5.28; N, 21.12%. IR (KBr): 3430, 3277, 2952, 2869, 1699, 1651, 1579, 1554, 1450, 1359, 1333, 1311, 1291, 1249, 1217 cm^{-1}.

This compound was obtained also from **3** and the enamines **4k** and **4m** in CH_2Cl_2 after acidic work-up of the reaction mixture.

*1-(5-Methoxyfuroxano[3,4-d]-6,7-dihydropyrimidin-7-yl)propan-2-one (**5d**).* M.p. 184–185 °C (lit.[8] m.p. 184–185 °C). ^{1}H NMR (DMSO-d_6), δ 2.11 (s, 3H, CH_3), 3.05 (m_c, 2H, CH_2), 3.80 (s, 3H, OCH_3), 5.04 (t, J = 2.2 Hz, 1H, 7-H), 8.23 (br. s, 1H, NH); ^{13}C NMR (DMSO-d_6), δ 30.2 (q, CH_3), 43.2 (t, CH_2), 43.6 (d, C-7), 54.3 (q, OCH_3), 104.5 (s, C-7a), 158.5, 160.8 (2s, C-3a and C-5), 204.9 (s, CO); UV (MeOH): λ_{max} 242 nm (log ϵ = 3.8). IR (KBr): 3436, 3244, 1716, 1656, 1565, 1549, 1459, 1438, 1404, 1371, 1351, 1312, 1281, 1269 cm^{-1}.

*7-(4-Dimethylaminophenyl)-5-methoxyfuroxano[3,4-d]-6,7-dihydropyrimidine (**5e**).* M.p. 209–211 °C. ^{1}H NMR (DMSO-d_6), δ 2.90 [s, 6H, $N(CH_3)_2$], 3.87 (s, 3H, OCH_3), 5.74 (d, J = 1.8 Hz, 1H, 7-H), 6.72, 7.10 (AA′ BB′ system with J_{AB} = 8.7 Hz, 2 × 2H, ArH), 8.90 (br. s, 1H, NH); ^{13}C NMR (DMSO-d_6), δ 39.9 [q, $N(CH_3)_2$], 50.4 (d, C-7), 54.5 (q, OCH_3), 104.3 (s, C-7a), 112.2 (d, Ar), 124.4 (s, Ar), 127.8 (d, Ar), 150.7 (s, Ar), 157.7, 160.6 (2s, C-3a and C-5); UV (MeOH): λ_{max} 264 nm (log ϵ = 4.2). Anal. Calcd. for $C_{13}H_{15}N_5O_3$ (289.3): C, 53.97; H, 5.23; N, 24.21. Found: C, 54.09; H, 5.33; N, 23.91%. IR (KBr): 3413, 3195, 3062, 2959, 2855, 1651, 1611, 1580, 1519, 1482, 1446, 1373, 1305, 1265, 1251, 1204 cm^{-1}.

*7-(2-N-Methylpyrrolo)-5-methoxyfuroxano[3,4-d]-6,7-dihydropyrimidine (**5f**).* M.p. >230 °C. ^{1}H NMR (DMSO-d_6), δ 3.56 (s, 3H, NCH_3), 3.83 (s, 3H, OCH_3), 5.95 (br. s, 2H, 7-H and 5′-H), 6.07 (s, 1H, 4′-H), 6.73 (br. s, 1H, 3′-H), 8.85 (br.s, 1H, NH); ^{13}C NMR (DMSO-d_6), δ 33.7, 43.7, 54.6, 103.4, 106.9, 109.1, 124.2, 126.9, 157.8, 160.3; UV (MeOH), λ_{max} 232 nm (log ϵ = 4.2). Anal. Calcd. for $C_{10}H_{11}N_5O_3$ (249.2): C, 48.19; H, 4.45; N, 28.10. Found: C, 48.22; H, 4.64; N, 28.20%. IR (KBr): 3410, 3197, 3064, 2955, 2859, 1654, 1610, 1585, 1524, 1480, 1449, 1372, 1307, 1269, 1250, 1208 cm^{-1}.

