Pergamon

Tetrahedron Letters 42 (2001) 6429–6431

TETRAHEDRON LETTERS

A novel approach to the synthesis of 4-aryl-furan-3-ols

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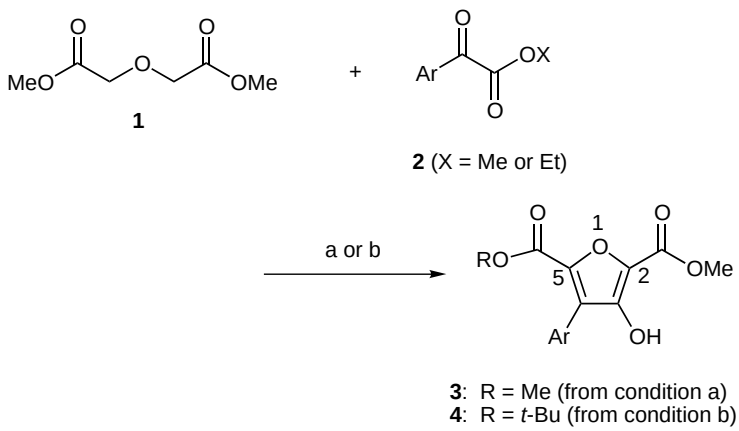
Received 21 June 2001; accepted 13 July 2001

Abstract—A novel, yet simple, method for the synthesis of 4-aryl-furan-3-ols is described. The condensation between dimethyl diglycolate **1** and various aryl glyoxylates **2** using KO*t*-Bu as base furnished a series of 4-aryl-furan-3-ols **4** bearing one *tert*-butyl ester and one methyl ester substituent. Such a mixed ester allowed easy differentiation of the two esters for selective chemical modification. In addition, these 4-aryl-furan-3-ols could be further transformed to other useful substituted furans through conversion to the triflates and subsequent metal-mediated reduction or coupling.

Furan moieties exist in numerous natural products, such as the kallolides[1] and the cembranolides,[2] as well as many pharmaceutical products.[3] Recently, we were interested in developing a general method to synthesize furan-3-ols with various aryl groups substituted at the 4-position. We anticipated that the condensation of dimethyl diglycolate[4] **1** with various aryl glyoxylates **2** under basic conditions would be a viable method to furnish such 4-aryl-furan-3-ols, especially because many aryl glyoxylates either are commercially available or can be easily prepared.[5] Indeed, when methyl phenyl-glyoxylate was used with NaOMe as the base (condition a in Scheme 1), the dimethyl ester **3** (Ar=Ph) was obtained in 81% yield. An interesting variation of this reaction was discovered when KO*t*-Bu was used in a mixture of toluene[6] and *t*-BuOH (condition b). Instead of the dimethyl ester **3**, a mixed ester **4**, bearing one methyl ester and one *tert*-butyl ester, was obtained in 72% yield.[7] The formation of the mixed ester **4** allowed for easy differentiation of the two esters for selective chemical modification. For example, the *tert*-butyl ester was expected to be more susceptible to acid hydrolysis whereas the methyl ester should undergo nucleophilic attack more readily. In this publication, we would like to report the application of this novel approach to the synthesis of 4-aryl-furan-3-ols.



Scheme 1. *Reagents and conditions*: (a) NaOMe, MeOH, 70°C, generating **3**. (b) KO*t*-Bu, *t*-BuOH–toluene (2:1), 70°C, generating **4**.

Keywords: furan; 4-aryl-furan-3-ol; mixed-ester; diglycolate; glyoxylate.

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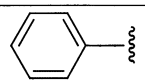
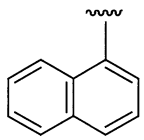
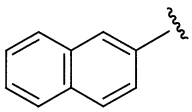
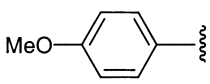
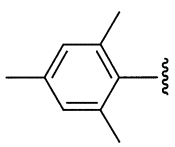
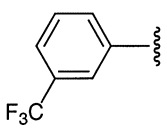
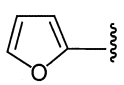
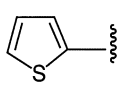
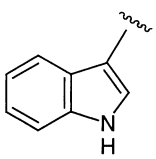
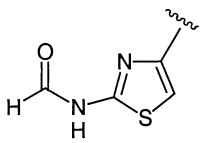
0040-4039/01/$ - see front matter
PII: S0040-4039(01)01284-9

