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Direct N- and C-vinylation with trimethoxyvinylsilane

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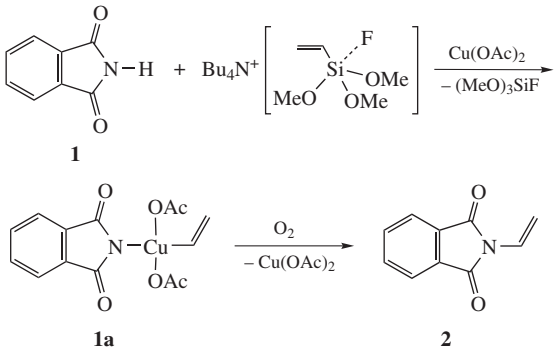
Treatment of nucleobases, nucleosides, 5-membered N-heterocycles and terminal alkynes with trimethoxyvinylsilane in the presence of copper(II) acetate–TBAF system as catalyst affords the vinylation products.

The development of new methods for catalytic C–N bond formation is highly challenging.[1] Notably, copper promoted C–N cross-coupling of amides with organometalloids have received a great deal of attention since initial reports.[2] Recently, Lam[3] reported very impressive results for the arylation of heteroarylcarboxamides with phenyl trimethoxysilane and tributylphenyltin under mild conditions. Lam's method is based on the α-nitrogen activating effect in the Cu-promoted N-arylation. Previously, very simple reaction conditions [$(MeO)_3SiCH{=}CH_2$, $Cu(OAc)_2$, TBAF, solvent] have been developed for the direct vinylation of aryl and hetaryl carboxamides. Note that formation of *N*,*N*-divinyl carboxamides was not observed, whereas the yield of *N*-vinyl amides strongly depended on the structure of initial amide and solvent nature.[4] Treating of 5-fluorouracil with acetylene in dioxane in the presence of cadmium(II) acetate at 220 °C and 9120 Torr within 2 h leads to the formation of the mixture of 1-vinyl- and 1,3-divinyl-5-fluorouracil in moderate yields.[5] 1-Vinyl-5-fluorouracil was obtained in 74% yield by elimination of HCl from 1-(2-chloroethyl)-5-fluorouracil with potassium *tert*-butoxide in DMSO.[6] More or less convenient procedure was described[7] for direct vinylation of trimethylsilyl-protected nucleobases with vinyl acetate as the reagent and the solvent in the presence of $Hg(OAc)_2$ and hydroquinone. Herein, we report a convenient method for the N-vinylation of nucleobases with trimethoxyvinylsilane under mild base-free conditions.

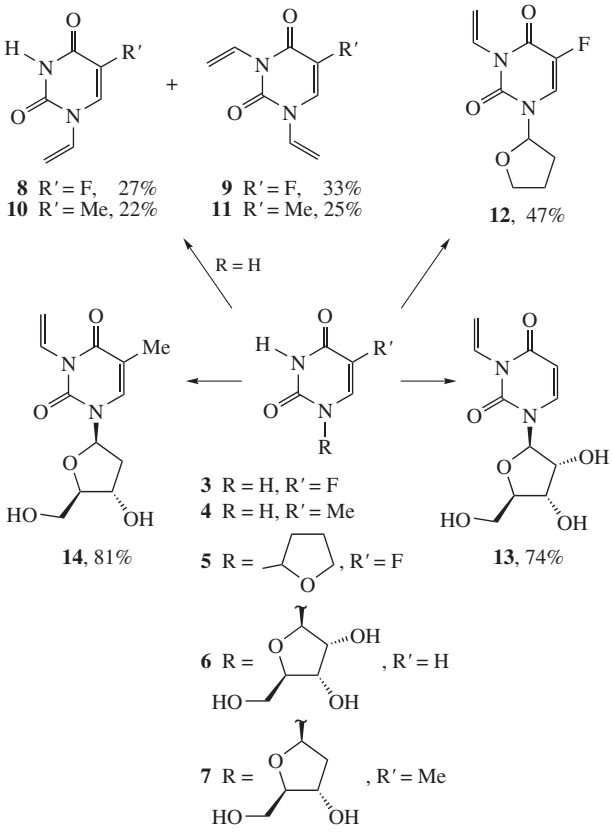
Initially, to improve the procedure, we studied N-vinylation of phthalimide **1** as a model compound with trimethoxyvinylsilane (Scheme 1).† Addition of copper(II) acetate to phthalimide followed by reaction with activated trimethoxyvinylsilane [$(MeO)_3SiCH{=}CH_2$ + TBAF] furnished the intermediate **1a**. Then **1a** in the presence of oxygen was subjected to reductive elimination with the formation of the desired *N*-vinylphthalimide **2**. In dichloromethane, the yield of **2** was as low as 17%. However, addition of 20% of methanol to the reaction mixture raised the yield of **2** as twofold. Notably, according to our experimental data DMF is not appropriate solvent for N-vinylation of imides under current reaction conditions.



