Pergamon

Tetrahedron 55 (1999) 4825–4830

TETRAHEDRON

An Easy One-step Synthesis of 4-Alkoxypyrimidines from Aliphatic Esters and Nitriles

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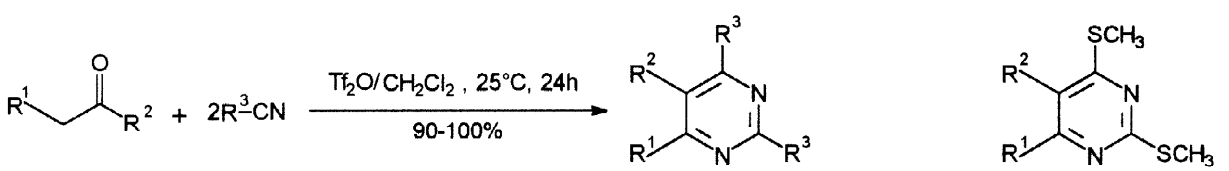
Received 7 December 1998; revised 25 January 1999; accepted 11 February 1999

Abstract: The reaction of aliphatic esters with aliphatic or aromatic nitriles in the presence of trifluoromethanesulfonic anhydride affords substituted 4-alkoxypyrimidines in good yields. A mechanism of the investigated reaction is proposed. © 1999 Elsevier Science Ltd. All rights reserved.

The cyclization of ketones with nitriles in the presence of triflic anhydride (Tf_2O) was shown by us to be a very useful method for the preparation of alkyl and arylpyrimidines **3**[1] (Scheme 1). This process leads to pyrimidines in excellent yields from easily available ketones **1** and nitriles **2**. These results have also allowed us to clarify the mechanism of the reaction between ketones and triflic anhydride.



1 **2** **3** **4**

Scheme 1

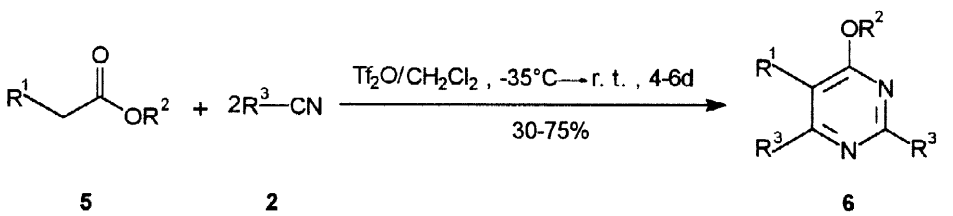
The extension of this synthetic procedure also permits the synthesis of functionalized 5-halopyrimidines, which are important for industrial applications as agrochemicals.[2] When our general method is applied for the reaction of ketones with Tf_2O and methyl thiocyanate, the strategical 2,4-bis(methylthio)pyrimidines **4** (Scheme 1), key intermediates for the synthesis of different, important substrates as aminopyrimidines and uracils, can be

PII: S0040-4020(99)00154-4

easily prepared.[3] Isoquinoline derivatives with the papaverine backbone are of great interest due to their pharmacological properties and can also be obtained from phenylacetic esters and nitriles.[4]

Alkoxy and phenoxypyrimidines **6** are an interesting class of compounds since industrial applications as agrochemicals[5] and as useful components for chiral smectic C liquid crystal components for display devices[6] have been found. Compounds **6** are also important because simple derivatives of them display important pharmacological applications.[7] The reported methods for the preparation of **6** require several steps starting from the previously formed pyrimidine nucleus.[8,9]

We wish to report herein an expeditious synthesis of 4-alkoxypyrimidines **6** from simple starting materials such as aliphatic esters **5**, aliphatic or aromatic nitriles **2** and trifluoromethanesulfonic anhydride (Tf_2O). The reaction is carried out in dichloromethane at -35°C to room temperature and affords the 4-alkoxypyrimidines **6** (Scheme 2) in moderate to good yields (Table).



