ORGANIC LETTERS

2000
Vol. 2, No. 21
3389−3391

Chemoselective Reactions of Amidines: Selective Formation of Iminopyrimidine Regioisomers

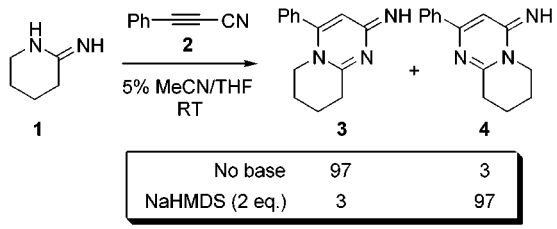
John A. McCauley,* Cory R. Theberge, and Nigel J. Liverton

Department of Medicinal Chemistry, Merck Research Laboratories, West Point, Pennsylvania 19486

john_mccauley@merck.com

Received August 24, 2000

ABSTRACT

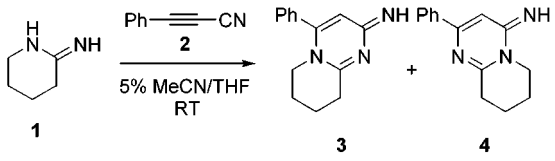


The dramatic effect of base on the chemoselectivity of the reaction of amidines with substituted 3-phenyl-2-propynylnitriles is demonstrated. Amidine 1 can be added to cyanoalkyne 2 to give iminopyrimidine isomer 3 with high selectivity. The addition of 2 equiv of NaHMDS completely reverses the selectivity of the reaction, yielding isomer 4 almost exclusively. This method has been used to prepare a variety of substituted 4-iminopyrimidines.

During recent work in our laboratories we became interested in the synthesis of 4-iminopyrimidines fused to carbocycles (e.g., **4**). 4-Pyrimidones analogous to **4** have been synthesized by the addition of cyclic amidines to β-ketoesters;[1] however, the conversion of the resultant pyrimidone to the iminopyrimidine was nontrivial. To circumvent this problem, we tried to access the iminopyrimidine directly by adding an amidine to a β-ketonitrile, but this strategy failed.[2]

We then reasoned that Michael addition of an amidine to a cyanoalkyne followed by ring closure would be an alternative route to this structural class. 3-Phenyl-2-propynenitrile (**2**, Scheme 1)[3] was prepared via a published procedure and exposed to 2-iminopiperidine in THF.[4,5] The reaction proceeded very cleanly, and of the two possible regioisomeric products that can be formed in this reaction, the 1,2-cyclic isomer (**3**) predominated in a 97:3 ratio.[6] We were very pleased with this straightforward route to the 4-iminopyrimidine class of compounds; however, we were also interested in a synthesis of regioisomer **4**.

Scheme 1



(1) (a) Le Berre, A.; Renault, C. *Bull. Soc. Chim. Fr.* **1969**, 3139−3146. (b) Le Berre, A.; Renault, C. *Bull. Soc. Chim. Fr.* **1969**, 3146−3151. (c) Langlois, M.; Guilloneau, C.; VoVan, T.; Jolly, R.; Maillard, J. *J. Heterocycl. Chem.* **1983**, *20*, 393−398.

(2) For the synthesis of iminopyrimidines, see: (a) Brown, D. J.; Ienega, K. *J. Chem. Soc., Perkin Trans. 1* **1974**, 372−378. (b) Wamhoff, H.; Thiemig, H.-A. *Chem. Ber.* **1986**, *119*, 1070−1076.

(3) Luo, F.-T.; Wang, M.-W.; Wang, R.-T. *Org. Synth.* **1997**, *75*, 146−152.

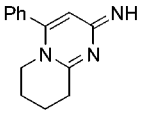
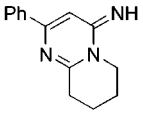
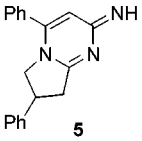
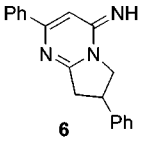
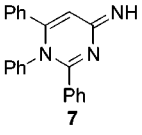
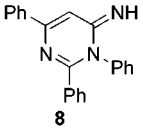
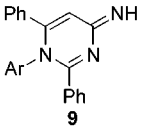
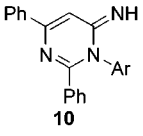
(4) 3-Phenyl-2-propynenitrile (**2**) has been used in a similar fashion for the preparation of 5-aminopyrazoles and 3-aminothiophene-2-carbonitriles; see: (a) Fomum, Z. T.; Ifeadike, P. N. *J. Heterocycl. Chem.* **1985**, *22*, 1611−1614. (b) Ren, W.-Y.; Rao, K. V. B.; Klein, R. S. *J. Heterocycl. Chem.* **1986**, *23*, 1757−1763.

