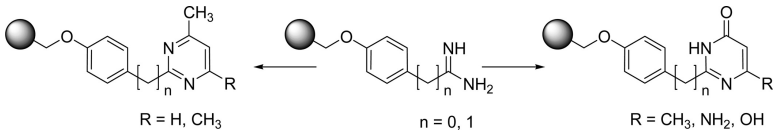
Report

Solid-Phase Synthesis of Structurally Diverse 2-Alkyl- and 2-Aryl-Pyrimidines from Support-Bound Amidines

Joko Cesar

J. Comb. Chem., **2005**, 7 (4), 517-519• DOI: 10.1021/cc050017j • Publication Date (Web): 13 May 2005



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 1 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

Solid-Phase Synthesis of Structurally Diverse 2-Alkyl- and 2-Aryl-Pyrimidines from Support-Bound Amidines

Jožko Cesar*

Faculty of Pharmacy, University of Ljubljana, Aškerčeva 7, 1000 Ljubljana, Slovenia

Received February 9, 2005

The pyrimidine moiety is one of the most widespread heterocycles in biologically occurring compounds, such as nucleic acids and vitamin B_1, and is an important constituent of numerous drug molecules in many therapeutic areas. Pyrimidine chemistry in solution is well-established.[1] The principal synthesis of pyrimidines consists of condensing two-nitrogen-containing building blocks, for example, amidines, guanidines, ureas, isoureas, thioureas, and isothioureas, with 1,3-dielectrophilic three-carbon units. These reactions typically proceed under alkaline conditions.

In recent years, considerable attention has been put into developing solid-phase synthesis of pyrimidines and generation of pyrimidines-containing libraries. In the first approach, this was achieved by condensation of amidines with the support-bound dielectrophiles, such as α,β-unsaturated ketones under air atmosphere,[2a,b] with the resin-bound 2-methylene malonates, followed by oxidation of dihydropyrimidines,[2c] with immobilized dialkylaminopropenones,[2d,e] cyclic malonate,[2f] and γ-ketosulfones.[2g] In the last three cases, the products were released from the resin during the condensation. The second approach was to use polymer-bound thiouronium salts which were condensed with acetylenic ketones,[3a] activated methylenemalononitriles,[3b] β-ketoesters,[3c] and ethyl cyanoacetate and aromatic aldehydes.[3d]

We have recently developed a solid-phase synthesis of amidines from resin-bound nitriles through amidoximes.[4] We decided to explore their ability for further transformation into 2-alkyl- and 2-arylpyrimidines and 3*H*-pyrimidin-4-ones on the solid phase. The support-bound 4-hydroxybenzamidine (**1a**) and 2-(4-hydroxyphenyl)acetamidine (**1b**) were prepared by first attaching 4-hydroxybenzonitrile and 4-hydroxybenzyl cyanide to the Wang resin (0.9−1.1 mmol/g, 100−200 mesh; Acros Organics) by Mitsunobu coupling. Nitriles were then transformed into amidoximes by treatment with hydroxylamine,[5] and these were reduced to the support-bound amidines **1a** and **1b** with tin(II) chloride ($SnCl_2 \cdot 2H_2O$). After cleavage, the resin loadings of amidines were determined to be 0.86 mmol/g for **1a** and 0.82 mmol/g for **1b**, and the purities of the released products were 89% from **1a** and 87% from **1b**.

To establish the optimal reaction conditions for the solid-phase conversion of amidines into pyrimidines, the condensation of resin-bound 4-hydroxybenzamidine (**1a**) with ethyl cyanoacetate was studied, as presented in Scheme 1 and Table 2.

Scheme 1. Condensation of **1a** with Ethyl Cyanoacetate

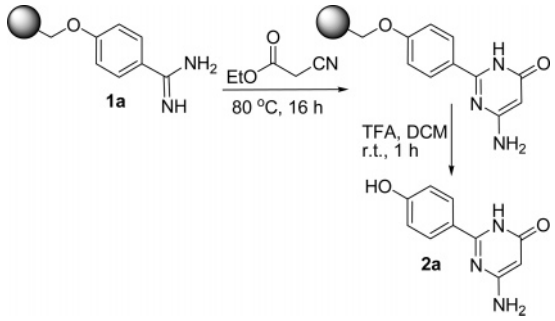


Table 1. Optimization of Condensation between Resin-Bound 4-Hydroxybenzamidine (**1a**) and Ethyl Cyanoacetate

solvent	base	equiv[a]	% conversion
DMF	no base	10	no product
$MeO(CH_2)_2OH$	no base	10	no product
DMF	KOtBu	10	23
$MeO(CH_2)_2OH$	NaOMe	10	85
$MeO(CH_2)_2OH$	NaOMe	20	96

[a] Ethyl cyanoacetate and the base were added in a 1:1 ratio.

