A General Procedure for the Synthesis of 2-Substituted Pyrimidine-5-Carboxylic Esters

Pavel Zhichkin,[a] David J. Fairfax,*[a] Shane A. Eisenbeis[b]

[a] Albany Molecular Research Inc., 21 Corporate Circle, PO Box 15098, Albany, NY 12212, USA

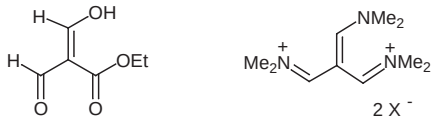
[b] Pfizer Global Research and Development, Groton Laboratories, Pfizer Inc., Eastern Point Road, Groton, CT 06340, USA
Fax +1(518)4640289; E-mail: DavidF@albmolecular.com

Received 6 November 2001; revised 12 February 2002

Abstract: A method for the synthesis of 2-substituted pyrimidine-5-carboxylic esters is described. The sodium salt of 3,3-dimethoxy-2-methoxycarbonylpropen-1-ol (**3**) has been found to react with a variety of amidinium salts to afford the corresponding 2-substituted pyrimidine-5-carboxylic esters.

Keywords: heterocycles, pyrimidines, condensation, amidinium salt, esters

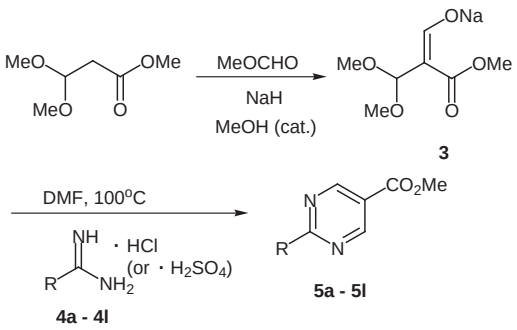
Although several methods for the synthesis of pyrimidine 5-carboxylic derivatives have been reported,[1,2] a high yielding, direct method for the synthesis of pyrimidines that lack substitution in the 4-position still remains challenging. Indeed, the only reported[2] direct method involves a low yielding condensation of amidines with ethyl 2,2-diformylacetate (**1**). The use of vinamidinium salts of general formula **2** as triformylmethane equivalents, which afford 5-formyl pyrimidines, also serves as an indirect route to these species (Figure).[3] Recently, the original bisperchlorate derivative of this reagent has been found to be highly shock sensitive[4] and therefore of limited preparatory use. This report also describes the use of the easily handled tetrafluoroborate derivative of **2**, a reagent that undergoes a similar condensation with amidines to afford the corresponding 5-formylpyrimidine derivative. Gupton[5] has also reported the hexafluorophosphate derivative of **2**. In a similar vein, Davies and co-workers have described an improved synthesis of vinamidinium hexafluorophosphate salts that have been utilized in the synthesis of a variety of polyfunctionalized pyridines.[6]



1 **2**

Figure

Since we recently required a general and direct method for the synthesis of 2-substituted pyrimidine-5-carboxylic esters, our attention focused on the use of the sodium salt of 3,3-dimethoxy-2-methoxycarbonylpropen-1-ol (**3**). This reagent can be easily prepared by condensation of methyl formate with methyl 3,3-dimethoxypropionate in the presence of sodium hydride as in the Scheme.[7] The resulting sodium salt **3** was readily isolated by filtration and appeared to be stable at room temperature if stored under a nitrogen atmosphere. After some experimentation, it was discovered that this reagent undergoes a very facile condensation reaction with a variety of amidinium salts to afford the corresponding pyrimidine derivatives in moderate to excellent yields.



Scheme

Results are outlined in Table 1. The reaction appears to be quite general, with a variety of functional groups being tolerated by these conditions. Of particular note are entries 1 and 7 where superior yields to those previously reported[2] were obtained. Also of interest is compound **5f**, which contains a methylthio substituent at the 2- position of the pyrimidine. Since the 2-alkylthio group in this class of compounds can be readily displaced by amines,[8] chlorine,[9] cyanide,[10] and palladium mediated alkylation using alkylzinc reagents,[11] compound **5f** represents a potential entry into a variety of 2-substituted pyrimidine-5-carboxylic esters.