(5) Identical selectivity was observed when the solvent was 5% MeCN/THF.

10.1021/ol006499j CCC: $19.00
Published on Web 09/14/2000

Our attempts to alter the selectivity of this reaction began with protection of the secondary amine of **1** followed by addition to cyanoalkyne **2**. This reaction cleanly gave the Michael adduct; however, attempts to remove a variety of protective groups [allyl, benzyl, silyl] in the presence of the nitrile failed. During these investigations we noticed that the addition of base affected the distribution of reaction products.[7] After optimization, we have found that using 2 equiv of NaHMDS in 5% MeCN/THF completely reverses the selectivity of the reaction, giving **4** as the major product in a 97:3 ratio (Entry 1, Table 1).

Table 1. Reaction of 3-Phenyl-2-propynenitrile with Amidines

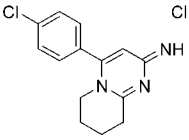
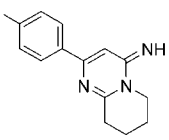
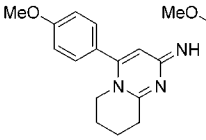
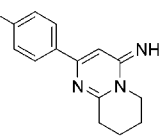
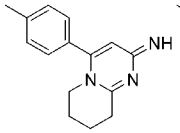
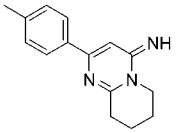
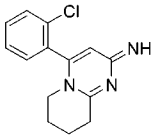
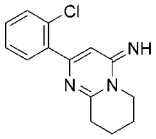
	products		conditions[9] and results		
	A	B	NaHMDS	A : B	yield
1	 **3**	 **4**	0 eq.	97 : 3	65%
			2 eq.	3 : 97	52%
2	 **5**	 **6**	0 eq.	95 : 5	61%
			2 eq.	2 : 98	63%
3	 **7**	 **8**	0 eq.	95 : 5	25%
			2 eq.	5 : 95	31%
4	 **9**	 **10**	0 eq.	90 : 10	5%
			2 eq.	3 : 97	32%

Ar = 3,4-dichlorophenyl

We have extended this methodology to include 2-imino-4-phenylpyrrolidine[8] (**20**, entry 2), as well as unsymmetrical monosubstituted acyclic amidines (entries 3 and 4). All of the cases were run under the same conditions[9] and show a similar reversal of selectivity in the presence of base.[10,11] Addition of MeCN is crucial to the success of the reaction involving NaHMDS; when 100% THF is employed as solvent, the reaction gives many side products. Furthermore, if less than 2 equiv of NaHMDS is used, the reaction proceeds well but seems to be nonchemoselective. This information has led us to hypothesize that the dianion of the amidine is formed and that the acetonitrile aids in solubility of the dianion.

Cyclic amidines seem to react more quickly and give higher yields. Preliminary investigation indicates that the ring closure step is slower in the case of acyclic amidines. The reaction is also tolerant of substituents on the phenyl ring of the cyanoalkyne,[3] as shown in Table 2.

Table 2. Reaction of 2-Iminopiperidine with Cyanoalkynes

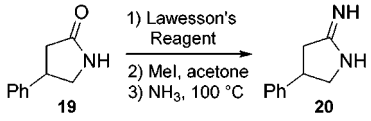
	products		conditions[9] and results		
	A	B	NaHMDS	A : B	yield
5	 **11**	 **12**	0 eq.	96 : 4	52%
			2 eq.	1 : 99	61%
6	 **13**	 **14**	0 eq.	97 : 3	60%
			2 eq.	2 : 98	55%
7	 **15**	 **16**	0 eq.	98 : 2	56%
			2 eq.	2 : 98	58%
8	 **17**	 **18**	0 eq.	70 : 30	15%
			2 eq.	2 : 98	48%

The reactions recorded in entries 4 and 8, however, behaved somewhat differently than the other examples. In the absence of base, the selectivity and yield both degraded substantially. We believe this is due to the steric congestion associated with the ring closing step to form compounds **9** and **17**. After the Michael addition occurs, the aryl group at position 6 (pyrimidine numbering) and the substituent on N-1 must come into close proximity in order to close the