*2-(5-Methoxyfuroxano[3,4-d]-6,7-dihydropyrimidin-7-yl)-1-phenylethanone (**5g**).* M.p. 198–200 °C (lit.[8] 194–196 °C). ^{1}H NMR (DMSO-d_6), δ 3.64 (m_c, 2H, CH_2), 3.79 (s, 3H, OCH_3), 5.28 (br. s, 1H, 7-H), 7.50–7.96 (m, 5H, Ph), 8.31 (s, 1H, NH); ^{13}C NMR (DMSO-d_6), δ 39.0 (t, CH_2), 43.9 (d, C-7), 54.4 (q, OCH_3), 104.8 (s, C-7a), 128.0, 128.8, 133.7 (3d, Ar), 135.9 (s, Ar), 158.6, 160.9 (2s, C-3a and C-5), 196.1 (CO); UV (MeOH), λ_{max} 243 nm (log ϵ = 4.3). Anal. Calcd for $C_{13}H_{12}N_4O_4$ (288.3): C, 54.17; H, 4.20; N, 19.44. Found: C 54.10; H, 4.23; N, 19.51%. IR (KBr): 3430, 1680, 1652, 1574, 1543, 1449, 1363, 1294, 1254, 1223 cm^{-1}.

*2-(5-Methoxyfuroxano[3,4-d]-6,7-dihydropyrimidin-7-yl)cyclopentanone (**5h**).* M.p. 197–200 °C. ^{1}H NMR (DMSO-d_6), δ 1.73–2.23 (m, 6H, 3 × CH_2), 2.75 (m_c, 1H, CH), 3.81 (s, 3H, OCH_3), 5.22 (br. s, 1H, 7-H), 8.42 (br. s, 1H, NH); ^{13}C NMR (DMSO-d_6), δ 19.7, 22.4, 37.6 (3t, 3 × CH_2), 46.5 (d, C-7), 49.5 (d, CH), 54.5 (q, OCH_3), 103.5 (C-7a), 158.2 (C-3a), 161.4 (C-5), 215.8 (CO); UV (MeOH), λ_{max} 243 nm (log ϵ = 3.9). Anal. Calcd for $C_{10}H_{12}N_4O_4$ (252.2): C, 47.62; H, 4.80; N, 22.21. Found: C, 47.58; H, 4.72; N, 22.30%. IR (KBr): 3432, 3277, 2960, 2880, 1722, 1653, 1584, 1549, 1444, 1394, 1379, 1342, 1313, 1304, 1279, 1252, 1212 cm^{-1}.

*Phenyl (5-methoxyfuroxano[3,4-d]-6,7-dihydropyrimidin-7-yl)acetate (**5i**).* M.p. 205–206 °C. ^{1}H NMR (DMSO-d_6), δ 3.09 (dd, ^2J = 16.4 Hz, ^3J = 4.6 Hz, 1H, 1/2 × CH_2), 3.24 (dd, ^2J = 16.4 Hz, ^3J = 4.2 Hz, 1H, 1/2 × CH_2), 3.81 (s, 3H, OCH_3), 5.28 (t, J = 4.4 Hz, 7-H), 7.03–7.47 (m, 5H, Ph), 8.65 (br.s, 1H, NH); ^{13}C NMR (DMSO-d_6), δ 36.0 (t, CH_2), 44.6 (d, C-7), 54.5 (q, OCH_3), 103.8 (s, C-7a), 121.4, 126.0, 129.5 (3d, Ar), 150.0 (s, Ar), 158.4, 160.8 (2s, C-3a and C-5), 167.9 (s, CO_2Ph); UV (MeOH), λ_{max} 239 nm (log ϵ = 3.9). Anal. Calcd for $C_{13}H_{12}N_4O_5$ (304.3): C, 51.32; H, 3.98; N, 18.41. Found: C, 51.27; H, 3.95; N, 18.45%. IR (KBr): 3430, 3323, 3009, 2951, 1727, 1648, 1577, 1552, 1535, 1487, 1449, 1393, 1361, 1321, 1288, 1255, 1233 cm^{-1}.

*Methyl 2-(5-methoxyfuroxano[3,4-d]-6,7-dihydropyrimidin-7-yl)-2-methylpropionate (**5j**).* M.p. 173–174 °C. ^{1}H NMR (DMSO-d_6), δ 1.13, 1.16 (2s, 2 × 3H, 2 × CH_3), 3.59 (s, 3H, CO_2CH_3), 3.82 (s, 3H, OCH_3), 4.95 (s, 1H, 7-H), 8.68 (s, 1H, NH); ^{13}C NMR (DMSO-d_6), δ 20.8, 21.2 (2q, 2 × CH_3), 50.1 [s, $C(CH_3)_2$], 52.6 (q, CO_2CH_3), 53.7 (d, C-7), 54.7 (q, OCH_3), 103.1 (s, C-7a), 158.9, 161.3 (2s, C-3a and C-5), 173.7 (CO_2CH_3); UV (MeOH), λ_{max} 239 nm (log ϵ = 3.8), 256 nm (log ϵ = 3.8). Anal. Calcd for $C_{10}H_{14}N_4O_5$ (270.2): C, 44.44; H, 5.22; N, 20.73. Found: C, 44.46; H, 5.14; N, 20.82%. IR (KBr): 3432, 3309, 3073, 2988, 2956, 2844, 1724, 1643, 1574, 1548, 1532, 1463, 1440, 1392, 1374, 1308, 1282, 1268 cm^{-1}.

