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New Approach to the Practical Synthesis of Tri- or Tetrasubstituted Pyrimidine Derivatives: A Four-Component Coupling Reaction from a Functionalized Silane, Two Types of Aromatic Nitriles, and Acetals

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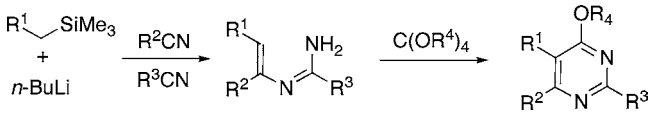
ABSTRACT



A new approach to the synthesis of tri- or tetrasubstituted pyrimidines by a four-component coupling reaction using a functionalized silane, two types of aromatic nitriles, and an acetal is described. The efficient transformation of the pyrimidine framework consisting of an isoxazolyl ring and an ethoxy group to the 1,3,8-triazanaphthalene skeleton also proceeded in nearly quantitative yield.

The synthesis of pyrimidines has attracted considerable interest in the scientific community, as this skeleton is present in many natural products and a variety of biologically active substances. Although various procedures for the synthesis of pyrimidine derivatives have been reported,[1] most have been restricted to methodologies involving a Pinner synthesis (3,4- and 1,6-bond forming reactions, path a);[2] 1,2- and 2,3-bond forming reactions (path b),[3] 1,2- and 3,4-bond forming reactions (path c),[4] 4,5- and 1,6-bond forming reactions (path d);[5] and 2,3- and 4,5-bond forming reactions (path e).[6] The development of a completely new approach to pyrimidine synthesis has not been extensively pursued (3,4- and 4,5-bond forming reactions; path f in Scheme 1).[7]

Previously, we reported that an *N*-silyl-1-azaallyl anion[8] reacts smoothly with Michael acceptors, such as 1,2-diketones and α,β-unsaturated ketones, to produce polysubstituted pyrroles and pyridine derivatives.[9] During our ongoing research on the synthesis of other nitrogen-contain-

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(1) (a) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 4th ed.; Blackwell Science Ltd.: Cambridge, MA, 2000; pp 194−232. (b) Erian, A. W. *Chem. Rev.* **1993**, *93*, 1991.

(2) For selected papers for the pyrimidine synthesis via path a, see: (a) Taylor, E. C.; Knoff, R. J.; Meyer, R. F.; Holmes, A.; Hoefle, M. L. *J. Am. Chem. Soc.* **1960**, *82*, 5711. (b) Inoue, S.; Saggiomo, A. J.; Nodiff, E. A. *J. Org. Chem.* **1961**, *26*, 4504. (c) Bredereck, H.; Effenberger, F.; Botsch, H.; Rehn, H. *Chem. Ber.* **1965**, *98*, 1081. (d) Chauhan, S. M. S.; Junjappa, H. *Synthesis* **1974**, 880. (e) Kreutzberger, A.; Tesch, U.-H. *Chem. Ber.* **1976**, *109*, 3255. (f) Potts, K. T.; Cipullo, M. J.; Ralli, P.; Theodoridis, G. *J. Org. Chem.* **1983**, *48*, 4841. (g) Kvita, V. *Synthesis* **1986**, 786. (h) Schenone, P.; Sansebastiano, L.; Mosti, L. *J. Heterocycl. Chem.* **1990**, *27*, 295. (i) Papet, A.-L.; Marsura, A. *Synthesis* **1993**, 478. (j) Yamanaka, H.; Takekawa, T.; Morita, K.; Ishihara, T.; Gupton, J. T. *Tetrahedron Lett.* **1996**, *37*, 1829. (k) Wang, T.; Cloudsdale, I. S. *Synth. Commun.* **1997**, *27*, 2521. (l) Ghosh, U.; Katzenellenbogen, J. A. *J. Heterocycl. Chem.* **2002**, *39*, 1101.

(3) For selected papers on pyrimidine synthesis via path b, see: Eilingfeld, H.; Patsch, M.; Scheuermann, H. *Chem. Ber.* **1968**, *101*, 2426.

(4) For selected papers on pyrimidine synthesis via path c, see: (a) Sing, Y. L.; Lee, L. F. *J. Heterocycl. Chem.* **1989**, *26*, 7. (b) Alberola, A.; Andrês, C.; Ortega, A. G.; Pedrosa, R.; Vicente, M. *Synth. Commun.* **1987**, *17*, 1309.