5 **2** **6**

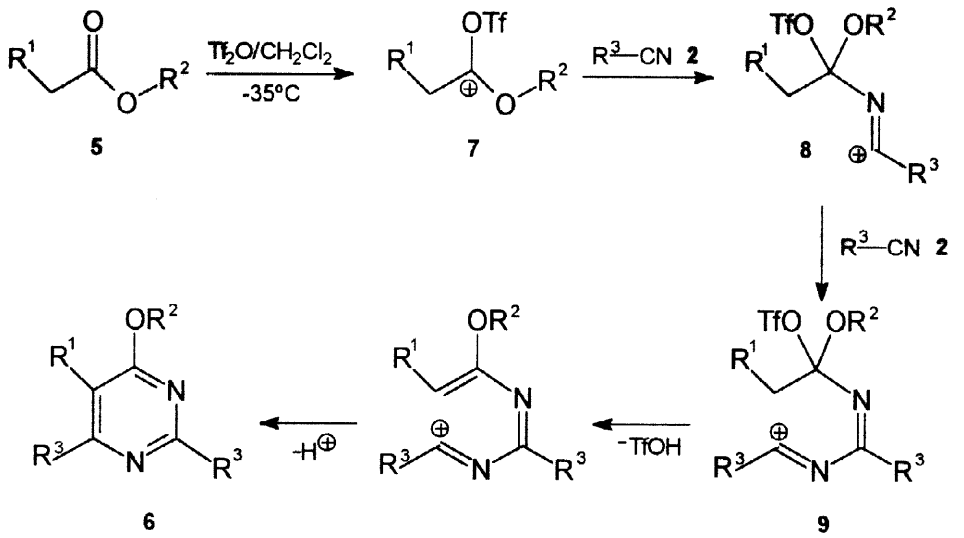
Scheme 2

Table. 4-Alkoxypyrimidines **6** prepared

5	R^1	R^2	**2**	R^3	**6**	R^1	R^2	R^3	Yield [a]
a	H	Et	**a**	Me	**a**	H	Et	Me	30
b	H	Ph	**b**	Ph	**b**	H	Ph	Me	55
c	Me	Et			**c**	Me	Et	Me	75
d	Me	nBu			**d**	Me	nBu	Me	65
e	nBu	Et			**e**	nBu	Et	Me	70
					f	Me	Et	Ph	60

[a] % Yield of isolated product.

To the formation of **6**, we suggest an analogous mechanistic route as that for the formation of pyrimidines from ketones and nitriles in the presence of Tf_2O,[1] involving an alkoxy(triflyloxy)carbenium ion **7**. In the presence of nitriles **2**, **7** is trapped by the nucleophile, whereby a resonance-stabilized nitrilum species **8** is formed. A second molecule of nitrile **2** reacts with the intermediate **9** to give 4-alkoxypyrimidines **6**, after elimination of triflic acid, cyclization, and loss of a proton (Scheme 3).



Scheme 3

In summary, we have presented an expeditious one-step procedure for the preparation of biologically and technically interesting 4-alkoxypyrimidines starting from readily available aliphatic esters and aliphatic or aromatic nitriles in the presence of Tf_2O.

Acknowledgements: We are gratefully acknowledged to the DGICYT (Spain, Grant PB 91-0314 and PB95-0911) for financial support. We thank "Centro de Espectroscopía de la UCM" for determining NMR and MS spectra and "Servicio de Microanálisis Elemental de la UCM" for CHN analyses.

EXPERIMENTAL SECTION

All reagents were commercial grade and were used as received unless otherwise indicated. Melting points were determined on a Gallenkamp apparatus and are uncorrected. ^{1}H-NMR spectra were obtained with a Varian VXR300S at 300 MHz and a Bruker AC 250 at 250 MHz with TMS as the standard. ^{13}C-NMR spectra were performed on the same instruments at 75 MHz and 62.89 MHz, respectively. Infrared spectra were taken with a Perkin-Elmer 781 instrument. Mass spectra were performed using a HP 5989A quadrupole instrument at 70 eV with a source temperature of 250 °C. CHN Analyses: Perkin Elmer 2400. Elution chromatography: Merck silica gel 77340. 1000 (70-230 mesh ASTM). Reaction solvents were distilled from an appropriate drying agent before use.

