Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 9181–9184

TETRAHEDRON LETTERS

Microwave-enhanced Sonogashira coupling reaction of substituted pyrimidinones and pyrimidine nucleosides

Elena Petricci, Marco Radi, Federico Corelli* and Maurizio Botta*

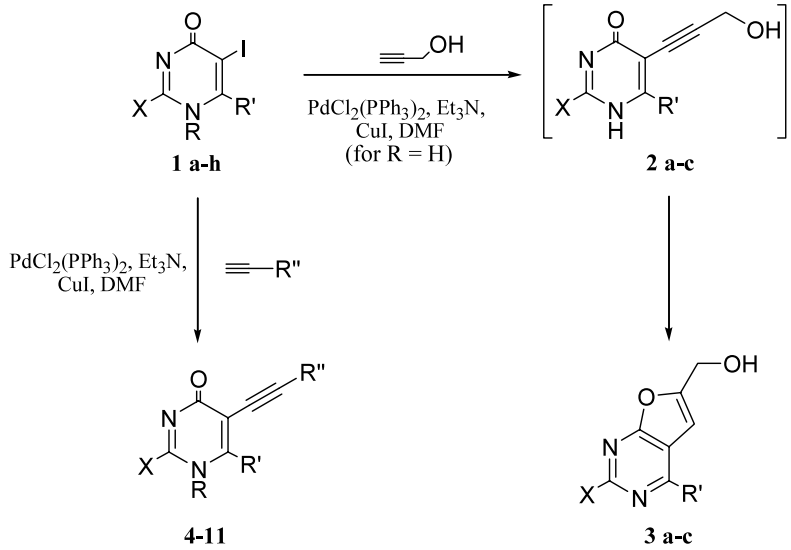
Dipartimento Farmaco Chimico Tecnologico, Università degli Studi di Siena, Via Aldo Moro, 53100 Siena, Italy

Received 8 August 2003; revised 1 October 2003; accepted 6 October 2003

Abstract—Direct microwave-enhanced Sonogashira coupling of several pyrimidinones and uridine with alkynes, $PdCl_2(PPh_3)_2$, Et_3N and CuI to give the corresponding 5-alkynyl derivatives is described.

Many nucleoside analogues substituted at the C-5 position of the heterocycle, especially those in the 2′-deoxyuridine series, are known to have potent biological properties and have been investigated as antiviral and anticancer agents.[1,2] During our studies on the synthesis of antiviral compounds with a pyrimidine nucleus,[3] 5-iodinated compounds[4] were found to be important synthetic intermediates in the formation of new carbon–carbon or carbon–heteroatom bonds via replacement of their iodine atom with electrophiles.[5] Since C-5 iodinated compounds can be efficiently and rapidly prepared from inexpensive starting materials using a microwave-assisted methodology recently developed in our laboratories,[4] electrophilic substitution of iodine was investigated with the aim of synthesizing new C-5 substituted pyrimidinones and pyrimidine nucleosides as potential antiviral and anticancer agents.

Several groups have described methods, for the palladium-catalyzed coupling of olefins with 5-iodo derivatives of uracil based on the pioneering studies of Heck;[6] Bergstrom[7] was the first to report useful procedures for



Scheme 1.

Keywords: microwave; Sonogashira coupling reaction; pyrimidinones; nucleosides.
* Corresponding author. Fax: +39-577-234333; e-mail: botta@unisi.it

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.10.028

this carbon–carbon bond formation at C-5. Others have since described C-5 couplings based on these precedents.[2a,8–11]

According to traditional methods alkynyl derivatives can be obtained in good yields starting from 5-iodinated pyrimidinone derivatives using classical Sonogashira coupling conditions,[5a] after protection at N-1 or the 2–4 positions of uracils; when the reaction is carried out on nucleosides full protection of the sugar hydroxyls is required.[2a,10,12–14] We therefore decided to study the cross-coupling reaction of a series of unprotected pyrimidinones, pyrimidinethiones and uracils with an alkyne using standard Sonogashira coupling conditions.[5a] In a first approach (Scheme 1), compounds **1a–c** (0.2 mmol)[4] were coupled with propargyl alcohol (0.6 mmol) in DMF solution in the presence of Et_3N (0.4 mmol), $PdCl_2(PPh_3)_2$ (0.02 mmol), and CuI (0.06 mmol) at room temperature. Under these conditions the expected alkynyl derivatives **2a–c** could neither be isolated nor detected and **3a–c** were obtained in moderate yields (Table 1, Method A).[15] Compounds **1a–c** reacted smoothly while **1d** did not react at all. Changing the reaction conditions (i.e. temperature, time or catalyst) did not improve the yields.

