A Concise Synthesis of Alkoxy-Substituted Pyrimidine Derivatives Based upon a Three-Component Access to Functionalized Enamides

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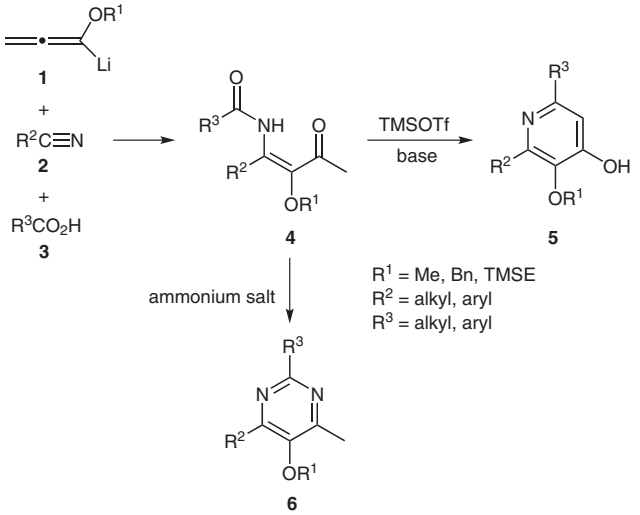
Abstract: Substituted enamides were prepared by a three-component reaction of lithiated alkoxyallenes, nitriles, and carboxylic acids. Their subsequent condensation with ammonium salts provided alkoxy-substituted pyrimidine derivatives. This two-step method is highly flexible with respect to the substitution pattern at C-2 and C-6. The C-4 and C-5 positions can smoothly be functionalized employing either Pd-catalyzed couplings or oxidation methods.

Key words: allenes, enamides, pyrimidines, ammonium salts, nonaflates, Pd catalysis

The pyrimidine substructure is important in functional materials and many biologically active natural products.[1] Compounds including this heterocyclic core have shown antiviral, antibacterial, antimicrobial, antifungal, or anticancer activity.[1] This broad range of application makes the development of new and efficient pyrimidine syntheses very valuable. As a consequence, a variety of pyrimidine syntheses have been reported in the literature.[2] Most of them start from 1,3-dicarbonyl compounds or amidines. Only a few deal with enamides as precursors for pyrimidine derivatives.[3] In this communication we describe a mild and efficient route towards alkoxy-substituted pyrimidines **6** by treatment of enamides of type **4** with ammonium salts (Scheme 1).



Scheme 1 4-Hydroxypyridine and pyrimidine syntheses starting from lithiated alkoxyallenes **1**, nitriles **2**, and carboxylic acids **3**

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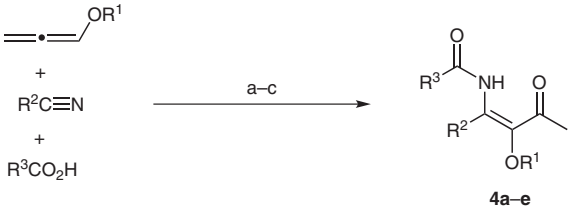
In our previous work we demonstrated that alkoxyallenes are versatile C-3 building blocks for a variety of heterocyclic compounds being intermediates of natural or interesting unnatural products.[4] We recently described an interesting formation of enamides such as **4** that were generated by a novel and mechanistically intriguing three-component synthesis using lithiated alkoxyallenes, nitriles, and carboxylic acids as precursors.[5] The scope of the reaction with respect to the alkoxyallenes, nitriles, and carboxylic acids is fairly broad. Subsequent Mukaiyama-type aldol condensation using trimethylsilyl triflate and base provided highly substituted 4-hydroxypyridine derivatives **5** in good yield (Scheme 1).

In general, enamides **4a–e** could be obtained by following the reported procedure[6] in reasonable to good yields (the mechanism of this reaction has been discussed in ref. 5). In case of benzonitrile, benzoic acid ($R^2 = R^3 = Ph$), and different alkoxyallenes (R^1 = Me, Bn, or TMSE) the yields were between 36% and 54%. Changing the nitrile to 2-thiophenenitrile (R^1 = TMSE, R^2 = 2-thienyl, R^3 = Ph) the expected product was formed in 74% yield. The best result was obtained with methoxyallene, cyclopropylnitrile, and cyclopropane carboxylic acid (R^1 = Me, $R^2 = R^3$ = *c*-Pr, 75%) as precursors (Table 1).

