Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 2063–2065

3-Substituted 4-pyranones: a rapid approach using microwave heating

Omar D. Lopez,* Jason T. Goodrich, Fukang Yang and Lawrence B. Snyder

Discovery Chemistry, Bristol-Myers Squibb Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, CT 06492, USA

Received 2 January 2007; revised 25 January 2007; accepted 26 January 2007
Available online 1 February 2007

Abstract—A rapid synthesis of 3-substituted pyranones using palladium-catalyzed cross-coupling reactions under microwave irradiation is described. The desired products were consistently obtained in 5 min at 100 °C in good yields.

Pyranones are poly-functional heterocycles that can be found in complex natural products, such as ilikonapyrone (**1**),[1–3] tridachione (**2**),[4] and LL-Z1220[5,6] (**3**) (Fig. 1). They can also be valuable intermediates for the synthesis of related heterocycles, such as pyridones, which have been known to have biological activity.[7,8] Among the simplest naturally occurring pyran-4-ones, Kojic acid (**4**) has been a versatile building block towards the synthesis of more complex structures.[9] More recently, simple pyran-4-ones such as **5**, have been shown to be inhibitors of DNA-Dependent Protein Kinase (DNA-PK).[10]

Although a number of methods have been described in the literature for the preparation of pyran-4-ones, most of them involve multistep condensations of highly functionalized acyclic precursors and/or harsh reaction conditions.[3,11,12] We were interested in the preparation of 3-substituted pyran-4-ones, and a survey of the literature showed that it is possible to replace the 5-hydroxy group of Kojic acid with aromatic groups using cross-coupling techniques (Scheme 1).[13] Nevertheless, we found that when using triflate **7**[14] as the coupling partner with a variety of stannanes (Scheme 2), the yields and reaction times varied considerably depending on the substrates.

For example, when tributylphenyl tin was used under the reported conditions,[13] the reaction proceeded to completion in 24 h at rt in a 70% yield. On the other

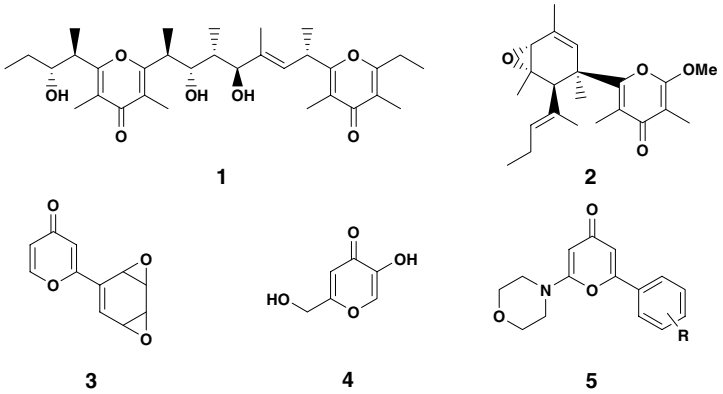
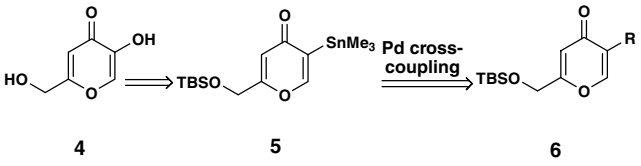


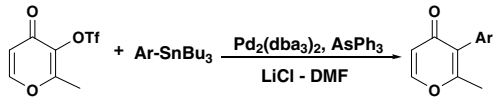
Figure 1.

* Corresponding author. Tel.: +1 203 677 6003; fax: +1 203 677 7702; e-mail: omar.lopez@bms.com

0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2007.01.151



Scheme 1.



Scheme 2.

hand, if tributylfuranyl tin was used, the reaction did not proceed until it was heated to 100 °C for 2 h and the isolated yield was 60%.

Microwave irradiation in organic synthesis has been a subject of intense research recently and although it has been shown that Stille cross-coupling reactions[15] are suitable for flash heating,[16,17] to our knowledge, this methodology has not been applied to the preparation of substituted pyran-4-ones. Herein, we wish to report a fast and efficient synthesis of pyran-4-ones using Stille cross-coupling conditions under microwave heating from commercially available starting materials.