1 **1a** **2**

Scheme 1

Next, we investigated the applicability of the elaborated procedure in the vinylation of imide moieties of nucleobases. In the case of 5-fluorouracil **3**, a mixture of 1-vinyl-5-fluorouracil **8**[5,6] and 1,3-divinyl-5-fluorouracil **9**[5,6] was obtained (27% and 33% yields, respectively) (Scheme 2). Molecular structure of the compound **9** is outlined in Figure 1.‡ The vinyl groups are slightly unfolded to the pyrimidine cycle. The torsion angles C(8)–C(7)–N(1)–C(6) and C(11)–C(10)–N(3)–C(4) are equal to 5.2(5)



Scheme 2 *Reagents and conditions*: $(MeO)_3SiCH{=}CH_2$, $Cu(OAc)_2$, TBAF, CH_2Cl_2–MeOH (5:1).

† *General procedure for N-vinylation*. 1 M TBAF solution in dioxane (2 mmol) was added to a mixture of imide (1 mmol), trimethoxyvinylsilane (2 mmol), and copper(II) acetate (1 mmol) in 10 ml of dichloromethane–methanol (5:1). The reaction mixture was stirred at 30 °C and monitored by TLC until complete disappearance of the starting compound. The pure product was isolated by column chromatography on silica gel using chloroform–ethanol (15:1 or 10:1) as an eluent.

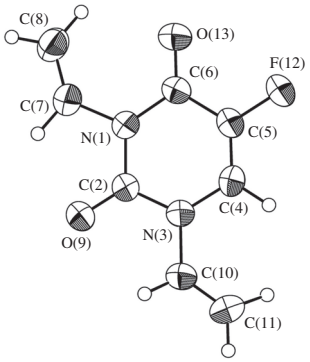


Figure 1 ORTEP molecular structure of 1,3-divinyl-5-fluorouracil **9**.

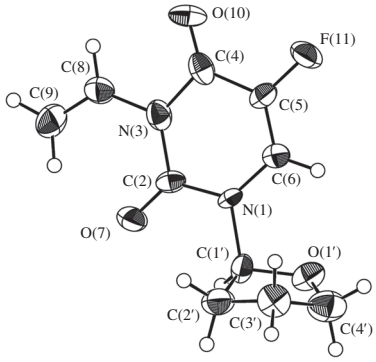
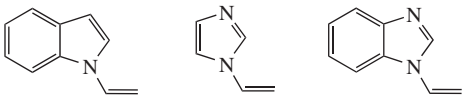


Figure 2 ORTEP molecular structure of 3-vinylftorafur **12**.