Table 1 Three-Component Synthesis of Enamides **4a–e** Starting from Alkoxyallenes[a]



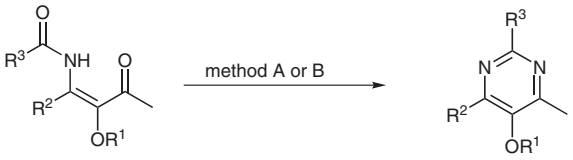
R^1	R^2	R^3		Yield (%)
Me	Ph	Ph	**4a**	45
Bn	Ph	Ph	**4b**	54
TMSE[b]	Ph	Ph	**4c**	36
TMSE	2-thienyl	Ph	**4d**	74
Me	*c*-Pr[c]	*c*-Pr	**4e**	75

[a] Reagents and conditions: (a) alkoxyallene (1.0 or 3.0 equiv), *n*-BuLi (1.1 or 2.7 equiv), Et_2O, –40 °C, 20 min; (b) nitrile (1.5 or 1.0 equiv), 30 min at –40 °C; –78 °C, 4 h; (c) carboxylic acid (3.0 or 6.0 equiv), warm up to r.t. overnight.
[b] TMSE = trimethylsilylethyl.
[c] *c*-Pr = cyclopropyl.

Pyrimidine derivative **7a** (R^1 = Me, R^2 = R^3 = Ph) was prepared employing two different methods. We first applied modified conditions as described by Taddei for the synthesis of 2,4-disubstituted quinazolines.[7] In method A, 16 equivalents of ammonium bicarbonate dissolved in methanol at 70 °C were necessary to obtain pyrimidine **7a** in 65% yield. By employing other solvents like toluene, 1,2-dichloroethane, or water no conversion or only poor yields were observed. With method B the yield of **7a** increased to 73% by changing the ammonia source to ammonium acetate. With this modification less ammonium salt (8.0 equiv) and lower temperature are sufficient.[8] It should be noted here that experiments employing other ammonia sources like ammonium chloride or aqueous ammonia (25%) were not successful or gave only traces of **7a**.

Pyrimidine derivatives **7b–e** could be obtained in the same manner using either method A or B. The corresponding benzyl- or trimethylsilylethyl-protected pyrimidine derivatives **7b–d** (R^2 = Ph or 2-thienyl, R^3 = Ph) could be isolated in higher yields (74–86%) whereas the cyclopropyl-substituted pyrimidine **7e** was obtained in 56% yield (Table 2).

Table 2 Synthesis of Alkoxy-Substituted Pyrimidine Derivatives **7a–e**



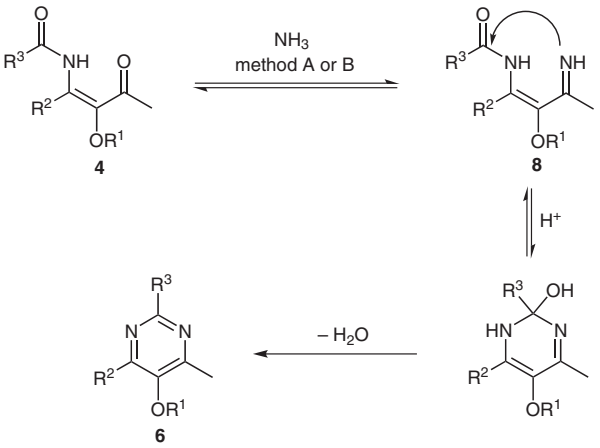
4a–e **7a–e**

R^1	R^2	R^3		Yield (%)	Method[a]
Me	Ph	Ph	**7a**	65, 73	A, B
Bn	Ph	Ph	**7b**	75	A
TMSE	Ph	Ph	**7c**	86	B
TMSE	2-thienyl	Ph	**7d**	74	A
Me	*c*-Pr	*c*-Pr	**7e**	56	B

[a] Method A: NH_4HCO_3 (16 equiv), MeOH, sealed tube, 65 °C, 1 d; method B: NH_4OAc (8.0 equiv), MeOH, sealed tube, 60–65 °C, 1 d.

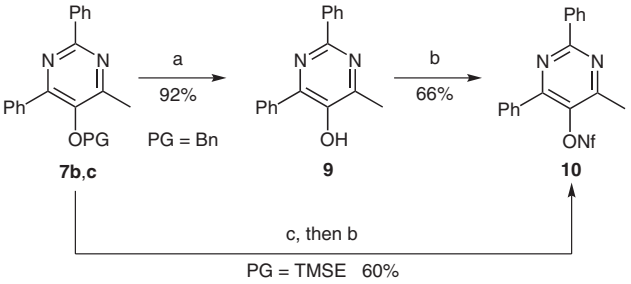
The formation of pyrimidine derivatives **7a–e** can be rationalized by the mechanism depicted in Scheme 2. Upon heating of enamide **4** with the ammonium salt an imine **8** is formed. Acid-catalyzed cyclization of the imine followed by dehydration furnishes pyrimidine derivative **6**.