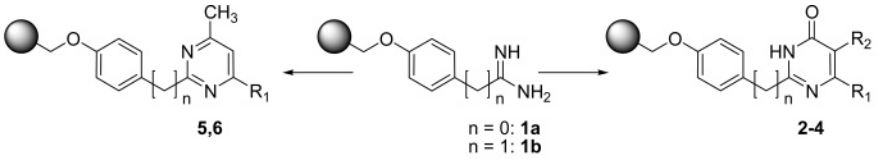
All reactions were carried out at 80 °C and allowed to proceed overnight. After washing, the product was cleaved, and the ratio between 6-amino-2-(4-hydroxyphenyl)-3*H*-pyrimidin-4-one (**2a**) and the parent 4-hydroxybenzamidine was determined by HPLC and NMR. Under neutral conditions using DMF or 2-methoxyethanol as solvent, essentially no formation of product was observed. When potassium *tert*-butoxide was added as a base in DMF, ∼20% of **2a** was formed. Using sodium methoxide as a base in 2-methoxyethanol resulted in ∼85% conversion, with 15% of amidine unreacted. When both ethyl cyanoacetate and sodium methoxide were added in a 20-fold excess, only a trace of parent amidine was observed after cleavage.

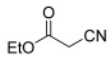
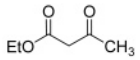
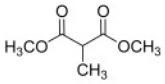
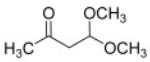
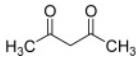
These conditions were then applied to study condensations of resin-bound amidines **1a** and **1b** with a variety of different 1,3-dielectophiles.[6] The results are presented in Table 2. Amidines were reacted with ethyl cyanoacetate, ethyl acetoacetate (β-oxo ester), dimethyl methylmalonate (β-diester), acetylacetaldehyde dimethylacetal (β-oxo aldehyde), and acetylacetone (β-diketone) to furnish structurally diverse pyrimidines and 3*H*-pyrimidin-4-ones. Products were generally obtained in high yield, and their purities were comparable to those of parent amidines. The notable exception was the reaction of support-bound 2-(4-hydroxyphenyl)-acetamidine (**1b**) with acetylacetone, which did not lead to the expected 2,4-dimethylpyrimidine derivative. Under the above-described reaction conditions, most of the amidine remained unreacted. Though various reactions conditions were applied (prolonged reaction time, higher temperature,

* To whom correspondence should be addressed. Phone: +386-1-4769-500. Fax: +386-1-4258-031. E-mail: jozko.cesar@ffa.uni-lj.si.

10.1021/cc050017j CCC: $30.25
Published on Web 05/13/2005

Table 2. Results of Condensation of Support-Bound 4-Hydroxybenzamidine (**1a**) and 2-(4-Hydroxyphenyl)acetamidine (**1b**) with 1,3-Dielectrophilic Reagents



Entry	Reagent	n	R_1	R_2	Yield[a] (%)	Purity[b] (%)
2a		0	NH_2	H	89	81
2b		1	NH_2	H	82	77
3a		0	CH_3	H	91	81
3b		1	CH_3	H	90	89
4a		0	OH	CH_3	91	86
4b		1	OH	CH_3	85	84
5a		0	H	-	89	85
5b		1	H	-	90	83
6a		0	CH_3	-	81	71

[a] Yield of isolated product purified by flash chromatography (silica gel; $CHCl_3$/ MeOH/ NH_3). Yields are relative to the resin-bound amidines. [b] HPLC purity of crude product, determined with UV detector at 220 nm. HPLC was performed using a Eurospher C_{18} 250 × 4.6 mm column at 0.8 mL/min flow rate. Phase A: 0.1% TFA in H_2O. Phase B: 0.1% TFA in MeCN. Gradient 5−70% B over 25 min, then 70% B for 5 min, and back from 70 to 5% B over 5 min.

milder base), complex mixtures of products and parent amidine were usually obtained (results not shown). However, poor reactivity of longer chain amidines with β-diketones compared to other dielectrophiles has been documented.[7]

In conclusion, we have demonstrated that support-bound amidines can be efficiently transformed into pyrimidines and 3*H*-pyrimidin-4-ones on the solid phase in the presence of sodium methoxide as a base. The same reaction conditions can be applied to yield structurally diverse pyrimidine derivatives. With numerous different 1,3-dielectrophiles available, we believe the method can be used for generating diverse pyrimidine-containing libraries. Since the resulting pyrimidines remain attached to the resin, their different substitution patterns should allow their further transformations on the solid-support,[8] which will be studied.