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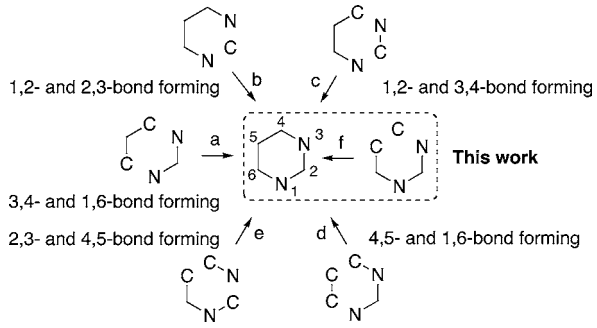
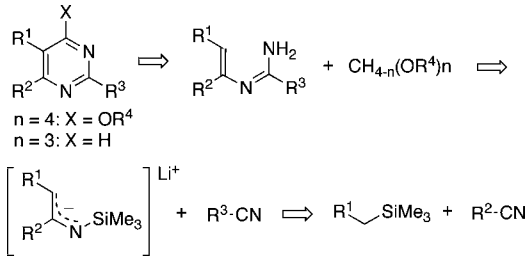
Scheme 1



ing heterocycles, we found that the reaction of a vinyl amidine, formed from the 1-azaallyl anion and an aromatic nitrile, with an acetal could lead to the production of a pyrimidine derivative (Scheme 2). We report herein on a

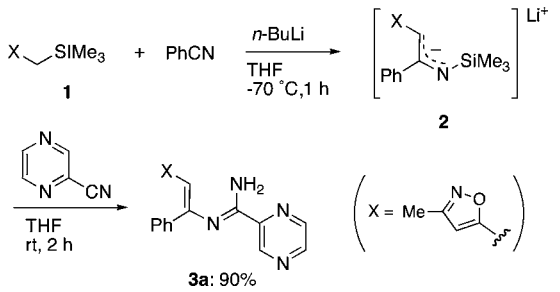
Scheme 2



highly effective and novel method for the synthesis of tri- or tetrasubstituted pyrimidine derivatives by the four-component coupling reaction of a functionalized silane, two types of an aromatic nitrile, and an acetal. We also present details of a new approach to the synthesis of 1,3,8-triazanaphthalene starting from a tetrasubstituted pyrimidine via an intramolecular cyclization.

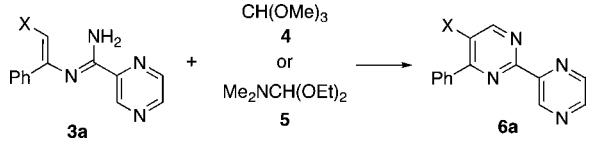
We initially examined a one-pot synthesis of an amidine derivative. When the functionalized silane **1** was reacted with benzonitrile in THF at −70 °C for 1 h in the presence of *n*-BuLi, 1-azaallyl anion **2** was generated in situ, and after addition of 2-cyanopyrazine, the desired amidine **3a** was produced in 90% yield (Scheme 3).

Scheme 3. One-Pot Synthesis of Amidine Derivative **3a**



The reaction of this amidine with an acetal was then investigated under several conditions, and the results are shown in Table 1. When amidine **3a** was reacted with trimethyl orthoformate (**4**) in THF, the expected cyclization reaction did not proceed (runs 1 and 2). However, when acetal **4** was used in the absence of solvent, a small amount of the desired 2,4,5-trisubstituted pyrimidine **6a** was produced (run 3). The structure of **6a** was confirmed by ^{1}H and ^{13}C NMR spectroscopy and by mass spectrometry. We next chose *N*,*N*-dimethylformamide diethylacetal (**5**) as an appropriate substrate, as the amide anion was expected to be a better leaving group than a methoxy anion. As expected, when cyclization of the amidine with the *N*,*O*-acetal was conducted in THF at 70 °C for 24 h, the yield of product **6a** was increased to 62% (run 5). Moreover, it was noteworthy

Table 1. Reaction of Amidine **3a** with Acetals **4** and **5** Leading to the Trisubstituted Pyrimidine **6a**[a]



run	acetal	solvent	temp (°C)	time (h)	yield (%)[b]
1	**4**	THF	rt	24	trace
2	**4**	THF	reflux	24	trace
3	**4**		100	24	6
4	**5**	THF	rt	24	13
5	**5**	THF	reflux	24	62
6	**5**		100	2	90
7	**5**		130	2	99

[a] X = 3-methyl-5-isoxazolyl. [b] Isolated yields.

(5) For selected papers on pyrimidine synthesis via path d, see: (a) Guzmân, A.; Romero, M.; Talamâs, F. X.; Villena, R.; Greenhouse, R.; Muchowski, J. M. *J. Org. Chem.* **1996**, *61*, 2470. (b) Guzmân, A.; Romero, M.; Talamâs, F. X.; Muchowski, J. M. *Tetrahedron Lett.* **1992**, *24*, 3449.