The presence of protecting groups like benzyl or trimethylsilylethyl allows an easy and mild deprotection to 5-hydroxypyrimidine derivatives such as **9** (Scheme 3). The benzyl group of **7b** was smoothly cleaved by hydrogen in presence of Pd/C catalyst, which furnished **9** in very good yield (92%). The hydroxy function could subsequently be converted into a nonaflyl group using nonafluorobutanesulfonyl fluoride in presence of a base. Pyrimidyl nonaflate **10** was isolated in 66% yield. The trimethylsilylethyl-protected pyrimidine **7c** was first treated with TFA and a subsequent nonaflation led to compound **10** in 60% yield over two steps.[9]



4 **8** **6**

Scheme 2 Proposed mechanism of the pyrimidine formation



7b,c **9** **10**

Scheme 3 Cleavage and nonaflation of different alkoxypyrimidines. *Reagents and conditions*: (a) H_2 (1.0 bar), Pd/C (10 mol%), MeOH, r.t., 1 d; Nonaflation: (b) NaH (3.0 equiv), NfF (3.0 equiv), THF, r.t., 1 d; (c) TFA–CH_2Cl_2 (1:3), r.t., 2 h.

We have earlier shown that nonaflates represent ideal precursors for Pd-catalyzed coupling reactions.[10] Here we demonstrate a first coupling of pyrimidyl nonaflate **10** with phenylacetylene carried out under standard Sonogashira conditions. The expected product **11** was provided in 73% yield (Scheme 4).

Moreover, the methyl group which is present in all of the synthesized pyrimidine derivatives could easily be functionalized. The oxidation of pyrimidine **7a** to aldehyde **12** was performed under Riley conditions in very good yield (90%). Further Pinnick oxidation afforded the carboxylic acid **13** in 66% yield (Scheme 5).

In conclusion, a variety of substituted pyrimidine derivatives are available by a two-step procedure employing α-lithiated alkoxyallenes, nitriles, and carboxylic acids as suitable precursors. We could demonstrate that functionalizations in two different positions are possible by using standard Pd-coupling reactions or oxidation methods.

Acknowledgment

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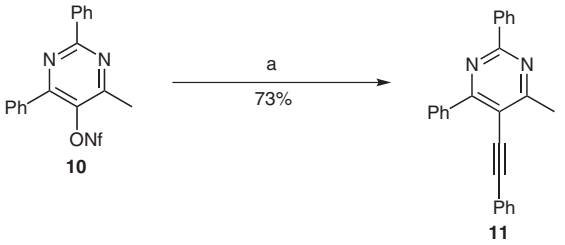
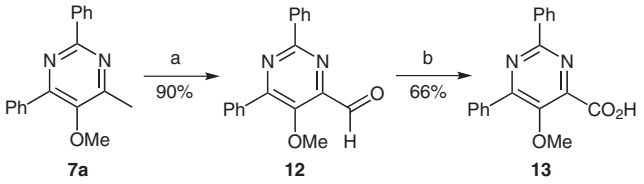


Scheme 4 Pd-catalyzed coupling reactions with pyrimidyl nonaflate **10**. *Reagents and conditions*: a) Sonogashira reaction: $Pd(OAc)_2$ (5 mol%), Ph_3P (20 mol%), CuI (5 mol%), phenylacetylene, *i*-Pr_2NH–DMF (1:2), 70 °C, 3 h.



Scheme 5 Oxidation of pyrimidine derivative **7a**. *Reagents and conditions*: (a) SeO_2 (2.0 equiv), dioxane, sealed tube, 80 °C, 2 d; (b) $NaClO_2$ (1.3 equiv), aq NaH_2PO_4–*t*-BuOH (1:1).

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(6) **Typical Procedure for the Synthesis of Enamide 4c**
Trimethylsilylethoxyallene (2.45 g, 15.7 mmol) was dissolved in Et_2O (32 mL) and *n*-BuLi (6.90 mL, 17.2 mmol, 2.5 M in hexanes) was added at –40 °C. After 25 min at –50 °C to –40 °C benzonitrile (2.40 mL, 23.5 mmol) was added. After stirring for 4 h at this temperature benzoic acid (5.74 g, 47.0 mmol, dissolved in 15 mL Et_2O) was added, and the mixture was warmed up over night to r.t. The mixture was quenched with sat. aq $NaHCO_3$ soln and extracted three times with Et_2O (30 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated. Column chromatography (SiO_2, EtOAc–hexane, 1:10) and subsequent recrystallization in hexane provided **4c** (2.14 g, 36%) as colorless solid (mp 65 °C).
Analytical Data for (*E*)-*N*-{3-Oxo-1-phenyl-2-[2-(trimethylsilyl)ethoxy]but-1-enyl}benzamide (4c)
^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.15 (s, 9 H, $SiMe_3$), 0.66–0.71 (m, 2 H, CH_2Si), 2.40 (s, 3 H, CH_3), 3.33–3.38 (m, 2 H, OCH_2), 7.36–7.55, 7.95–7.98 (2 m, 10 H, Ph), 12.40 (br s, 1 H, NH) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = –1.7 (q, $SiMe_3$), 18.6 (t, CH_2Si), 27.5 (q, CH_3), 71.5 (t, OCH_2), 127.8, 128.4, 128.68, 128.73, 132.3, 132.6, 133.7 (5 d, 2 s, Ph)*, 137.6, 143.3 (2 s, C=C), 165.2, 202.9 (2 s, C=O) ppm; *overlapping Ph signals. IR (KBr): ν = 3400 (NH), 3110–2995 (=CH), 2960–2895 (CH), 1730–1580 (C=O, C=C) cm^{-1}. Anal. Calcd for $C_{22}H_{27}NO_3Si$ (381.5): C, 69.25; H, 7.13; N, 3.67. Found: C, 69.05; H, 7.08; N, 3.69.