In conclusion, we have reported an improved method for the synthesis of 2-substituted pyrimidine-5-carboxylates, and a potential route to a wide variety of 2 substituted pyrimidine-5-carboxylic esters via 2-methylmercapto derivative, **5f**.

Synthesis 2002, No. 6, 29 04 2002. Article Identifier:
1437-210X,E;2002,0,06,0720,0722,ftx,en;M04901SS.pdf.

ISSN 0039-7881

Table 1 Condensation Reactions of the Sodium Salt of 3,3-Dimethoxy-2-carbomethoxypropen-1-ol (**3**) with Amidinium Salts **4a**–**4l** affording Pyrimidines **5a**–**5l**.

Entry	Amidinium Salt	Counter Ion	R	Product	Yield
1	**4a**	Cl	Me	**5a**	74%
2	**4b**	Cl	*i*Pr	**5b**	69%
3	**4c**	Cl	*t*Bu	**5c**	39%
4	**4d**	Cl	$PhOCH_2$	**5d**	79%
5	**4e**	HSO_4	MeO	**5e**	58%
6	**4f**	HSO_4	MeS	**5f**	62%
7	**4g**	Cl	Ph	**5g**	90%
8	**4h**	Cl	4-ClC_6H_5	**5h**	88%
9	**4i**	Cl	3-$NO_2C_6H_5$	**5i**	82%
10	**4j**	Cl	4-$H_2NCOC_6H_5$	**5j**	83%
11	**4k**	Cl	thiophen-2-yl	**5k**	81%
12	**4l**	Cl	2,5-dichloro-4-pyridyl	**5l**	84%

Reagents and solvents were used as received from commercial vendors, and no further attempts were made to purify or dry these items. TLC was performed using 1'× 3' Analtech OF 350 silica gel plates with fluorescent indicator. TLC plates were visualized with either iodine vapors or UV light. ^{1}H NMR spectra were recorded on a Bruker AC 300 MHz Nuclear Magnetic Resonance Spectrometer, using $CDCl_3$ as solvent with TMS as an internal reference. Melting points were obtained using an Electrothermal melting point apparatus and are uncorrected. IR was performed using KBr pellets and obtained on a Perkin-Elmer Spectrum 1000 Ff-Infrared Spectrophotometer. Low resolution mass spectroscopic analyses were performed on a PESciex API150EX spectrometer (APCI) by direct insertion. Elemental analyses were performed by Quantitative Technologies Inc., Whitehouse, NJ.

Sodium Salt of 3,3-Dimethoxy-2-methoxycarbonylpropen-1-ol (3)

A 250 mL, three-neck, round-bottom flask equipped with a magnetic stirrer and a reflux condenser was purged with N_2. The flask was then charged sequentially with methyl 3,3-dimethoxypropionate (5.22 g, 35.3 mmol), anhyd 1,2-dimethoxyethane (25 mL), anhyd methyl formate (5 mL), 60% NaH (1.70 g, 42.5 mmol), and the mixture warmed to 40−50 °C until evolution of H_2 gas was observed. The reaction mixture was then cooled in an ice/H_2O bath and slowly allowed to reach ambient temperature overnight with stirring. Anhyd Et_2O (25 mL) was added, and the resulting suspension was filtered under N_2, washed with anhyd Et_2O (10 mL), and vacuum dried (15 mmHg at 40 °C) for 2 h to give 3.51 g (50%) of sodium 3,3-dimethoxy-2-carbomethoxyprop-1-en-1-oxide as a hydroscopic white powder.

^{1}H NMR (CD_3OD): δ = 3.33 (s, 6 H), 3.60 (s, 3 H), 5.31 (s, 1 H), 8.89 (s, 1 H).

^{13}C NMR (CD_3OD): δ = 49.9, 50.2, 98.2, 104.1, 170.5, 179.3.

Pyrimidines 5a−5l; Typical Procedure

To a soln of the amidinium salt **4** (2.0 mmol) in anhyd DMF (4 mL) was added sodium 3,3-dimethoxy-2-carbomethoxyprop-1-en-1-oxide [(**3**), 0.46g, 2.32mmol] and the reaction mixture heated at 100 °C under N_2 for 1 h. After this time the reaction was cooled to r.t. and H_2O (15 mL) added. After addition of H_2O, immediate precipitation of the product was usually observed. The solids were then collected by filtration, washed with H_2O (2.5 mL) and vacuum dried. If precipitation was not observed on addition to H_2O, the mixture was extracted with CH_2Cl_2 (25 mL). The extract was then dried over $MgSO_4$. Filtration and concentration of the filtrate on a rotary evaporator then afforded the crude product. This material was further purified by flash column chromatography on silica gel. Satisfactory physical and spectral analyses were performed on known compounds, and elemental analyses were obtained on all new compounds (Table 2).

