Preparation of Pyrimidine-*N*-oxides by Condensation of Functionalized Enamides with Hydroxylamine Hydrochloride

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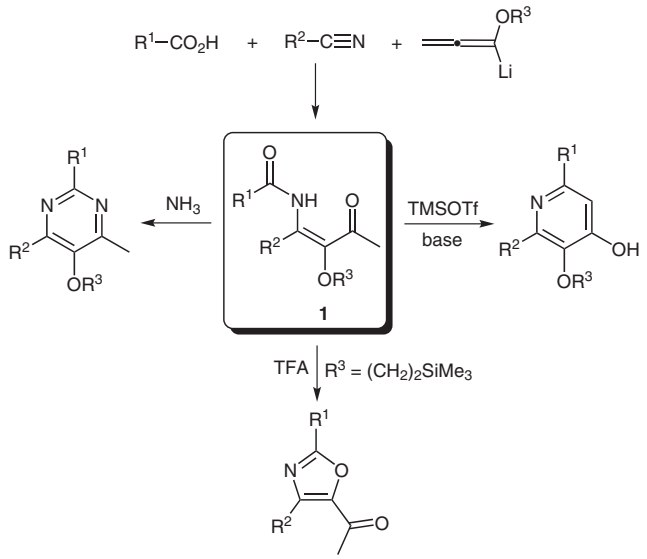
Dedicated to Professor Helmut Vorbrüggen on the occasion of his 80th birthday

Abstract: β-Alkoxy-β-ketoenamides and hydroxylamine hydrochloride smoothly provide pyrimidine-*N*-oxides under very mild conditions. Alkyl, aryl, and heteroaryl substituents are compatible with this new method. By treatment with acetic acid anhydride these pyrimidine-*N*-oxides undergo a rearrangement furnishing highly functionalized 6-acetoxymethyl-substituted pyrimidine derivatives in good yields. Our method, which is based on a three-component reaction of alkoxyallenes, nitriles, and carboxylic acids, therefore constitutes a highly flexible route to densely substituted pyrimidine derivatives.

Key words: pyrimidines, *N*-oxides, enamides, hydroxylamine, condensation, 3,3-sigmatropic rearrangement

We recently discovered and subsequently exploited a novel three-component reaction, which employs lithiated alkoxyallenes[1] [$(R^3O)LiC{=}C{=}CH_2$], nitriles (R^2CN), and carboxylic acids (R^1CO_2H) and furnishes synthetically highly versatile β-alkoxy-β-ketoenamides **1**. These served as flexible building blocks for the synthesis of specifically functionalized heterocycles such as pyridine,[2] pyrimidine,[3] and oxazole[4] derivatives (Scheme 1).



Scheme 1 β-Alkoxy-β-ketoenamides **1** as key building blocks for the synthesis of pyridine, oxazole, and pyrimidine derivatives

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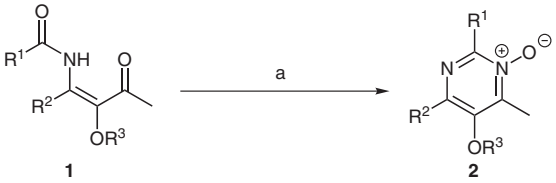
The pyrimidines are formed when enamides **1** were treated with ammonium acetate under appropriate conditions (ca. 65 °C for several hours). In this letter we report the extremely smooth preparation of pyrimidine-*N*-oxides **2** when enamides **1** were mixed with hydroxylamine hydrochloride at room temperature (Scheme 2). Furthermore, we describe the rearrangement of these *N*-oxides into pyrimidines with an acetoxymethyl side chain by treatment of **2** with acetic acid anhydride.



Scheme 2 Preparation of pyrimidine-*N*-oxides **2**. *Reagents and conditions*: a) $NH_2OH{\cdot}HCl$, MeOH, r.t., 1–3 d.

Combination of a range of differently substituted enamides **1** bearing alkyl, aryl, or heteroaryl substituents R^1 and R^2 with hydroxylamine hydrochloride in methanol at room temperature provided the desired pyrimidine-*N*-oxides **2** in good to excellent yields (Table 1). The conditions are very mild and the products are easily purified by column chromatography. The spectroscopic data fully confirm the existence of the pyrimidine ring, excluding the conceivable formation of 1,2,6-oxadiazepine derivatives.