Reaction of a different alkyne, namely (trimethylsilyl)acetylene, with **1a** afforded alkynyl derivative **4** in poor yield (Table 1, Method A), the same reaction with **1d** to give **6** failed.

Microwave activation as a non-conventional energy source is becoming a very popular and useful technique in organic chemistry, as demonstrated by the rapidly growing number of annual publications on this topic.[16–19] The combination of solvent-free reaction conditions and microwave irradiation leads to significantly reduced reaction times, enhanced conversions and, sometimes, higher selectivity, with several advantages for the eco-friendly approach, termed green chemistry.[20]

Recently, Leadbeater[21] and Kabalka[22] have described microwave-enhanced Sonogashira coupling for aromatic compounds, but to the best of our knowledge microwave-assisted cross-coupling of uracils and related nucleosides has never been reported. Consequently, the possibility of exploiting microwave radiation as a means to improve the efficiency of these cross-coupling reactions was investigated.

In a typical experiment (Scheme 1), compounds **1a–h** (0.2 mmol) were mixed with DMF (1 ml), the appropriate alkyne (0.6 mmol), Et_3N (0.4 mmol), $PdCl_2(PPh_3)_2$ (0.02 mmol), CuI (0.06 mmol) and irradiated with microwaves for 5 min at 40°C.[23] After removing volatiles in vacuo, the solid residue was dissolved in a CH_2Cl_2/MeOH (1:1) solution and stirred at room temperature for 30 min in the presence of AMBERLITE® IRA-400 (Cl) ion-exchange resin. After filtration and evaporation of the solvent, the solid was purified by flash chromatography to provide **3a–c**[15] and **4–11** as pure compounds in 48–82% yields (Table 1, Method B).[24]

It is worth noting that not only pyrimidinones **1a–c**, but also uracils **1d–h** could be efficiently coupled with alkynes under microwave irradiation (Table 1). Coupling reactions with propargyl alcohol afforded the bicyclic compounds **3a–c** in good yields and no alkynyl derivatives were detected. Similar results were obtained also using DIPEA instead of TEA which is supposed to increase the conversion rate of the alkynyl derivative into the cyclic product.[1,14]

Only with the use of a different alkyne was it possible to obtain the alkynyl derivatives **4–11**. This methodology has also been applied to uridine **1h**, which was transformed into the corresponding 5-alkynyluridine **11** in 70% yield with no need for protection of the sugar hydroxyls as reported in the literature for similar compounds.[12–14]

Table 1. Cross-coupling and reaction yields

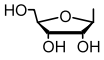
Starting material	Compd	X	R	R′	R″	Yield (%)		Mp (°C) (lit.)
						Method A	Method B	
1a	**3a**	CH_3O	H	CH_3	–	40	80	118–121
	4	CH_3O	H	CH_3	$SiMe_3$	10	76	273–274
	5	CH_3O	H	CH_3	Ph	–	65	129–132
1b	**3b**	CH_3S	H	CH_3	–	43	82	127–130
1c	**3c**	CH_3S	H	H	–	40	82	123–125
1d	**6**	OH	H	H	$SiMe_3$	0	52	273–275 (275–276)[25]
	7	OH	H	H	Ph	–	65	124–127 (not reported)[26]
1e	**8**	OH	H	CH_3	$SiMe_3$	–	50	274–275 (not reported)[13]
1f	**9**	SH	H	CH_3	$SiMe_3$	–	48	277–279
1g	**10**	SH	H	H	$SiMe_3$	–	48	272–274
1h	**11**	OH		H	Ph	–	70	137–141

Table 2. Variation in catalysts and base

Starting pyrimidine	Catalyst	Base	Products (% yield)
1a	$PdCl_2(PPh_3)_2$	Et_3N	**3a** (80)
1a	$Pd(PPh_3)_4$	Et_3N	**3a** (69)
1a	$PdCl_2(PPh_3)_2$	DIPEA	**3a** (81)
1a	$PdCl_2(PPh_3)_2$	Et_3N	**4** (76)
1a	$Pd(PPh_3)_4$	Et_3N	**4** (69)
1d	$PdCl_2(PPh_3)_2$	Et_3N	**6** (52)
1d	$Pd(PPh_3)_4$	Et_3N	**6** (47)
1d	$PdCl_2(PPh_3)_2$	DIPEA	**6** (52)

$PdCl_2(PPh_3)_2$ showed better catalyst properties than $Pd(PPh_3)_4$, which gave alkynyl derivatives in lower yields (Table 2).[17]

In conclusion, an efficient and extremely rapid methodology for the coupling of C-5 iodinated pyrimidinones, uracils and uridine into the corresponding alkynyl derivatives has been reported. The use of microwave radiation afforded the coupling products in a few minutes and in good yield.