and –21.7(5)°, respectively. In the crystal structure of **9** there is a shortened intermolecular contact O(13)···H(4), which can be described as a weak hydrogen bond of CH···O type [C···O, 3.190(7) Å; H···O, 2.26 Å; C–H···O, 157°]. Vinylation of thymine **4** proceeds similarly, the corresponding 1-vinylthymine **10**[7] and 1,3-divinylthymine **11**§ were obtained in 22% and 25% yields. Use of Ftorafur **5** as substrate under the same conditions (Scheme 2) gave 3-vinylftorafur **12**§ in 47% yield, which was dropped to 27% while performing the procedure in DMF. Molecular structure of compound **12** is given in Figure 2.‡ Five-membered cycle is characterized by the envelope conformation: atom C(3′) is deviated from the plane of C(2′)–C(1′)–O(1)–C(4′) by 0.529(17) Å. Likewise **9**, in the crystal structure of **12** there is a weak intermolecular hydrogen bond of CH···O type between atoms O(10) and H(6) [C···O, 3.163(18) Å; H···O, 2.39 Å; C–H···O, 137°]. Since Ftorafur is a known anticancer agent, we investigated *in vitro* activity of **12** on human fibrosarcoma (HT-1080) and mice hepatoma (MG 22A) tumor cell lines, and normal fibroblast cells (NIH 3T3), as well as *in vivo* antitumor activity on sarcoma S-180 on mice. Note that antitumor activity of 3-vinylftorafur **12** is comparable with that of Ftorafur, however, **12** exhibits much lower acute toxicity (LD_{50} = 1940 mg kg^{-1}).

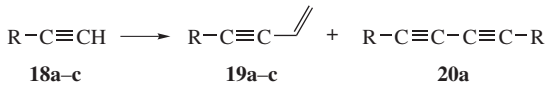
Then we tried to adopt this method for vinylation of unprotected nucleosides. Direct vinylation of uridine **6** and thymidine **7** with trimethoxyvinylsilane led to 3-vinyl derivatives **13** and **14**§ in very good yields (74% and 81%, respectively). Surprisingly, these compounds were obtained as sole products; sugar hydroxy groups remained intact.

According to Lam's theory[3] and our investigations,[4] the presence of carbonyl group near the reaction centre is necessary for the formation of a copper(II) acetate intermediate complex. To verify scope and limitations of trimethoxyvinylsilane as a source of vinyl group, we investigated its interaction with five-membered heterocycles such as indole, imidazole and benzimidazole in the presence of copper(II) acetate and TBAF in DMF and dichloromethane. The corresponding *N*-vinyl derivatives **15**,[8(a),(b)] **16**,[8(c)–(f)] and **17**[8(f),(g)] were obtained in moderate yields. Therefore, the presence of carbonyl group in a substrate is not crucial for the current procedure.



	15	**16**	**17**
DMF	50%	38%	60%
CH_2Cl_2	45%	29%	34%

Encouraged by these results we studied the possibility of C-vinylation of terminal alkynes **18a–c** using the here developed procedure¶ (Scheme 3, Table 1). In the most of conventional solvents (entries 1–7) the reaction of phenylacetylene **18a** was accompanied by formation of side diyne **20a**. Luckily, in dioxane (entry 8) the yield of the target enyne **19a** was as high as 81%, while the fraction of homocoupled alkyne **20a** was low. On



18a–c **19a–c** **20a**

a R = Ph
b R = C(OH)Me$_2$
c R = 1-hydroxycyclohexyl

Scheme 3 *Reagents ans conditions*: $(MeO)_3SiCH{=}CH_2$, $Cu(OAc)_2$, TBAF, solvent.

Table 1 Vinylation of terminal alkynes **18a–c** with trimethoxyvinylsilane.