Preparation of 4-Alkoxypyrimidines **6**. *General Procedure.*

In a typical procedure, a solution of Tf_2O (10.15 g, 36 mmol) in CH_2Cl_2 (15 mL) was added dropwise to a stirred solution of **ester 1** (30 mmol) and nitrile **2** (63 mmol) in CH_2Cl_2 (25 mL) at -35°C. The mixture was allowed to reach room temperature and stirred for the appropriate time (3-5 days). The formation of 4-alkoxypyrimidines can be monitored by IR spectroscopy or tlc. The excess of nitrile was removed in vacuo and the residue dissolved in CH_2Cl_2 (100 mL). The organic layer was hydrolysed by dropwise addition of aqueous saturated solution of sodium hydrogen carbonate, separated, washed with brine, dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel) using ether/pentane as eluent.

4-Ethoxy-2,6-dimethylpyrimidine **6a**. Reaction time: 3 days. Purification of crude product by column chromatography (60% Et_2O/pentane) gave the *title compound* **6a** (1.37 g, 30%) as a pale yellow liquid, b.p. 39-41 °C/ 0.01 torr; [Found: C, 62.98; H, 7.85; N, 18.22. $C_8H_{12}N_2O$ requires C,63.13; H, 7.95; N, 18.41%]; ν_{max} (liquid film) 1600, 1560, 1345, 1175 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.32 (1H, s), 4.35 (2H, q, *J* 6.5 Hz, $OC\underline{H}_2CH_3$), 2.54 (3H, s, $C\underline{H}_3$), 2.37 (3H, s, $C\underline{H}_3$), 1.33 (3H, t, *J* 6.5 Hz, $OCH_2C\underline{H}_3$); δ_C (75 MHz, $CDCl_3$) 170.44, 168.29, 167.81, 104.31, 62.83, 26.68, 24.60, 15.26; *m/z* (EI, 70 eV) 152 (4, M^+), 137 (85), 124 (70), 67 (100 %).

4-Phenoxy-2,6-dimethylpyrimidine **6b**. Reaction time 4 days. The crude product was purified by column chromatography (80% Et_2O/pentane) to give the *title compound* **6b** (3.30 g, 55%) as a pale yellow oil, b.p. 37-39 °C/ 0.01 torr; [Found: C, 71.59; H, 5.99; N, 13.71. $C_{12}H_{12}N_2O$ requires C, 71.97; H, 6.04; N, 14.00%]; ν_{max} (liquid film) 1575, 1480, 1350, 1200 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.43 (2H, t, *J* 8.5 Hz), 7.28 (1H, t, *J* 8.5 Hz), 7.12 (2H, d, *J* 8 Hz) 6.48 (s, 1H), 2.58 (3H, s, $C\underline{H}_3$), 2.42 (3H, s, $C\underline{H}_3$); δ_C (75 MHz, $CDCl_3$) 169.82, 168.79, 168.07, 152.42, 129.63, 125.38, 121.28, 102.75, 25.64, 23.91; *m/z* (EI, 70 eV) 200 (100, M^+), 185 (13), 172 (25), 118 (78), 107 (12%).

4-Ethoxy-2,5,6-trimethylpyrimidine **6c**. Reaction time 4 days. Purification of crude product by column chromatography (75% Et_2O/pentane) gave the *title compound* **6c** (3.73 g, 75%) as a colorless oil b.p. 54-56 °C/ 0.8 torr; [Found: C,64.89; H, 7.97; N, 16.29. $C_9H_{14}N_2O$ requires C, 65.03; H, 8.49; N, 16.85%]; ν_{max} (liquid film) 1575, 1410, 1375, 1340, 1120 cm^{-1}; δ_H (300 MHz, $CDCl_3$) δ 4.28 (2H, q, *J* 7.5 Hz, $OC\underline{H}_2CH_3$), 2.42 (3H, s, $C\underline{H}_3$), 2.28 (3H, s, $C\underline{H}_3$), 1.96 (3H, s, $C\underline{H}_3$), 1.27 (3H, t, *J* 7.5 Hz, $OCH_2C\underline{H}_3$); δ_C (75 MHz, $CDCl_3$) 166.87, 163.57, 163.39, 111.24, 61.65, 25.26, 21.21, 14.23, 9.87; *m/z* (EI, 70 eV) 166 (53, M^+), 151 (68), 139 (74), 138 (100%).