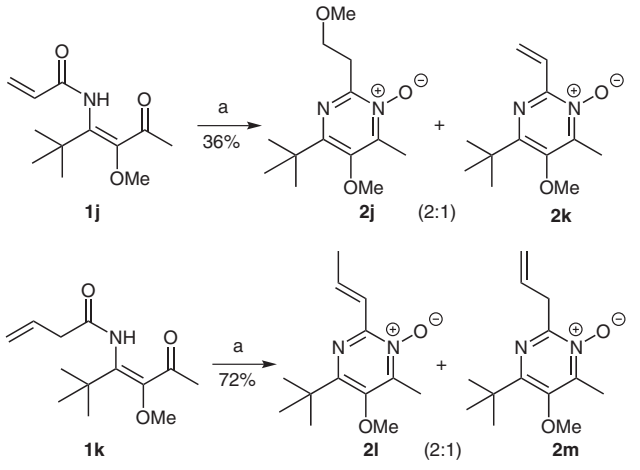
The treatment of enamide **1j**, containing an acryl amide substructure, with hydroxylamine hydrochloride not only delivered the expected vinyl-substituted pyrimidine-*N*-oxide **2k** (Scheme 3) but as major component **2j**. This product arises from an addition of methanol to the double bond (probably occurring at the stage of **1j**). For precursor **1k** with the unconjugated double bond the formation of pyrimidine-*N*-oxides proceeded smoothly and we isolated a 2:1 mixture of compound **2l** with an isomerized double bond together with the primary cyclization product **2m** bearing an allyl substituent.

The mechanism of the pyrimidine-*N*-oxide formation is fairly straightforward and briefly illustrated in Scheme 4. After oxime generation its nitrogen intramolecularly attacks the amide carbon and after water displacement the final product with the *N*-oxide moiety is formed. Very likely all steps proceed under acid catalysis.

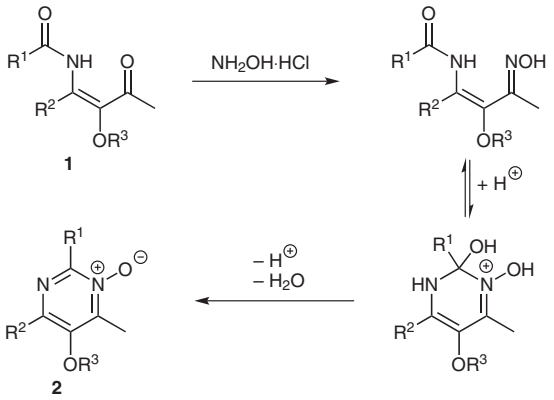
Table 1 Preparation of Pyrimidine-*N*-oxides **2** from Enamides **1**

Enamide	R^1	R^2	R^3	Product	Yield (%)
1a	Ph	*i*-Pr	Me	**2a**	61
1b	Ph	*t*-Bu	Me	**2b**	97
1c	PhHC=CH	*t*-Bu	Me	**2c**	72
1d	2-thienyl-HC=CH	*t*-Bu	Me	**2d**	85
1e	2-furanyl-HC=CH	*t*-Bu	Me	**2e**	74
1f	2-thienyl	2-thienyl	Me	**2f**	59
1g	*c*-Pr	1-adamantyl	Me	**2g**	67
1h	*c*-Pr	*c*-Pr	TMSE[a]	**2h**	65
1i	*c*-Pr	1-adamantyl	TMSE[a]	**2i**	84

[a] TMSE = 2-(trimethylsilyl)ethyl.

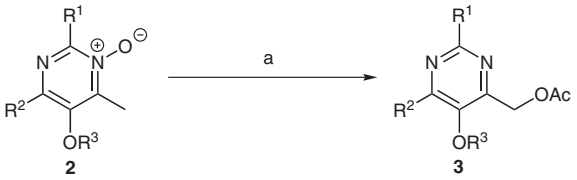


Scheme 3 Formation of pyrimidine-*N*-oxides **2j–m**. *Reagents and conditions*: a) $NH_2OH{\cdot}HCl$, MeOH, r.t., 1 d.