When dimethyl ester **3** obtained from the NaOMe reaction (condition a) was treated with KO*t*-Bu (condition b), **4** was obtained in 79% yield. This result indicated that, under condition b, **3** was likely to be an intermediate involved during the reaction between **1** and **2** to yield **4**. It is noteworthy that only one *tert*-butyl ester was formed, even when KO*t*-Bu was used in large excess. Under the basic reaction condition b, the methyl ester at the 2-position of the furan was resonance-stabilized by the anion of the furan-3-ol, making this methyl ester resistant to exchange with *tert*-butoxide ion. The methyl ester at the 5-position, however, did not have such stabilization and was therefore more reactive. Consequently, only the methyl ester at the 5-position reacted with the excess *tert*-butoxide ion to afford **4**. The structure of **4** was supported by the NOE observed between the protons of the *tert*-butyl group and those of the phenyl group.

Table 1. Yields of the reaction in Scheme 1 with various Ar groups

Ar	Yield (%)
	72
	66
	70
	70
	63
	60
	67
	64
	63
	70

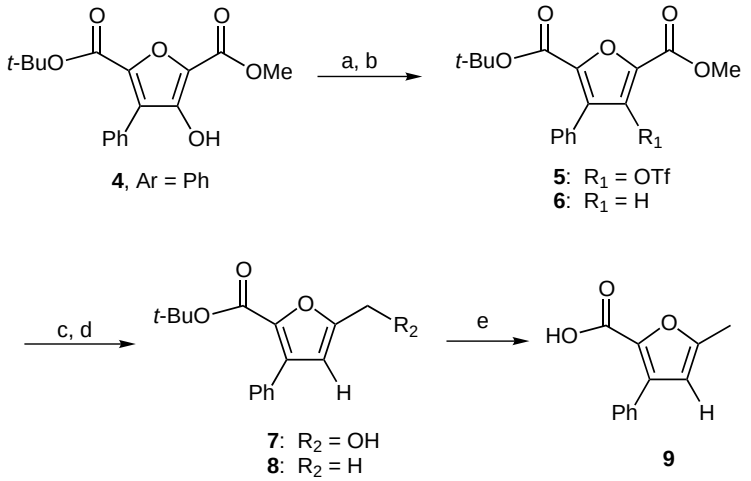
This condensation reaction has also been shown to work for glyoxylates bearing phenyl groups with various substituents and heteroaromatic groups, as shown in Table 1. The yields were consistently around 60–70%. Even for a bulky aryl group such as the 2,4,6-trimethylphenyl group, a yield of 63% was obtained. This method is therefore useful for the synthesis of furan-3-ols with various aryl substituents at the 4-position.

This approach to the synthesis of furan-3-ols can be further extended to the synthesis of tri-substituted and tetra-substituted furans. The furan-3-ols can be readily converted to their corresponding triflates, which in turn can be converted to H or alkyl groups, via metal-assisted reduction or coupling, to furnish tri-substituted and tetra-substituted furans respectively. Such an application is demonstrated in the synthesis of carboxylic acid **9**, a key intermediate in the synthesis of the furo[2,3-*c*]-isoquinoline alkaloids.[8] With the current discovery, **9** can now be efficiently synthesized from **4** in a five-step sequence and the overall yield is much higher than that of the method previously reported.[8] The furan-3-ol **4** was first converted to its triflate **5** (93%). Upon treatment with $Pd(PPh_3)_2Cl_2$, NEt_3 and HCOOH in DMF at 80°C, **5** was reduced to the tri-substituted furan **6** (90%).[9] The methyl ester was expected to be more susceptible to nucleophilic attack than the *tert*-butyl ester. Indeed, treatment with superhydride in THF selectively reduced the methyl ester to its corresponding primary alcohol **7** (93%). Alcohol **7** was further reduced to **8** under hydrogenolysis conditions (98%). Finally, acid hydrolysis of the *tert*-butyl ester furnished the acid **9** (95%) (Scheme 2).[10]

In summary, a novel synthesis of 4-aryl-furan-3-ols has been developed.[11] From dimethyl diglycolate which has two identical methyl esters, a mixed ester furan product with one *tert*-butyl ester and one methyl ester was formed, allowing easy differentiation of these two esters. This method not only offers a general approach to the synthesis of furan-3-ols, but can also be extended to the synthesis of other substituted furans via the triflates of these furan-3-ols.