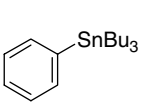
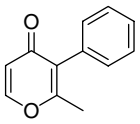
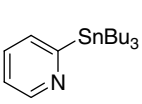
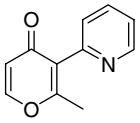
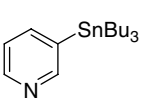
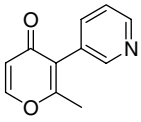
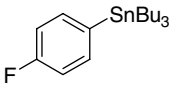
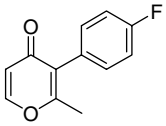
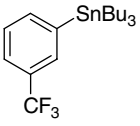
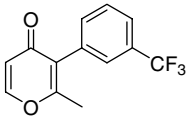
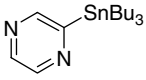
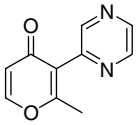
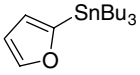
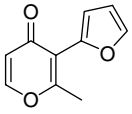
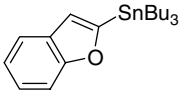
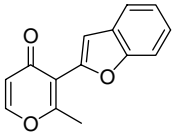
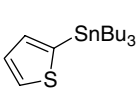
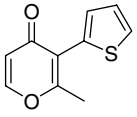
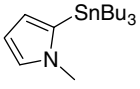
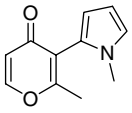
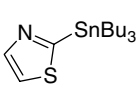
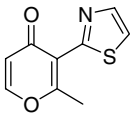
A typical procedure involves the irradiation of a mixture of pyrone triflate **7**, a stannane (**8**), $Pd_2(dba)_3$, $AsPh_3$,[18] and LiCl[19] in DMF under microwave irradiation at 100 °C for 5 min, followed by purification of the crude products by flash chromatography on silica gel (Table 1).[20]

All the reactions proceeded to completion (as determined by HPLC) and the isolated yields of the coupling products **9a**–**k** consistently ranged between 60% and 80%.[21]

For example, when stannane **8b** was coupled to pyranone triflate **7** under microwave irradiation, the resulting 2-pyridine-substituted pyrone was obtained in a 68% yield. When the same reaction was conducted in a preheated oil bath under otherwise identical conditions, after 30 min, the reaction proceeded only to 70% conversion (HPLC analysis). The reaction was complete only after heating for 120 min with an isolated yield of 70%. Without Pd catalyst, no reaction occurred under the same conditions. When stannane **8k** was subjected to the reaction conditions under microwave radiation, a 72% isolated yield of the corresponding thiazole-substituted pyrone was obtained. However, when the reaction was attempted in a preheated oil bath, it only proceeded to 30% completion after heating for 48 h. These results demonstrate the advantages of using microwave radiation for the acceleration of these cross-coupling reactions.

As shown in Table 1, these reaction conditions worked well for a variety of aryl stannanes. It is well worth

Table 1. Coupling of aryl stannanes with pyran-4-one triflate **7**

Entry	Stannane	Product	Yield (%)
a			77
b			68 0[a] 70[b]
c			60
d			75
e			66
f			72
g			80 60[c]
h			67
i			71
j			78
k			72 30[d]

[a] Same reaction conditions but without the addition of Pd catalyst.
[b] Same reaction conditions but heating with an oil bath at 100 °C for 120 min.
[c] Same reaction conditions as in Ref. 13 while heating in an oil bath at 100 °C for 120 min.
[d] Same reaction conditions but heating with an oil bath at 100 °C for 48 h.

noticing that the yield of the reaction was not greatly influenced by the substitution on the aromatic ring (entries **a**,**d**,**e**), the presence of heteroatoms (entries **b**,**c**,**f**) or when using five-membered-ring heterocycles (entries **g**–**k**).

In summary, we have demonstrated an efficient and rapid method for the Stille cross-coupling reactions of aryl stannanes with pyran-4-one triflate **7** under microwave heating. Further studies using Heck and Suzuki cross-coupling conditions for the synthesis of 3-substituted pyran-4-ones are underway and will be reported in due course.