Entry	Substrate	Solvent	Yield of **19** (%)	Yield of **20** (%)
1	**18a**	DMF	36	45
2	**18a**	CH_2Cl_2	32	56
3	**18a**	CH_2Cl_2–MeOH (5:1)	5	22
4	**18a**	MeCN	38	36
5	**18a**	Toluene	17	22
6	**18a**	Acetone	33	42
7	**18a**	DMSO	38	34
8	**18a**	Dioxane	81	4
9	**18b**	Dioxane	47	—
10	**18c**	Dioxane	52	—

‡ Diffraction data were collected on a Nonius KappaCCD diffractometer using graphite monochromated MoKα radiation (λ = 0.71073 Å). The crystal structures of **9** and **12** were solved by direct methods[9] and refined by full-matrix least squares.[10]

Crystal data for **9**: $C_8H_7FN_2O_2$, monoclinic, a = 6.6735(4), b = = 11.7772(8) and c = 10.5198(8) Å, V = 825.8(1) Å^3, Z = 4, μ = 0.122 mm^{-1}, d_{calc} = 1.465 g cm^{-3}, space group $P2_1/a$. A total of 1900 independent reflection intensities ($2\theta_{max}$ = 55°) was collected at room temperature. For structure refinement, 1104 reflections with $I > n\sigma(I)$ were used. The final R-factor is 0.071.

Crystal data for **12**: $C_{10}H_{11}FN_2O_3$, orthorhombic, a = 9.310(1), b = = 9.711(2) and c = 11.385(2) Å, V = 1029.4(3) Å^3, Z = 4, μ = 0.120 mm^{-1}, d_{calc} = 1.460 g cm^{-3}, space group $P2_1nb$. A total of 1186 independent reflection intensities ($2\theta_{max}$ = 55°) was collected at 253 K. For structure refinement, 702 reflections with $I > n\sigma(I)$ were used. The final R-factor is 0.074.

CCDC 762232 and 762233 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2011.

§ For characteristics of compounds **11**–**14**, see Online Supplementary Materials.

¶ Some previous methods for enyne synthesis are given under ref. 11.

moving to aliphatic α-hydroxyalkynes **18b**,**c**, the corresponding enyne alcohols **19b**,**c** were obtained as sole products in 47% and 52% yields, respectively.

In summary, the herein developed very simple reaction conditions [$(MeO)_3SiCH{=}CH_2$, $Cu(OAc)_2$, TBAF, solvent] for direct vinylation of nucleobases, nucleosides, 5-membered N-heterocycles and terminal acetylenes can promote wider use of such an important transformation in fine organic synthesis.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2011.11.011.

References

1 S. V. Ley and A. W. Thomas, *Angew. Chem. Int. Ed.*, 2003, **42**, 5400.

2 (*a*) P. Y. S. Lam, C. G. Clark, S. Saubern, J. Adams, K. Averill, D. M. T. Chan and A. P. Combs, *Synlett*, 2000, 674; (*b*) P. Y. S. Lam, C. G. Clark, S. Saubern, J. Adams, M. P. Winters, D. M. T. Chan and A. Combs, *Tetrahedron Lett.*, 1998, **39**, 2941; (*c*) D. A. Evans, J. L. Katz and T. R. West, *Tetrahedron Lett.*, 1998, **39**, 2937; (*d*) D. M. T. Chan, K. L. Monaco, R.-P. Wang and M. P. Winters, *Tetrahedron Lett.*, 1998, **39**, 2933.

3 (*a*) P. Y. S. Lam, S. Deudon, E. Hauptman and C. G. Clark, *Tetrahedron Lett.*, 2001, **42**, 2427; (*b*) P. Y. S. Lam, G. Vincent, D. Bonne and C. G. Clark, *Tetrahedron Lett.*, 2002, **43**, 3091.

4 P. Arsenyan, A. Petrenko and S. Belyakov, *Tetrahedron Lett.*, 2008, **49**, 5255.

5 (*a*) M. G. Voronkov, Z. V. Stepanova, A. V. Afonin and V. K. Voronov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1987, 672 (*Bull Acad. Sci. USSR, Div. Chem. Sci.*, 1987, **36**, 614); (*b*) Z. V. Stepanova, G. G. Skvortsova, V. K. Voronov and A. V. Afonin, *Khim. Geterotsikl. Soedin.*, 1986, 567 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1986, **22**, 469].