(6) For selected papers on pyrimidine synthesis via path e, see: (a) Pourzal, A.-A. *Synthesis* **1983**, 717. (b) Martínez, A. G.; Fernandez, A. H.; Alvarez, R. M.; Losada, M. C. S.; Vilchez, D. M.; Subramanian, L. R.; Hanack, M. *Synthesis* **1990**, 881. (c) Martînez, A. G.; Fernândez, A. H.; Fraile, A. G.; Subramanian, L. R.; Hanack, M. *J. Org. Chem.* **1992**, *57*, 1627. (d) Martînez, A. G.; Fernândez, A. H.; Âlvarez, R. M.; Vilchez, M. D. M.; Gutiêrrez, M. L. L.; Subramanian, L. R. *Tetrahedron* **1999**, *55*, 4825. (e) Ghosez, L.; Jnoff, E.; Bayard, P.; Sainte, F.; Beaudegnies, R. *Tetrahedron* **1999**, *55*, 3387.

(7) For example, sets of numbers in 3,4- and 1,6-bond forming reactions shown in Scheme 1 denote the position of bonds formed between N(3)−C(4) and N(1)−C(6).

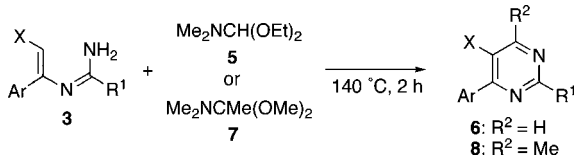
(8) (a) Konakahara, T.; Sato, K. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1241. (b) Mangelinckx, S.; Giubellina, N.; Kimpe, N. D. *Chem. Rev.* **2004**, *104*, 2353.

(9) (a) Konakahara, T.; Kurosaki, Y. *J. Chem. Res.* **1989**, 130. (b) Konakahara, T.; Watanabe, A.; Maehara, K.; Nagata, M.; Hojahmat, M. *Heterocycles* **1993**, *35*, 1171. (c) Konakahara, T.; Mojahmat, M.; Sujimoto, K. *Heterocycles* **1997**, *45*, 271. (d) Konakahara, T.; Hojahmat, M.; Tamura, S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2803. (e) Hojahmat, M.; Konakahara, T.; Tamura, S. *Heterocycles* **2000**, *53*, 629. (f) Konakahara, T.; Ogawa, R.; Tamura, S.; Kakehi, A.; Sakai, N. *Heterocycles* **2001**, *55*, 1737. (g) Konakahara, T.; Sugama, N.; Yamada, A.; Kakehi, A.; Sakai, N. *Heterocycles* **2001**, *55*, 313.

that increasing the reaction temperature to 130 °C without any reaction solvent dramatically improved the product yield to 99% (runs 6 and 7).

To examine the general applicability of this cyclization, the reactions of five types of amidines with several acetals were carried out under the above-optimized conditions, and the results are summarized in Table 2. With

Table 2. Cyclization of Amidine **3** with Acetal **5** or **7**[a]



	amidine **3**					
run	Ar	R^1		acetal		yield (%)[b]
1	4-MeO−C_6H_4	2-pyrazyl	**3b**	**5**	**6b**	88
2	4-Me_2N−C_6H_4	2-pyrazyl	**3c**	**5**	**6c**	90
3	4-Cl−C_6H_4	2-pyrazyl	**3d**	**5**	**6d**	92
4	Ph	4-CF_3−C_6H_4	**3e**	**5**	**6e**	90
5	Ph	2-pyrimidyl	**3f**	**5**	**6f**	97
6	4-MeO−C_6H_4	2-pyrazyl	**3b**	**7**	**8b**	80
7	4-Me_2N−C_6H_4	2-pyrazyl	**3c**	**7**	**8c**	82

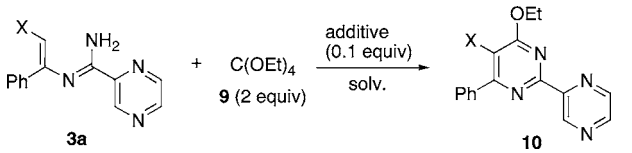
[a] X = 3-methyl-5-isoxazolyl. [b] Isolated yields.

amidines containing an electron-donating group, an electron-withdrawing group, and a heterocycle, when these systems were treated with acetal **5**, the desired trisubstituted pyrimidines **6** were obtained in all cases, in good to excellent yields (runs 1−5). Similarly, by employing acetal **7**, the present reaction could be adapted to the preparation of a tetrasubstituted pyrimidine containing an alkyl group on C-4 atom (runs 6 and 7).