Table 2 Physical and Spectral Data for Pyrimidines **5a**–**5l**.

Product	^{1}H NMR ($CDCl_3$) δ, 300 MHz	IR (KBr) (cm^{-1})	APCI Mass Spectrum (*m*/*z*)	Elemental Analysis	Melting Point (°C)
5a	2.83 (s, 3 H), 3.98 (s, 3 H), 9.19 (s, 2 H).	1719, 1592, 1558.	–	–	75–76[12]
5b	1.39 (t, 6 H), 3.31 (sept, 1 H), 3.98 (s, 3 H), 9.22 (s, 2 H).	1735, 1589, 1544.	–	–	26–28[13]
5c	1.43 (s, 9 H), 3.97 (s, 3 H), 9.21 (s, 2 H).	1726, 1590, 1546.	195 $(MH)^+$	Calcd: C, 61.84%; H, 7.27%; N, 14.42%. Found: C, 61.71%; H, 7.10%; N, 14.42%.	60–62
5d	4.00 (s, 3 H), 5.39 (s, 2 H), 6.94−7.03 (m, 3 H), 7.29 (d, 2 H), 9.31 (s, 2 H).	1721, 1587, 1558.	245 $(MH)^+$	Calcd: C, 63.93%; H, 4.95%; N, 11.47%. Found: C, 63.66%; H, 4.80%; N, 11.45%.	111–113
5e	3.95 (s, 3 H), 4.10 (s, 3 H), 9.05 (s, 2 H).	1724, 1604, 1551.	–	–	126–127[14]
5f	2.62 (s, 3 H), 3.96 (s, 3 H), 9.03 (s, 2 H).	1720, 1590, 1535.	–	–	92–93[14]

Table 2 Physical and Spectral Data for Pyrimidines **5a**–**5l**. (continued)

Product	^{1}H NMR ($CDCl_3$) δ, 300 MHz	IR (KBr) (cm^{-1})	APCI Mass Spectrum (*m*/*z*)	Elemental Analysis	Melting Point (°C)
5g	4.00 (s, 3 H), 7.49−7.60 (m, 3 H), 8.53 (d, 2 H), 9.32 (s, 2 H).	1719, 1586, 1541.	–	–	161–163[15]
5h	4.02 (s, 3 H), 7.50 (d, 2 H), 8.48 (d, 2 H), 9.32 (s, 2 H).	1719, 1581, 1539.	249 $(MH)^+$	Calcd: C, 57.96%; H, 3.65%; N, 11.27%. Found: C, 57.78%; H, 3.62%; N, 11.24%	177–179
5i	4.03 (s, 3 H), 7.71 (t, 1 H), 8.40 (d, 1 H), 8.88 (d, 1 H), 9.35−9.45 (m, 3 H).	1735, 1587, 1528.	260 $(MH)^+$	Calcd: C, 55.60%; H, 3.50%; N, 16.21%. Found: C, 55.45%; H, 3.58%; N, 16.26%.	169–170
5j	3.94 (s, 3 H), 7.55 (br s, 1 H), 8.06 (d, 2 H), 8.17 (br s, 1H), 8.52 (d, 2 H), 9.37 (s, 2 H).	1727, 1656, 1587.	258 $(MH)^+$	Calcd: C, 60.70%; H, 4.31%; N, 16.33%. Found: C, 60.60%; H, 4.21%; N, 16.25%.	309–312
5k	3.98 (s, 3 H), 7.20 (t, 1 H), 7.60 (d, 1 H), 8.11 (d, 1 H), 9.21 (s, 2 H).	1718, 1590, 1542.	221 $(MH)^+$	Calcd: C, 54.53%; H, 3.66%; N, 12.72%. Found: C, 54.77%; H, 3.69%; N, 12.80%.	187–190
5l	4.05 (s, 3 H), 8.34 (s, 2 H), 9.38 (s, 2 H).	1735, 1590, 1533.	285 $(MH)^+$	Calcd: C, 46.51%; H, 2.48%; N, 14.79%. Found: C, 46.63%; H, 2.44%; N, 14.84%.	142–145