(6) Ratios were measured by HPLC with UV detection at 214 nM. Data for compound **3·TFA**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.42 (br s, 1 H), 7.58−7.50 (m, 3 H), 7.38−7.35 (m, 2 H), 6.81 (s, 1 H), 6.73 (br s, 1 H), 3.84 (t, J = 5.8 Hz, 2 H), 3.10 (t, J = 6.6 Hz, 2 H), 2.03−1.94 (m, 4 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.5, 163.0, 157.4, 131.5, 130.6, 129.5, 128.3, 106.6, 50.3, 31.5, 21.8, 18.1 ppm; HRMS *m/z* 226.1353 [(M + H)$^+$, calcd for $C_{14}H_{16}N_3$ 226.1339]. Data for compound **4·TFA**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.74 (br s, 1 H), 9.18 (br s, 1 H), 8.04 (dd, J = 7.8, 1.5 Hz, 2 H), 7.56−7.43 (m, 4 H), 4.10 (t, J = 6.2 Hz, 2 H), 3.13 (t, J = 6.5 Hz, 2 H), 2.18−2.11 (m, 2 H), 2.02−1.98 (m, 2 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.2, 158.3, 157.7, 132.2, 129.1, 129.0, 127.5, 101.4, 47.0, 32.3, 21.4, 18.1 ppm; HRMS *m/z* 226.1351 [(M + H)$^+$, calcd for $C_{14}H_{16}N_3$ 226.1339].

(7) Similar observations in the case of amidine additions to β-ketoesters have been made (see ref 1a); however, the conditions reported for selectivity reversal [EtONa, EtOH, reflux], when applied to our system, gave primarily Michael addition of ethoxide to the cyanoalkyne.

(8) The starting amidine for entry 2 (**20**) was prepared from 4-phenyl-2-pyrrolidinone (**19**)[12] as shown:



pyrimidine ring. In the case of compound **17**, the 2-Cl substituent seems to have a greater steric effect than a 4-substituent. A major byproduct in both of these reactions is one in which both amidine nitrogens undergo Michael addition to a cyanoalkyne. This observation is consistent with a slow ring-closing step. In the presence of base, as expected, compounds **10** and **18** are formed selectively and in satisfactory yield.

In conclusion, we have developed a facile one-step synthesis of regioisomeric 4-iminopyrimidines and have shown the effect of base and solvent on chemoselectivity. Further investigation of the scope and mechanism of this reaction is underway in these laboratories.

Acknowledgment. We thank Ms. Joan Murphy and Dr. Steve Pitzenberger for NMR structural assignment of compounds **3** and **4**. We also thank Dr. David A. Claremon for helpful discussions.

OL006499J

(9) **Procedure A.** Amidine **1** (60 mg, 0.61 mmol) was dissolved in 5% MeCN/THF (5 mL) at room temperature. Cyanoalkyne **2** (77 mg, 0.61 mmol) was added in one portion, and the reaction mixture was stirred for 2 h. The reaction mixture was poured onto ethyl acetate and aqueous $NaHCO_3$, and the layers were separated. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by preparative reverse-phase HPLC to give **3·TFA** (134 mg, 65% yield) as a white solid. **Procedure B.** Amidine **1** (60 mg, 0.61 mmol) was dissolved in 5% MeCN/THF (5 mL) at room temperature. NaHMDS (1.0 M/THF, 1.22 mL, 1.22 mmol) was added dropwise, and the solution was stirred at room temperature for 5 min. Cyanoalkyne **2** (77 mg, 0.61 mmol) was then added in one portion. The reaction mixture turned dark red and was stirred for 5 min. The reaction mixture was poured onto ethyl acetate and aqueous $NaHCO_3$, and the layers were separated. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by preparative reverse-phase HPLC to give **4·TFA** (107 mg, 52% yield) as a white solid.

(10) Unsubstituted amidines have been used as dinucleophiles in the preparation of iminopyrimidine and pyrimidone derivatives; however, these cases do not have the possibility of regioisomeric products. See: (a) Todd, A. R.; Bergel, F. *J. Chem. Soc*. **1937**, 364−367. (b) Foldi, Z.; Salamon, A. *Chem. Ber*. **1941**, 1126−1128. (c) Nishigaki, S.; Aida, K.; Senga, K.; Yoneda, F. *Tetrahedron Lett.* **1969**, *4*, 247−250. (d) Wamhoff, H.; Materne, C. *Ann. Chem.* **1971**, *754*, 113−118.

(11) For a recent example of the effect of solvent on addition reactions of biselectrophiles, see: Vasudevan, A.; Mavandadi, F.; Chen, L.; Gangjee, A. *J. Org. Chem.* **1999**, *64*, 634−638.

(12) Zelle, R. E. *Synthesis* **1991**, 1023−1026.