References and notes

1. Faulkner, D. J. *Nat. Prod. Rep.* **1988**, *5*, 613–663.
2. Manker, D. C.; Faulkner, D. J.; Stout, T. J.; Clardy, J. *J. Org. Chem.* **1989**, *54*, 5371–5374.
3. Arimoto, H.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1990**, *31*, 5491–5494.
4. Ireland, C.; Faulkner, D. J.; Solheim, B. A.; Clardy, J. *J. Am. Chem. Soc.* **1978**, *100*, 1002–1003.
5. Borders, D. B.; Shu, P.; Lancaster, J. E. *J. Am. Chem. Soc.* **1972**, *94*, 2540–2541.
6. Altenbach, H. J.; Lex, J.; Linkenheil, D.; Voss, B.; Vogel, E. *Angew. Chem.* **1984**, *96*, 991–992.
7. Batchelor, J. F.; Yeates, C. L.; (Wellcome Foundation Ltd., UK). Patent application: EP91-302031, EP447164, 1991.
8. Carlson, G. R.; (Rohm and Haas Co., USA). Patent application: US76-689219, US4051142, 1977.
9. Brtko, J.; Rondahl, L.; Fickova, M.; Hudecova, D.; Eybl, V.; Uher, M. *Centr. Eur. J. Publ. Health* **2004**, *12*, S16–S18.
10. Hollick, J. J.; Golding, B. T.; Hardcastle, I. R.; Martin, N.; Richardson, C.; Rigoreau, L. J. M.; Smith, G. C. M.; Griffin, R. J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3083–3086.
11. Arimoto, H.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1990**, *31*, 5619–5620.
12. Kim, H.-S.; Yoon, Y. H. *Bull. Korean Chem. Soc.* **1993**, *14*, 159–160.
13. Kamino, T.; Kuramochi, K.; Kobayashi, S. *Tetrahedron Lett.* **2003**, *44*, 7349–7351.
14. Trifluoromethane sulfonic anhydride (5.97 mL, 35.4 mmol) was added dropwise, over 15 min at 0 °C, to a solution of 3-hydroxy-2-methyl-4*H*-pyran-4-one (3.72 g, 29.55 mmol) in pyridine (100 mL). The mixture was stirred at ambient temperature for 3 1/2 h. and then, diluted with 100 mL EtOAc. The organic phase was washed with satd aq $NaHCO_3$ (3×300 mL), water (2×200 mL), and brine (100 mL), dried ($MgSO_4$), filtered, and evaporated under vacuum. The resulting brown oil was submitted to flash chromatography (40% EtOAc/hexanes) to afford pyrone triflate **7** as an off-white solid (7.3 g). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.27 (d, $J = 5.80$ Hz, 1H), 6.62 (d, $J = 5.80$ Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 169.84 (s, 1C), 161.63 (s, 1C), 156.91 (s, 1C), 138.51 (s, 1C), 117.89 (q, $J = 320$ Hz, 1C), 116.19 (s, 1C), 15.11 (s, 1C). LC/MS = 259.21 $(M+H)^+$.
15. Stille, J. K. *Angew. Chem.* **1986**, *98*, 504–519.
16. Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284.
17. Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717–727.
18. Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585–9595.
19. Casado, A. L.; Espinet, P.; Gallego, A. M. *J. Am. Chem. Soc.* **2000**, *122*, 11771–11782.
20. *Representative procedure*: $Pd_2(dba)_3$ (0.039 mmol) was added to a mixture of triflate **7** (0.1 g, 0.39 mmol), tributylphenyl tin (0.13 mL, 0.39 mmol), triphenyl arsine (0.24 g, 0.078 mmol), and lithium chloride (0.049 g, 1.17 mmol) in 1.5 mL anhydrous DMF in a microwave reaction vessel. The reaction was heated at 100 °C for 5 min in a Smith Creator® microwave. Volatiles were removed under reduced pressure and the remaining residue was diluted with CH_2Cl_2 and filtered through a plug of Celite. The filtrate was concentrated and purified by flash chromatography eluting with 20% ethyl acetate/hexanes. Compound **9a** was isolated as colorless needles (77% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.70 (d, $J = 5.80$ Hz, 1H), 7.41 (t, $J = 7.32$ Hz, 2H), 7.35 (d, $J = 7.32$ Hz, 1H), 7.21–7.24 (m, 2H), 6.40 (d, $J = 5.80$ Hz, 1H), 2.18 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ ppm 177.60 (s, 1C), 163.29 (s, 1C), 154.28 (s, 1C), 132.53 (s, 1C), 130.11 (s, 2C), 128.63 (s, 1C), 128.53 (s, 2C), 128.07 (s, 1C), 16.70 (s, 1C), 18.78 (s, 1C). HRMS Anal. Calcd for $C_{12}H_{11}O_2$ $(M+H)^+$ 187.5288; found: 187.5237.
21. All new compounds (**9a**–**k**) have spectral and analytical data in agreement with the indicated structures.