Acknowledgements

We thank Ms. Debbie Zink for providing the mass spectral data.



Scheme 2. *Reagents and conditions*: (a) Tf_2O, *i*-Pr_2NEt, CH_2Cl_2, −78°C. (b) $Pd(PPh_3)_2Cl_2$, NEt_3, HCOOH, DMF, 80°C. (c) $LiHBEt_3$, THF, rt. (d) H_2 (balloon), $Pd(OH)_2$, MeOH, rt. (e) HCOOH, rt.

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1. Look, S. A.; Burch, M. T.; Fenical, W.; Qi-tai, Z.; Clardy, J. *J. Org. Chem.* **1985**, *50*, 5741.
2. Fenical, W.; Okeeda, R. K.; Basnadurraga, M. M.; Culver, P.; Jacobs, R. S. *Science* **1981**, *212*, 1512.
3. For a list of methods to synthesize furans, see: Wipf, P.; Rahman, L. T.; Rector, S. R. *J. Org. Chem.* **1998**, *63*, 7132 and references cited therein.
4. Dimethyl diglycolate **1** was prepared from diglycolyl chloride, MeOH and NEt_3 in CH_2Cl_2 in 95% yield.
5. For example, see: Rossi, R.; Carpita, A.; Pazzi, P.; Mannina, L.; Valensin, D. *Tetrahedron* **1999**, *55*, 11343.
6. As *tert*-butanol has a relatively low melting point (25°C), toluene was used as a co-solvent to ensure homogeneity of the reaction mixture, especially during the additions of reagents.
7. The dimethyl ester **3** existed as a minor product in 5%.
8. A discussion of the syntheses and biological activities of furo[2,3-*c*]isoquinolines and furo[2,3-*b*]quinoline alkaloids can be found in: Ito, K.; Yakushijin, K.; Yoshina, S. *J. Heterocyclic Chem.* **1978**, *15*, 301 and references cited therein.
9. Chen, Q.; He, Y.; Yang, Z. *J. Chem. Soc., Chem. Commun.* **1986**, 1452.
10. Data for **9**: ^1H NMR (CD_3OD) δ 2.39 (3H, s), 6.36 (1H, s), 7.33–7.58 (5H, m); ^{13}C NMR (CD_3OD) δ 12.4, 111.0, 115.3, 127.7, 127.8, 129.2, 132.6, 136.3, 136.7, 156.1. IR 3018, 1674, 1541, 1494. HRMS calcd for $C_{12}H_{10}O_3$ 202.0630, found 202.0635.
11. A typical procedure to prepare **4** is as follows: to a solution of **1** (1.0 g, 6.2 mmol) in toluene (20 mL) and *tert*-butanol (40 mL) was added methyl phenylglyoxylate **2** (Ar=Ph) (1.05 mL, 7.4 mmol) followed by KO*t*-Bu (24.7 mL of a 1 M solution in *t*-BuOH, 24.7 mmol) at room temperature. The mixture was stirred at 70°C for 2 hours. After acidification with cold 0.1N HCl and aqueous work-up (EtOAc), the mixture was subjected to chromatography to yield 1.41 g of **4** with Ar=Ph (72%) and 85 mg of **3** (5%). **4**: ^1H NMR (CD_3OD) δ 1.36 (s, 9H), 3.92 (3H, s), 7.38–7.42 (5H, m); ^{13}C NMR (CD_3OD) δ 27.0, 51.0, 82.9, 123.6, 125.8, 127.7, 128.1, 129.2, 130.2, 141.3, 151.4, 158.0, 160.1. IR 3372, 1720, 1675, 1621, 1550, 1500. HRMS calcd for $C_{17}H_{18}O_6$ 318.1103, found 318.1107.