6 H.-J. Gi, Y. Xiang, R. F. Schinazi and K. Zhao, *J. Org. Chem.*, 1997, **62**, 88.

7 R. Dalpozzo, A. Nino, L. Maiuolo, A. Procopio, R. Romeo and G. Sindona, *Synthesis*, 2002, 172.

8 (*a*) A. Y. Lebedev, V. V. Izmer, D. N. Kazyul'kin, I. P. Beletskaya and A. Z. Voskoboynikov, *Org. Lett.*, 2002, **4**, 623; (*b*) W. Reppe, *Justus Liebigs Ann. Chem.*, 1956, **601**, 81; (*c*) N. S. Shaglaeva, O. V. Lebedeva, Yu. N. Pozhidaev, R. G. Sultangareev, S. S. Bochkareva and L. A. Es'kova, *Zh. Fiz. Khim.*, 2007, **81**, 406 (*Russ. J. Phys. Chem. A*, 2007, **81**, 335); (*d*) R.-J. Song, C.-L. Deng, Y.-X. Xie and J.-H. Li, *Tetrahedron Lett.*, 2007, **48**, 7845; (*e*) B. N. Laskorin, N. G. Zhukova, O. N. Grishina, G. G. Skvortsova, E. S. Domnina and S. A. Ostrovskii, *Zh. Prikl. Khim.*, 1982, **55**, 506 [*J. Appl. Chem. USSR* (*Engl. Transl.*), 1982, **55**, 555]; (*f*) V. N. Voropaev, E. S. Domnina, N. P. Glazkova and G. G. Skvortsova, *Zh. Prikl. Khim.*, 1983, **56**, 2123 [*J. Appl. Chem. USSR* (*Engl. Transl.*), 1983, **56**, 2289]; (*g*) D. Bogdal and K. Jaskot, *Synth. Commun.*, 2000, **30**, 3341; (*h*) V. F. Kukharev, V. K. Stankevich, G. R. Klimenko, V. G. Popova, L. E. Belozerov and E. S. Domnina, *Zh. Prikl. Khim.*, 1984, **57**, 1980 [*J. Appl. Chem. USSR* (*Engl. Transl.*), 1984, **57**, 2137].

9 (*a*) A. Altomare, M. Burla, M. Camalli, G. Cascarano, C. Giacovazzo, A. Guagliardi, A. Moliterni and R. Spagna, *J. Appl. Crystallogr.*, 1999, **32**, 115.

10 S. Mackay, W. Dong, C. Edwards, A. Henderson, C. J. Gilmore, N. Stewart, K. Shankland and A. Donald, *maXus, Integrated Crystallography Software*, Bruker-Nonius and University of Glasgow, 2003.

11 (*a*) X. Tang, S. Woodward and N. Krause, *Eur. J. Org. Chem.*, 2009, 2836; (*b*) B. Kang, D. Kim, Y. Do and S. Chang, *Org. Lett.*, 2003, **5**, 3041; (*c*) J. Waser, J. C. Gonzalez-Gomez, H. Nambu, P. Huber and E. M. Carreira, *Org. Lett.*, 2005, **7**, 4249; (*d*) F. D. Lewis, M. C. Sajimon, X. Zuo, M. Rubin and V. Gevorgyan, *J. Org. Chem.*, 2005, **70**, 10447; (*e*) I. N. Nazarov, *Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk*, 1938, 704 (in Russian); (*f*) B. A. Trofimov, L. N. Sobenina, S. E. Korostova, A. I. Mikhaleva, N. I. Shishov, V. D. Feldman, S. G. Shevchenko and A. N. Vasilev, *Zh. Prikl. Khim.*, 1987, **60**, 1366 (in Russian); (*g*) A. C. Davis and R. F. Hunter, *J. Appl. Chem.*, 1959, **9**, 137.

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