It is worth noting that no alkynyl derivatives were detected using propargyl alcohol and only cyclic compounds **3a–c** could be isolated in high yield; only the use of (trimethylsilyl)acetylene or phenylacetylene as electrophiles allowed the preparation of alkynyl derivatives **4–11**.

Both alkynyl derivatives and cyclic compounds are valuable synthetic intermediates[14] and are endowed with potential antiviral and anticancer activity; the biological evaluation of some of the compounds we have synthesized is in progress.

Acknowledgements

The University of Siena (PAR 2001), support from the Research Training Network (HPRN-CT-2000-00018) and from FIRB 2001 (RBAU01LR5P) are gratefully acknowledged. M.B. wishes to thank the Merck Research Laboratories for the 2002 Academic Development Program (ADP) Chemistry Award.

References

1. (a) Srinivasan, S.; McGuian, C.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 391–393; (b) McGuian, C.; Barucki, H.; Blewett, S.; Carangio, A.; Erichsen, J. T.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J. *J. Med. Chem.* **2000**, *43*, 4993–4997; (c) Kumar, R.; Nath, M.; Tyrrel, D. L. J. *J. Med. Chem.* **2002**, *45*, 2032–2040; (d) Yoo, S. J.; Kim, H. O.; Lim, Y.; Kim, J.; Jeong, L. S. *Bioorg. Med. Chem.* **2002**, *10*, 215–226; (e) Awano, H.; Shuto, S.; Baba, M.; Kira, T.; Shigeta, S.; Matsuda, A. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 367–370; (f) Lin, T.-S.; Chen, M.-S.; McLaren, C.; Gao, Y.-S.; Ghazzouli, I.; Prusoff, W. H. *J. Med. Chem.* **1987**, *30*, 440–445.
2. (a) Hannah, D. R.; Sherer, E. C.; Davies, R. V.; Titman, R. B.; Laughton, C. A.; Stevens, M. F. G. *Bioorg. Med. Chem.* **2000**, *8*, 739–750; (b) Lin, T.-S.; Luo, M.-Z.; Liu, M.-C. *Tetrahedron* **1995**, *51*, 1055–1068; (c) Khan, S. I.; Grinstaff, M. W. *Tetrahedron Lett.* **1998**, *39*, 8031–8034.
3. (a) Saladino, R.; Crestini, C.; Palamara, A. T.; Danti, M. C.; Manetti, F.; Corelli, F.; Garaci, E.; Botta, M. *J. Med. Chem.* **2001**, *44*, 4554–4562; (b) Botta, M.; Corelli, F.; Maga, G.; Manetti, F.; Renzulli, M.; Spadari, S. *Tetrahedron* **2001**, *57*, 8357–8367; (c) Nizi, E.; Botta, M.; Corelli, F.; Manetti, F.; Messina, F.; Maga, G. *Tetrahedron Lett.* **1998**, *39*, 3307–3310; (d) Botta, M.; Saladino, R.; Anzini, M.; Corelli, F. *Nucleosides Nucleotides* **1994**, *8*, 1769–1777; (e) Mugnaini, C.; Botta, M.; Coletta, M.; Corelli, F.; Focher, F.; Marini, S.; Renzulli, M. L.; Verri, A. *Bioorg. Med. Chem.* **2003**, *11*, 357–366.
4. Paolini, L.; Petricci, E.; Corelli, F.; Botta, M. *Synthesis* **2003**, 1039–1042.
5. (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467–4471; (b) Abarbri, M.; Thibonnet, J.; Bérillon, L.; Dehmel, F.; Rottländer, M.; Knochel, P. *J. Org. Chem.* **2000**, *65*, 4618–4634; (c) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483; (d) Tsvetkov, A. V.; Latyshev, G. V.; Lukashev, N. V.; Beletskaya, I. P. *Tetrahedron Lett.* **2002**, *43*, 7267–7270.
6. Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146–151.
7. (a) Ruth, J. L.; Bergstrom, D. E. *J. Org. Chem.* **1978**, *43*, 2870–2876; (b) Bergstrom, D. E.; Ogawa, M. K. *J. Am. Chem. Soc.* **1978**, *100*, 8106–8112.
8. Arai, I.; Davis, G. D. *J. Heterocyclic Chem.* **1978**, *15*, 351–353.
9. Jones, A. S.; Verhelst, G.; Walker, R. T. *Tetrahedron Lett.* **1979**, *20*, 4411–4414.
10. (a) Robins, M. J.; Barr, P. J. *Tetrahedron Lett.* **1981**, *22*, 421–424; (b) Robins, M. J.; Barr, P. J. *J. Org. Chem.* **1983**, *48*, 1854–1862.
11. Rao, S. M.; Esho, N.; Sergeant, C.; Dembinski, R. *J. Org. Chem.* **2003**, in press.
12. (a) Kumarasinghe, E. S.; Peterson, M. A.; Robins, M. J. *Tetrahedron Lett.* **2000**, *41*, 8741–8745; (b) Hudson, R. H. E.; Li, G.; Tse, J. *Tetrahedron Lett.* **2002**, *43*, 1381–1386.
13. Kundu, N. G.; Schmitz, S. A. *J. Heterocyclic Chem.* **1982**, *19*, 463–465.
14. Agrofoglio, L. A.; Gillaizeau, I.; Saito, Y. *Chem. Rev.* **2003**, *103*, 1875–1916.
15. **3a**: Mp 118–121°C. ^{1}H NMR (CD_3OD, 200 MHz): δ 2.51 (s, 3H), 3.98 (s, 3H), 4.83 (s, 2H), 6.81 (s, 1H). MS-ES: $m/z=194$ (M^+). **3b**: Mp 127–130°C. ^{1}H NMR (CD_3Cl_3, 200 MHz): δ 2.61 (s, 3H), 2.66 (s, 3H), 4.79 (s, 2H), 6.63 (s, 1H). MS-ES: $m/z=210$ (M^+). **3c**: Mp 123–125°C. ^{1}H NMR (CD_3Cl_3, 200 MHz): δ 2.60 (s, 3H), 4.76 (s, 2H), 6.63 (s, 1H), 8.72 (s, 1H). MS-ES: $m/z=197$ (M+1).
16. (a) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199–9223; (b) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225–9283.
17. Dzierba, C. D.; Combs, A. P. In *Annu. Rep. Med. Chem.*; Doherty, A. M., Ed.; Elsevier Science: Amsterdam, 2002; Vol. 37, pp. 247–256 and references cited therein.
18. Kappe, C. O. *Curr. Opin. Chem. Biol.* **2002**, *4*, 154–161.
19. Hayes, B. L. *Microwave Synthesis*; CEM Publishing: PO Box 200, Matthews, NC 28105, USA, 2002.