*3-(5-Methoxyfuroxano[3,4-d]-6,7-dihydropyrimidin-7-yl)dihydrofuran-2-one (**5k**).* M.p. 184–186 °C. ^{1}H NMR (DMSO-d_6), δ 2.36 (m_c, 2H, CH_2), 3.33 (m, 1H, CH),

Table 3. Rate constants of the individual kinetic measurements of **3** with the nucleophiles **4f, 4k, 4l** and **4m**

Nuc	$[\mathbf{3}]_0$ (mol l^{-1})	$[Nuc]_0$ (mol l^{-1})	Solvent	Conversion (%)	k_2(20 °C) (M^{-1} s^{-1})
N-Methylpyrrole (**4f**)	2.337×10^{-1}	3.170×10^{-1}	DMSO	78	2.472×10^{-3} (NMR)[a]
	2.176×10^{-1}	3.202×10^{-1}	DMSO	86	2.786×10^{-3} (NMR)[a]
	2.345×10^{-1}	5.762×10^{-1}	DMSO	86	2.626×10^{-3} (NMR)[a]
1-(*N*-Morpholino)cyclohexene (**4k**)	1.240×10^{-4}	5.226×10^{-4}	CH_2Cl_2	58	2.636×10^{2} (UV–vis)[b]
	9.712×10^{-5}	1.023×10^{-3}	CH_2Cl_2	53	2.578×10^{2} (UV–vis)[b]
	6.166×10^{-5}	1.299×10^{-3}	CH_2Cl_2	55	2.688×10^{2} (UV–vis)[b]
2-(Trimethylsiloxy)-4,5-dihydrofuran (**4l**)	1.130×10^{-4}	4.661×10^{-4}	CH_2Cl_2	56	5.957×10^{2} (UV–vis)[b]
	7.357×10^{-5}	6.067×10^{-4}	CH_2Cl_2	67	5.850×10^{2} (UV–vis)[b]
	1.298×10^{-4}	1.338×10^{-3}	CH_2Cl_2	76	5.914×10^{2} (UV–vis)[b]
1-(*N*-Piperidino)cyclohexene (**4m**)	2.724×10^{-5}	2.425×10^{-4}	CH_2Cl_2		1.807×10^{4} (UV–vis)[b,c]
	2.724×10^{-5}	4.850×10^{-4}	CH_2Cl_2		1.844×10^{4} (UV–vis)[b,c]
	2.724×10^{-5}	7.275×10^{-4}	CH_2Cl_2		1.753×10^{4} (UV–vis)[b,c]
	2.724×10^{-5}	9.700×10^{-4}	CH_2Cl_2		1.645×10^{4} (UV–vis)[b,c]
	2.724×10^{-5}	1.212×10^{-3}	CH_2Cl_2		1.595×10^{4} (UV–vis)[b,c]

[a] The kinetics of the reaction were followed by ^{1}H NMR spectroscopy (200 MHz).
[b] The reaction was monitored photometrically at $\lambda = 301$ nm.
[c] Stopped-flow measurements.

3.80 (s, 3H, OCH_3), 4.26 (m_c, 2H, CH_2), 5.16 (br.s, 1H, 7-H), 8.66 (br.s, 1H, NH); ^{13}C NMR (DMSO-d_6), δ 23.4, 40.7, 46.8, 54.4, 66.5, 103.4, 158.4, 161.1, 175.3; UV (MeOH), λ_{max} 242 nm (log $\epsilon = 3.9$). Anal. Calcd for $C_9H_{10}N_4O_5$ (254.2): C, 42.53; N, 22.04. Found: C, 42.48; N, 21.90%. IR (KBr): 3433, 3275, 2956, 2863, 1721, 1652, 1581, 1547, 1448, 1362, 1317, 1295, 1255, 1216 cm^{-1}.

Kinetic investigations. The kinetic investigation of the reaction of 5-methoxyfuroxano[3,4-*d*]pyrimidine (**3**) with *N*-methylpyrrole (**4f**) in DMSO-d_6 at 20 °C was performed on a Varian Mercury 200 (200 MHz) NMR instrument. The UV–visible kinetic measurements (conventional and stopped-flow) and the data evaluation were carried out as described previously.[13] For details, see Table 3.

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