Scheme 4 Proposed mechanism for the condensation of β-alkoxy-β-ketoenamides **1** and hydroxylamine hydrochloride to pyrimidine-*N*-oxides

An interesting and synthetically useful subsequent reaction employs the known rearrangement of heterocyclic *N*-oxides into side-chain-functionalized products.[5] Heating of compounds **2** with acetic acid anhydride to 120 °C for 3 hours afforded the acetoxymethyl-substituted pyrimidine derivatives **3** in fair yields. This method allows a very elegant functionalization of the methyl group of pyrimidine derivatives obtained via enamides **1**, which usually contain this alkyl group. The rearrangement probably occurs by a 3,3-sigmatropic reaction of the intermediate O-acetylated species.[6] Table 2 collects the examples demonstrating that the efficacy of this step is generally good to excellent.



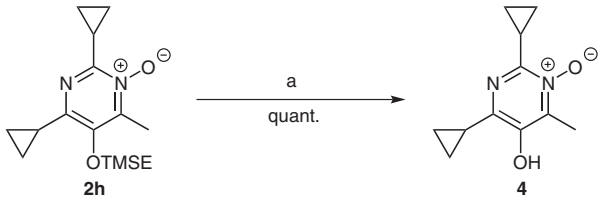
Scheme 5 Rearrangement of pyrimidine-*N*-oxides **2** into functionalized pyrimidines **3**. *Reagents and conditions*: a) Ac_2O, 120 °C, 3 h.

Table 2 Conversion of Pyrimidine-*N*-oxides **2** into Acetoxymethyl-Substituted Pyrimidines **3**

Precursor	R^1	R^2	R^3	Product	Yield (%)
2b	Ph	*t*-Bu	Me	**3a**	69
2c	PhHC=CH	*t*-Bu	Me	**3b**	70
2d	2-thienyl-HC=CH	*t*-Bu	Me	**3c**	81
2f	2-thienyl	2-thienyl	Me	**3d**	67
2h	*c*-Pr	*c*-Pr	TMSE	**3e**	91
2i	*c*-Pr	1-adamantyl	TMSE	**3f**	76

The 2-(trimethylsilyl)ethoxy-substituted pyrimidine derivatives allow O-deprotection under fairly mild conditions. Example **2h** demonstrates that a quantitative transformation into **4** is possible with trifluoroacetic acid (Equation 1). Compounds of type **4** should be excellent

candidates for transition-metal-catalyzed coupling reactions after their conversion into pyrimidinyl triflates or nonaflates.[7]



2h 4

Equation 1 Acid-induced deprotection of pyrimidine-*N*-oxide **2h** providing **4**. *Reagents and conditions*: a) TFA, CH_2Cl_2, r.t., overnight.

In this letter we have disclosed a new application of the easily available enamides **1**. Their conversion into pyrimidine-*N*-oxides occurs under very mild conditions and in very good yields. The *N*-oxide moiety allows a very simple transformation of the 6-methyl group into an acetoxymethyl group. Our methods should be of value for the synthesis of highly substituted pyrimidine derivatives, which are important for many applications.[8]

Typical Procedure for the Synthesis of *N*-[(1*E*)-1-*tert*-Butyl-2-methoxy-3-oxobut-1-enyl]phenylcarboxamide (1b)

Methoxyallene (2.00 g, 28.5 mmol) was dissolved in Et_2O (60 mL) and *n*-BuLi (12.5 mL, 31.3 mmol, 2.5 M in hexanes) was added at –40 °C. After 25 min at –50 °C to –40 °C pivaloylnitrile (4.69 mL, 42.8 mmol) was added. The solution was stirred at –40 °C for 30 min and then cooled to –78 °C. After stirring for 4 h at this temperature benzoic acid (10.4 g, 85.5 mmol) was added, and the mixture was warmed up overnight to r.t. The mixture was quenched with sat. aq $NaHCO_3$ solution (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated. Column chromatography (silica gel, hexane–EtOAc = 4:1, 1:1 to 1:3) provided 2.55 g (33%) **1b** as colorless solid, mp 117–119 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29 (s, 9 H, *t*-Bu), 2.36 (s, 3 H, Me), 3.55 (s, 3 H, OMe), 7.35–7.46, 7.75–7.90 (2 m, 3 H, 2 H, Ph) ppm, NH signal could not be detected. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 27.6 (q, Me), 28.6, 36.8 (q, s, *t*-Bu), 59.2 (q, OMe), 127.1, 128.6, 131.8 (3 d, Ph), 134.4, 135.4, 150.2 (3 s, Ph, C=C), 167.4 (s, CONH), 200.7 (s, C=O) ppm. IR (ATR): 3390 (NH), 3030–2830 (=CH, CH), 1700 (C=O), 1650, 1630 (C=C, C=O) cm^{-1}. Anal. Calcd for $C_{16}H_{21}NO_3$ (275.4): C, 69.79; H, 7.69; N, 5.09. Found: C, 69.51; H, 7.43; N, 5.11. HRMS (ESI-TOF): *m/z* calcd for $C_{16}H_{21}NO_3$ [M + Na]$^+$: 298.1414; found: 298.1416.