4-Butoxy-2,5,6-trimethylpyrimidine **6d**. Reaction time 4 days. Purification of crude product by colum chromatography (75% Et_2O/pentane) gave the *title compound* **6d** (3.78 g, 65%) as a pale yellow oil, b.p. 43-45 °C/0.01 torr; [Found: C, 67.77; H, 9.11; N, 14.16. $C_{11}H_{18}N_2O$ requires C, 67.99; H, 9.34; N, 14.43%]; ν_{max} (liquid film) 1585, 1425, 1370, 1345, 1130 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.34 (2H, t, *J* 6.8 Hz, $OC\underline{H}_2CH_2$), 2.52 (3H, s, $C\underline{H}_3$), 2.37 (3H, s, $C\underline{H}_3$), 2.07 (3H, s, $C\underline{H}_3$); 1.79-1.70 (2H, m, $OCH_2C\underline{H}_2$), 1.53-1.43 (2H, m, $CH_2C\underline{H}_2CH_3$); 0.97 (3H, t, *J* 6.5 Hz, $CH_2C\underline{H}_3$); δ_C (75 MHz, $CDCl_3$) 167.14, 163.65, 163.53, 111.45, 65.77, 30.85, 25.42, 21.35, 19.12, 13.69, 10.01; *m / z* (EI, 70 eV) 194 (28, M^+), 179 (10), 138 (100%).

4-Ethoxy-2,6-dimethyl-5-butylpyrimidine **6e**. Reaction time: 4 days. Purification of crude product by column chromatography (75% Et_2O/pentane) gave the *title compound* **6e** (4.36 g, 70%) as a colorless oil, b.p. 46-48 °C/0.1 torr; [Found: C, 69.00; H, 9.45; N, 13.13. $C_{12}H_{20}N_2O$ requires C, 69.18; H, 9.68; N, 13.45%]; ν_{max} (liquid film) 1575, 1420, 1335 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.35 (2H, q, *J* 7.6 Hz, $OC\underline{H}_2CH_3$), 2.50 (2H, t, *J* 7.0 Hz, $C\underline{H}_2CH_2$), 2.48 (3H, s, $C\underline{H}_3$), 2.34 (3H, s, $C\underline{H}_3$), 1.40-1.20 (4H, m, $C\underline{H}_2C\underline{H}_2$), 1.34 (3H, t, *J* 7.6 Hz, $OCH_2C\underline{H}_3$), 0.86 (3H, t, *J* 7.0 Hz, $CH_2C\underline{H}_3$); δ_C (75 MHz, $CDCl_3$) 166.96, 163.58, 163.40, 116.18, 61.59, 30.59, 25.36, 24.32, 22.42, 20.87, 14.25, 13.68; *m/z* (EI, 70 eV) 208 (29, M^+), 193 (15), 180 (58), 166 (11), 151 (25), 143 (100%).

4-Ethoxy-2,6-diphenyl-5-methylpyrimidine **6f**. Reaction time: 5 days. Purification of crude product by column chromatography (60% Et_2O/pentane) gave the *title compound* **6f** (5.22 g, 60%) as a white crystals, m.p. 94-96 °C (MeOH); [Found: C, 78.47; H, 6.44; N, 9.83. $C_{19}H_{18}N_2O$ requires C, 78.58; H, 6.25; N, 9.65%]; ν_{max} (KBr) 1590, 1520, 1420, 1170 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.63-8.59 (2H, dd, *J* 6.4, 2.2 Hz), 7.77-7.74 (2H, dd, *J* 6.6, 2.2 Hz); 7.55-7.50 (6H, m), 4.69 (2H, q, *J* 7.0 Hz, $OC\underline{H}_2CH_3$), 2.31 (3H, s, $C\underline{H}_3$), 1.56 (3H, t, *J* 7.0 Hz, $OCH_2C\underline{H}_3$); δ_C (62.89 MHz, $CDCl_3$) 168.42, 164.49, 160.55, 138.90, 137.99, 130.00, 129.27, 128.63, 128.17, 128.03, 127.93, 112.71, 62.35, 14.53, 12.16; *m/z* (EI, 70 eV) 290 (59, M^+), 275 (52), 261 (100), 104 (52%).

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