Sterically Hindered Bases. Synthesis of 2,4,6-Trisubstituted Pyrimidines

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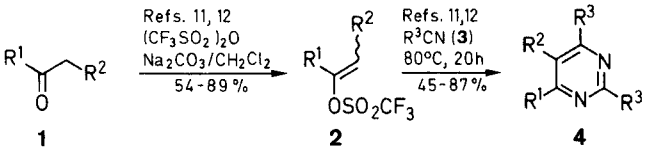
A new method for the synthesis of sterically hindered pyrimidines **7** by the reaction of alkynes **5** with nitriles **6** in the presence of trifluoromethanesulfonic acid is described. The pK_a*-values of some of the synthesized pyrimidines **7**, which can be used as non-nucleophilic bases, were determined in 50% aqueous ethanol.

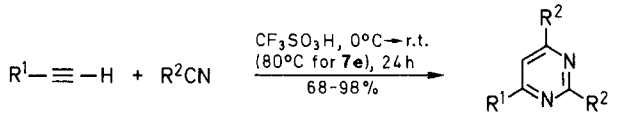
Sterically hindered non-nucleophilic bases such as tertiary aromatic[1] and aliphatic[2] amines, amidines,[3] cyanidines,[2,4] and pyridines[5-7] are extensively used in organic synthesis in alkylation,[8] elimination,[9] and acylation[10] reactions. The main disadvantage of these bases is that their preparation is tedious and time consuming involving several steps.[1-10]

We have reported earlier that vinyl triflates **2**, prepared easily from ketones **1**, are converted in the presence of aromatic or aliphatic nitriles **3** (80 °C, 20 h, ratio of **2**/**3** = 1 : 5) to tri- and tetraalkyl and -arylpyrimidines **4** in good yields (~ 70%).[11,12] Under these mild conditions alkynes **5** were shown to be reaction intermediates. Very recently Russian workers have reported[13] that the reaction of a mixture of vinyl chlorides, phenylacetylene and nitriles in the presence of trifluoromethanesulfonic acid affords pyrimidines in modest to good yields.



1 **2** **4**

We report herein the synthesis of sterically hindered pyrimidines **7** by direct treatment of substituted alkynes **5a–e** with alkyl and aryl nitriles **6a–e** with trifluoromethanesulfonic acid. The best yields of the substituted pyrimidines **7** were obtained by slowly adding a mixture of the alkyne **5** and the nitrile **6** to a stirred mixture of



5 **6** **7**

5–7	a	b	c	d	e
R^1	*t*-Bu	Ph	Ph	Ph	*t*-Bu
R^2	CH_3	CH_3	*t*-Bu	Ph	*t*-Bu

trifluoromethanesulfonic acid and nitrile **6** at 0 °C. By this method the substituted pyrimidines **7** given in the Table were obtained in very good yield (~ 95%). These yields are much higher than the yield (42% for **7e**) obtained by the reaction of **5** and **6** with phosphoric acid/boron trifluoride.[14] The latter method is dependent on the structure of the substrate and limited only to tertiary and aryl nitriles.[14]

Table. Pyrimidines **7** Prepared

Product	Yield[a] (%)	mp (°C) or bp (°C)/mbar	Molecular Formula or Lit. mp (°C) or bp (°C)/mbar	pK_a*
7a	68	61–62/4.5	61–62/4.5[12]	2.9
7b	94	95–96/0.7	95–96/0.7[12]	3.0
7c[b]	93	110–111/0.3	$C_{18}H_{24}N_2$[c] (268.4)	–[d]
7d	98	109–110/0.3	184–185[12]	–[d]
7e	80	76–77 ($EtOH/H_2O$)	78–80[12]	1.02[16]

[a] Yield of isolated product.

[b] New compound
IR (film): $\nu = 1570, 1530\ cm^{-1}$.
^1H-NMR ($CDCl_3$/TMS): $\delta = 1.5$ (s, 9H, t-C_4H_9 at C-6), 1.6 (s, 9H, t-C_4H_9 at C-2), 7.3 (m, 4H, $H_{arom} + H_{pyrimidine}$), 8.0 (m, $2H_{arom}$).
^{13}C-NMR ($CDCl_3$/TMS): $\delta = 29.43, 29.65, 37.68, 39.57, 108.2, 127.06, 128.59, 129.98, 138.5, 163.16, 176.19, 177.35$.
MS (100 eV): m/z (%) = 268 (M^+, 39), 267 ($M^+ - H$, 27), 253 ($M^+ - CH_3$, 100), 226 ($M^+ - C_3H_6$, 48).

[c] HRMS (100 eV): calc for $C_{18}H_{24}N_2$, 268. 1942; found m/z = 268. 1939 (M^+).

[d] Not determined.

The reaction of **5** and **6** in the presence of trifluoromethanesulfonic acid takes place by protonation of the alkyne **5** to form a vinyl cation intermediate, which successively reacts with two moles of nitrile **6**, followed by cyclization to give the pyrimidines **7**.[12]

The pyrimidines **7** prepared are soluble in common organic solvents. They can be purified as their hydrochloride salts by extracting them from organic solutions by washing with 10% hydrochloric acid (once for **7a,b**) or 30% hydrochloric acid (twice for **7c–e**).

The basicity of the pyrimidines **7** was determined potentiometrically in 50% aqueous ethanol as pK_a* values.[15] The pK_a* values should be very small in aprotic solvents, and any reverse order of the basicity is not to be expected.[16] In accordance with this, the basicity (and even greater the nucleophilicity) is reduced with the steric hindrance of the α-substituents, while it increases with the +I effect of the substituents (Table).[15–17] The pK_a* values of **7c** and **7d** could not be determined because they are insoluble in 50% ethanol. However, it is quite probable that both of them have a similar pK_a* value as **7e**, while it can be deduced from a comparison of **7a** with **7b** that the effect of a phenyl group on the basicity is similar to that of a *tert*-butyl group.

The pyrimidines **7a–d** are very suitable to be used as sterically hindered, non-nucleophilic bases, e.g. for the preparation of vinyl triflates and *gem*-bistriflates.[18] Their easy availability makes them comparabel to other common sterically hindered bases, e.g. 2,6-di-*tert*-butyl-4-methylpyridine.[19]

Further work on the application of these pyrimidines **7** in other reactions are in progress.

Substituted Pyrimidines 7; General Procedure:
To a stirred mixture of CF_3SO_3H (7.5 g, 50 mmol) and nitrile **6** (150 mmol) is added dropwise slowly a solution of the alkyne **5** (20 mmol) in nitrile **6** (150 mmol) at 0 °C. The mixture is stirred 24 h at r.t. (80 °C for **7e**) and the excess of nitrile is removed under reduced pressure. The residue is dissolved in CH_2Cl_2 (100 mL) and the organic phase is shaken well with 20% NaOH (100 mL). The organic phase is then washed with brine (3 × 50 mL), dried (Na_2SO_4), the solvent evaporated, and the product is purified by distillation or recrystallization. Known products are identified by IR, NMR, and mass spectra.

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