Acknowledgment. The author thanks Dr. Dušan Žigon and Dr. Bogdan Kralj from J. Stefan Institute, Ljubljana for HRMS spectra and Professor Roger Pain for critical reading of the manuscript.

Supporting Information Available. Characterization data, ^{1}H NMR, and HRMS spectra for all compounds listed in Table 2. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Brown, D. J. *The Pyrimidines*; John Wiley & Sons: New York, 1962; pp 31−81. (b) Hoffmann, M. G.; Nowak, A.; Müller, M. Pyrimidines. In *Methods of Organic Chemistry (Houben-Weyl)*; Schaumann, E. Ed.; Georg Thieme Verlag: Stuttgart, 1998; Vol. E9b/Part 1, Hetarenes IV; pp 1−249.

(2) (a) Marzinzik, A. L.; Felder, E. R. *J. Org. Chem.* **1998**, *63*, 723−727. (b) Katritzky, A. R.; Serdyuk, L.; Chassaing, C.; Toader, D.; Wang, X.; Forood, B.; Flatt, B.; Sun, C.; Vo, K. *J. Comb. Chem.* **2000**, *2*, 182−185. (c) Hamper, B. C.; Gan, K. Z.; Owen, T. J. *Tetrahedron Lett.* **1999**, *40*, 4973−4976. (d) Spivey, A. C.; Srikaran, R.; Diaper, C. M.; Turner, D. J. *Org. Biomol. Chem.* **2003**, *1*, 1638−1640. (e) Westman, J.; Lundin, R. *Synthesis* **2003**, 1025−1030. (f) Huang, X.; Liu, Z.; *J. Org. Chem.* **2002**, *67*, 6731−6737. (g) Kong, K.-H.; Chen, Y.; Ma, X.; Chui, W. K.; Lam, Y. *J. Comb. Chem.* **2004**, *6*, 928−933.

(3) (a) Obrecht, D.; Abrecht, C.; Grieder, A.; Villalgordo, J. M. *Helv. Chim. Acta* **1997**, *80*, 65−72. (b) Masquelin, T.; Sprenger, D.; Baer, R.; Gerber, F.; Mercadal, Y. *Helv. Chim. Acta* **1998**, *81*, 646−660. (c) Parlato, M. C.; Mugnaini, C.; Renzulli, M. L.; Corelli, F.; Botta, M. *ARKIVOC* **2004**, *Part v*, 349−363. (d) Kumar, A.; Sinha, S.; Chauhan, P. M. S. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 667−669.

(4) Cesar, J.; Nadrah, K.; Sollner Dolenc, M. *Tetrahedron Lett.* **2004**, *45*, 7445−7449.

(5) Use of free hydroxylamine and 2-methoxyethanol as a solvent gave somewhat purer products than the use of hydroxylamine hydrochloride and DIPEA in a mixture of THF and EtOH described in original procedure.

(6) Representative procedure for the preparation of 6-amino-2-(4-hydroxyphenyl)-3*H*-pyrimidin-4-one (**2a**): Resin **1a** (290 mg, 0.25 mmol) was allowed to swell in $MeO(CH_2)_2OH$ (2 mL) for 10 min. A solution of NaOMe (270 mg, 5.0 mmol) in $MeO(CH_2)_2OH$ (3 mL) and ethyl cyanoacetate (0.54 mL, 5.0 mmol) were added, and the mixture was stirred for 16 h at 80 °C. The mixture was then filtered, and the resin was washed with $MeO(CH_2)_2OH$ (3 × 10 mL), $H_2O/MeO(CH_2)_2OH$ 50/50 (3 × 10 mL), DMF (3 × 10 mL), MeOH (3 × 10 mL), and CH_2Cl_2 (3 × 10 mL). The product was cleaved from the support by treatment with the 50:50 (v/v) mixture of TFA and CH_2Cl_2 (5 mL) for 1 h, followed by filtration and washing of the residual resin with TFA (2 mL) and MeOH (3 mL). Solvents were evaporated from the filtrate, and the product was dried in a vacuum in the presence of solid NaOH at 60 °C to afford 81 mg of crude **2a** as the trifluoracetate salt.

(7) Yamanaka, H.; Edo, K.; Shoji, F.; Konno, S.; Sakamoto, T.; Mizugaki, M. *Chem. Pharm. Bull.* **1978**, *26*, 2160−2166.

(8) (a) Font, D.; Heras, M.; Villalgordo, J. M. *J. Comb. Chem.* **2003**, *5*, 311−321. (b) Gibson, C. L.; La Rosa, S.; Suckling, C. J. *Tetrahedron Lett.* **2003**, *44*, 1267−1270.

CC050017J