20. Varma, R. S. *Green Chem.* **1999**, *1*, 43–55.
21. Leadbeater, N. E.; Marco, M. *Org. Lett.* **2002**, *4*, 2973–2976.
22. Kabalka, G. W.; Wang, L.; Namboodiri, V.; Pagni, R. M. *Tetrahedron Lett.* **2000**, *41*, 5151–5154.
23. Microwave reactions were conducted using a CEM Discover Synthesis Unit (CEM Corp., Matthews, NC). The machine consists of a continuous focused microwave power delivery system with operator selectable power output from 0 to 300 W. The reaction was performed in glass vessels (capacity 10 ml) sealed with a septum. The pressure was controlled by a load cell connected to the vessel via a 14-gauge needle which penetrates just below the septum surface. The temperature of the contents of the vessel was monitored using a calibrated infrared temperature control mounted under the reaction vessel. All experiments were performed using a stirring option whereby the contents of the vessel are stirred by means of a rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the vessel. These reactions can be conducted using a domestic microwave oven (LG Electronics, model: MS-192A) with a maximum emitted power of 800 W. Using a domestic oven, the temperature of the reaction mixture at the end of microwave irradiation was found to be 70–100°C.
24. Spectroscopic and analytical data for compounds **4**–**11** are in agreement with the assigned structures.
25. Kundu, N. G.; Schmitz, S. A. *J. Heterocyclic Chem.* **1982**, *19*, 463–464.
26. Farina, V.; Hauck, S. I. *Synlett* **1991**, 157–159.