References

(1) (a) Urban, R.; Schnider, O. *Helv. Chim. Acta* **1958**, *41*, 1806. (b) Kohra, S.; Tominga, Y.; Hosomi, A. *J. Heterocycl. Chem.* **1988**, *25*, 959. (c) Lorente, A.; Vaquerizo, L.; Martin, A. *Heterocycles* **1995**, *41*, 71. (d) Guzman, A.; Romero, M.; Talamas, F. X.; Villena, R.; Greenhouse, R.; Muchowski, J. M. *J. Org. Chem.* **1996**, *61*, 2470.

(2) (a) Schenore, P.; Sansebastiano, L.; Mosti, L. *J. Heterocycl. Chem.* **1990**, *27*, 295. (b) Dyer, E.; Johnson, T. B. *J. Am. Chem. Soc.* **1934**, *56*, 222.

(3) Gupton, J. T.; Riesinger, S. W.; Smith, S. Q.; Bevirt, K. M.; Sikorski, J. A.; Dahl, M. L.; Arnold, A. *J. Heterocycl. Chem.* **1991**, *28*, 1281.

(4) Ragan, J. A.; McDermott, R. E.; Jones, B. P.; am Ende, D. J.; Clifford, P. J.; McHardy, S. J.; Heck, S. D.; Liras, S.; Segelstein, B. E. *Synlett* **2000**, 1172.

(5) Gupton, J. T.; Petrich, S.; Hicks, F. A.; Wilkinson, D.; Vargus, M.; Hosein, M.; Kirsten, N.; Sikorski, J. A. *Heterocycles* **1998**, *47*, 689.

(6) (a) Davies, I. W.; Taylor, M.; Marcoux, J.-F.; Wu, J.; Dormer, P. G.; Hughes, D.; Reider, P. J. *J. Org. Chem.* **2001**, *66*, 251. (b) Davies, I. W.; Marcoux, J.-F.; Wu, J.; Palucki, M.; Corley, E. G.; Robbins, M.; Tsou, N.; Ball, R. G.; Dormer, P.; Larsen, R. D.; Reider, P. J. *J. Org. Chem.* **2000**, *65*, 4571. (c) Davies, I.; Taylor, M.; Hughes, D.; Reider, P. J. *Org. Lett.* **2000**, *2*, 3385.

(7) Sweet, F.; Fissekis, J. D. *J. Am. Chem. Soc.* **1973**, *95*, 8741.

(8) (a) Miller, C. O.; Skoog, F.; Okumura, F. S.; Von Saltza, M. H.; Strong, F. M. *J. Am. Chem. Soc.* **1956**, *78*, 1375. (b) Arya, V. P.; David, J.; Grewal, R. S.; Marathe, S. B.; Patil, S. D. *Indian J. Chem., Sect. B* **1977**, *15*, 1129. (c) Takagi, K.; Masaaki, T.; Murakami, Y.; Kuniyoshi, O.; Ishii, K.; Morita, H.; Aotsuka, T. *J. Heterocycl. Chem.* **1987**, *24*, 1003. (d) Ple, N.; Turck, A.; Heynderickx, A.; Queguiner, G. J. *J. Heterocycl. Chem.* **1997**, *34*, 551.

(9) Ballard, E.; Johnson, T. B. *J. Am. Chem. Soc.* **1942**, *64*, 794.

(10) Garcia, M. A.; Herrera, F. A.; Moreno, J. F.; Munoz, M. P. J.; Alonso, M. C.; Subramanian, L. R. *Tetrahedron* **1996**, *52*, 7973.

(11) Angiolelli, M. E.; Casalnuovo, A. L.; Selby, T. E. *Synlett* **2000**, 905.

(12) May, C. D.; Sykes, P. *J. Chem. Soc. C* **1966**, 649.

(13) Guzman, A.; Romero, M.; Talamas, F. X. *J. Org. Chem.* **1996**, *61*, 2470.

(14) Budesinky, Z.; Vavrina, J. *Collect. Czech. Chem. Commun.* **1972**, *37*, 1720.

(15) Schwan, T. *J. Heterocycl. Chem.* **1977**, *14*, 695.