We next attempted the synthesis of a tetrasubstituted pyrimidine having an ethoxy group acting as the leaving group. Unfortunately, when the reaction of amidine **3a** with tetraethyl orthocarbonate (**9**) was carried out under the above conditions, the yield of the expected product **10** was moderate (run 1 in Table 3). To increase the product yield, the reaction was carried out using several different solvents and a Lewis acid as an additive, and the results are listed in Table 3. We found that when the reaction was conducted in PhMe at 110 °C in the presence of a catalytic amount of $ZnBr_2$, the desired product **10** was obtained in 80% yield (run 8).[10]

Finally, to illustrate the utility of an isoxazole ring,[11] we examined the transformation of pyrimidine **10** prepared by

Table 3. Reaction of Amidine **3a** with Acetal **9**[a]

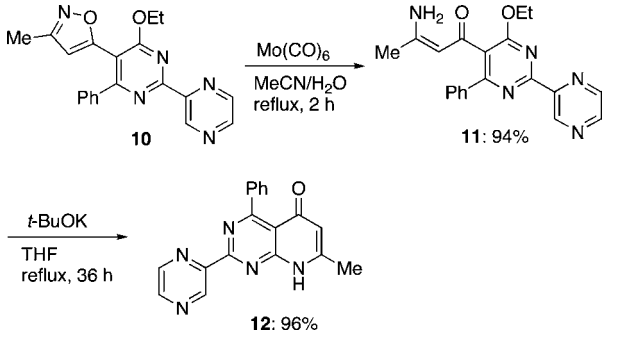


run	additive	solvent	temp (°C)	time (h)	yield (%)[b]
1			160	36	34
2		1,2-$C_6H_4Cl_2$	130	24	trace
3		PhMe	reflux	48	12
4	$ZnCl_2$	1,2-$C_6H_4Cl_2$	130	24	52
5	$Zn(OTf)_2$	1,2-$C_6H_4Cl_2$	130	24	6
6	$ZnBr_2$	1,2-$C_6H_4Cl_2$	130	24	73
7	$ZnCl_2$	PhMe	reflux	72	64
8	$ZnBr_2$	PhMe	reflux	65	80
9[c]	$ZnBr_2$	PhMe	reflux	60	78

[a] X = 3-methyl-5-isoxazolyl. [b] Isolated yields. [c] $ZnBr_2$ (0.4 equiv) was used.

the reaction described above to a 1,3,8-triazanaphthalene derivative (pyrido[2,3-d]pyrimidin-5(1*H*)-one), the analogous skeletons of which are widely distributed in natural products and biologically active substances (Scheme 4).[12]

Scheme 4. Synthesis of 1,3,8-Triazanaphthalene Derivative **12**



The reductive opening of the isoxazole ring with a catalytic amount of $Mo(CO)_6$ initially produced pyrimidine **11**;[13] intramolecular cyclization of the pyrimidine with the tethered amino group was then effected with base, leading to the production of the triazanaphthalene **12** in excellent yield.

In conclusion, we have reported a new synthesis of tri- or tetrasubstituted pyrimidines through the cyclization of a vinyl amidine and an acetal, and the four-component coupling reaction of a functionalized silane, two types of aromatic nitriles, and an acetal. We have also succeeded in transform-

(10) Typical Lewis acids, such as $AlCl_3$, BF_3•OEt_2, $Cu(OTf)_2$, and $MgBr_2$, were not effective for the reaction.

(11) We previously found that the isoxazole ring acts as a good substituent to promote in situ generation of this type of 1-azaallyl anion derivative,[9a] namely, the existence of the ring affects an easy preparation of this type of a vinyl amidine derivative. Actually, the reaction of the 1-azaallyl anion having a pyridine ring instead of the isoxazole ring with 2-cyanopyrazine did not produce the corresponding vinyl amidine in a practical yield (<10%). Although the reaction of a vinyl amidine involving other aromatic rings with an acetal was not examined, the reaction would proceed. The detailed results will be published elsewhere.

(12) (a) Gangjee, A.; Adair, O. O.; Queener, S. F. *J. Med. Chem.* **2003**, *46*, 5074. (b) Perner, R. J.; Gu, Y.-G.; Lee, C.-H.; Bayburt, E. K.; McKie, J.; Alexander, K. M.; Kohlhaas, K. L.; Wismer, C. T.; Mikusa, J.; Jarvis, M. F.; Kowaluk, E. A.; Bhagwat, S. S. *J. Med. Chem.* **2003**, *46*, 5249. (c) Sanmartîn, C.; Echeverrîa, M.; Mendîvil, B.; Cordeu, L.; Cubedo, E.; Garcîa-Foncillas, J.; Font, M.; Palop, J. A. *Bioorg. Med. Chem.* **2005**, *13*, 2031.

(13) Li, C.-S.; Lacasse, E. *Tetrahedron Lett.* **2002**, *43*, 3565.

ing a pyrimidine framework containing an isoxazolyl group and an ethoxy group to the 1,3,8-triazanaphthalene skeleton. Further investigations directed toward the preparation of other types of pyrimidine derivatives are currently in progress.

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Supporting Information Available: Experimental procedures and spectroscopic data of novel compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

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