Typical Procedure for the Synthesis of 4-*tert*-Butyl-5-methoxy-6-methyl-2-phenylpyrimidine-1-oxide (2b)

Enamide **1b** (1.40 g, 5.08 mmol) was dissolved in MeOH (16 mL) and $NH_2OH{\cdot}HCl$ (1.10 g, 15.9 mmol) was added. The solution was stirred at r.t. for 1 d. After addition of H_2O (15 mL), the mixture was extracted with CH_2Cl_2 (5 × 20 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated. Column chromatography (silica gel, hexane–EtOAc = 2:1 to 1:2) provided 1.34 g (97%) **2b** as colorless viscous oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.45 (s, 9 H, *t*-Bu), 2.58 (s, 3 H, Me), 3.85 (s, 3 H, OMe), 7.34–7.53, 8.55–8.63 (2 m, 3 H, 2 H, Ph) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 12.6 (q, Me), 29.0, 38.0 (q, s, *t*-Bu), 61.8 (q, OMe), 127.3, 128.2, 130.3, 132.5 (3 d, s, Ph), 149.1, 150.0, 151.8 (3 s, C-4, C-5, C-6), 156.4 (s, C-2) ppm. IR (ATR): 3050–2880 (=CH, CH), 1605, 1465 (C=C, C=N) cm^{-1}. Anal. Calcd for $C_{16}H_{21}N_2O_2$ (272.3): C, 70.56; H, 7.40; N, 10.29. Found: C, 69.93; H, 7.54; N, 9.92. HRMS (ESI-TOF): *m/z* calcd for $C_{16}H_{22}N_2O_2$ [M + H]$^+$: 273.1603; found: 273.1610. HRMS (ESI-TOF): *m/z* calcd for $C_{16}H_{21}N_2O_2Na$ [M + Na]$^+$: 295.1422; found: 295.1431.

Typical Procedure for the Synthesis of 4-*tert*-Butyl-5-methoxy-6-(acetoxymethyl)-2-phenylpyrimidine (3a)

In an ACE sealed tube, pyrimidine-*N*-oxide **2b** (878 mg, 3.22 mmol) was dissolved in Ac_2O (10 mL), and the solution was refluxed at 120 °C for 3 h. After cooling to r.t. the excess of Ac_2O was removed under reduced pressure. The residue was purified by column chromatography (silica gel, hexane–EtOAc = 8:1) to afford 699 mg (69%) **3a** as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.49 (s, 9 H, *t*-Bu), 2.21 (s, 3 H, OAc), 3.86 (s, 3 H, OMe), 5.33 (s, 2 H, CH_2O), 7.40–7.48, 8.35–8.53 (2 m, 3 H, 2 H, Ph) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.9 (q, O_2CMe), 29.2, 38.4 (q, s, *t*-Bu), 61.7 (t, 6-CH_2), 62.6 (q, OMe), 128.0, 128.3, 129.9, 137.7 (3 d, s, Ph), 150.4, 156.6, 157.8 (3 s, C-4, C-5, C-6), 169.2 (s, C-2), 170.8 (s, O_2CMe) ppm. IR (ATR): 3050–2865 (=CH, CH), 1750 (C=O), 1550, 1450 (C=C, C=N) cm^{-1}. HRMS (ESI-TOF): *m/z* calcd for $C_{18}H_{22}N_2O_3Na$ [M + Na]$^+$: 337.1528; found: 337.1540.

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