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(8) **Typical Procedure for the Synthesis of Pyrimidine 7c**
Enamide **4c** (350 mg, 0.917 mmol) and NH_4OAc (566 mg, 7.34 mmol) were placed in an ACE-sealed tube. The mixture was dissolved in MeOH (5.0 mL) and stirred for 1 d at 65 °C. After addition of H_2O and CH_2Cl_2 (5.0 mL) the layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2 (5.0 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated. Column chromatography (SiO_2, EtOAc–hexane, 1:10) provided **7c** (285 mg, 86%) as colorless oil.
Analytical Data for 4-Methyl-2,6-diphenyl-5-[2-(trimethylsilyl)ethoxy]pyrimidine (7c)
^{1}H NMR (500 MHz, $CDCl_3$): δ = –0.08 (s, 9 H, $SiMe_3$), 0.97–1.06 (m, 2 H, CH_2Si), 2.64 (s, 3 H, CH_3), 3.66–3.71 (m, 2 H, OCH_2), 7.41–7.53, 8.16–8.19, 8.47–8.50 (3 m, 10 H, Ph) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = –1.6 (q, $SiMe_3$), 18.9 (t, CH_2Si), 19.6 (q, CH_3), 71.1 (t, OCH_2), 128.0, 128.3, 128.4, 129.1, 129.77, 129.84, 136.4, 137.8 (6 d, 2 s, Ph), 148.2 (s, C-5), 156.6, 158.7, 162.4 (3 s, C-2, C-4, C-6) ppm. IR (film): ν = 3090–2870 (=CH, CH), 1680–1540 (C=C, C=N) cm^{-1}. Anal. Calcd for $C_{22}H_{26}N_2OSi$ (362.5): C, 72.88; H, 7.23; N, 7.73. Found: C, 72.63; H, 7.12; N, 7.78.

(9) **Typical Procedure for the Synthesis of Pyrimidyl Nonaflate 10**
Pyrimidine **7c** (285 mg, 0.786 mmol) was dissolved in a 1:2 mixture of TFA and CH_2Cl_2 (3.0 mL) and stirred for 30 min at r.t. After addition of H_2O and CH_2Cl_2 (5.0 mL) the layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2 (8.0 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The crude product was dissolved in THF (5.0 mL) and NaH (94 mg

2.36 mmol) was added. After 5 min NfF (0.42 mL, 2.36 mmol) was added, and the reaction mixture was stirred over night at r.t. After slowly addition of H_2O and EtOAc (5.0 mL) the layers were separated, and the aqueous layer was extracted twice with EtOAc (8.0 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated. Column chromatography (SiO_2, EtOAc–hexane, 1:10) provided **10** (257 mg, 60%) as colorless oil.

Analytical Data for 4-Methyl-2,6-diphenylpyrimidin-5-yl 1,1,2,2,3,3,4,4,4-Nonafluorobutane-1-sulfonate (10)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.77 (s, 3 H, CH_3), 7.49–7.56, 7.89–7.91, 8.52–8.55 (3 m, 10 H, Ph) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 20.5 (q, CH_3), 128.56, 128.58, 128.7, 129.5, 130.8, 129.9, 134.3, 136.3 (6 d, 2 s, Ph), 140.7 (s, C-5), 159.0, 162.0, 162.3 (3 s, C-2, C-4, C-6) ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ = –80.6, –109.8, –120.6, –125.8 (4 m, Nf) ppm. IR (film): ν = 3095–2855 (=CH, CH), 1605–1560 (C=C, C=N) cm^{-1}. ESI-TOF: *m/z* calcd for $[M + H]^+$: 545.0576; found: 545.0607. Anal. Calcd for $C_{21}H_{13}F_9N_2O_3S$ (544.4): C, 46.33; H, 2.41; N, 5.15. Found: C, 46.93; H, 2.18; N, 5.06.

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