Preparation of Novel 6-Substituted-4-Hydroxy-2*H*-Pyran-2-one-3-Carboxamides and Esters via Palladium-Catalyzed Cross-Coupling Methodology

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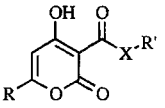
Received 6 December 1996

Abstract: Novel 6-substituted-4-hydroxy-2H-pyran-2-one-3-carboxamides and esters 1 were prepared in a 2-step procedure from known 7-chloro-2,2-dimethylpyrano[4,3-d]1,3-dioxin-4,5-dione 2. Palladium catalyzed cross coupling methodology was employed in the key transformation of 2 to 4. The strategy describes a significant improvement over known literature methods.

2*H*-Pyran-2-ones (2-pyrones) have secured themselves an important role as primary constituents in many known naturally occurring substances.[1] Considerable effort has appeared in the literature regarding the preparation of 4-hydroxy-2-pyrone derivatives and the subsequent elaboration of these materials to several known natural products.[2] During the course of our work involving the preparation of 2-pyrone analogs, a synthesis of 6-substituted-4-hydroxy-2-pyrone-3-carboxamides and esters (Figure 1) was needed for SAR development. While a few reported syntheses of 6-aryl-4-hydroxy-2-pyrone-3-carboxylic esters exist in the literature[1a, 3] none are amenable to rapid SAR evaluation of the 6-position of the pyrone nucleus.

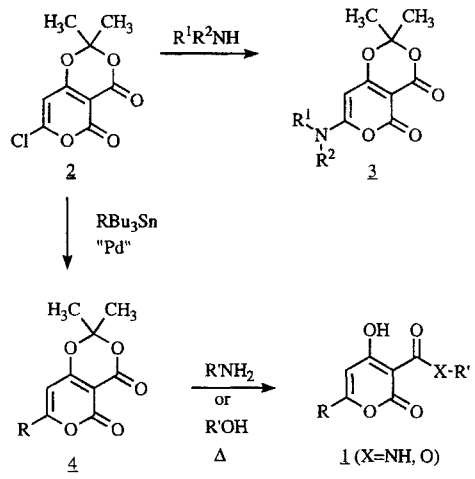


1 (R,R'=aryl/alkyl)
(X=NH,O)

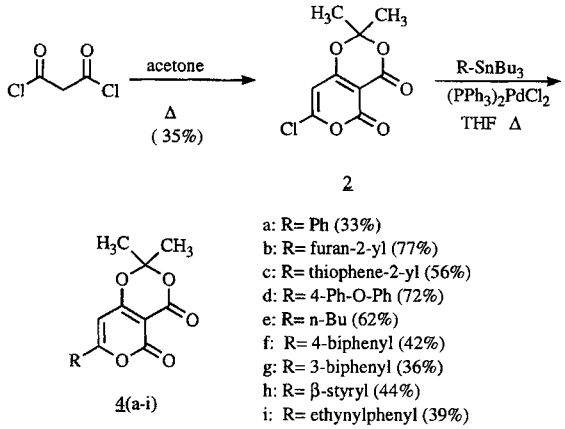
Figure 1

During the *de novo* preparation of representative analogs, a literature search revealed that previously reported 7-chloro-2,2-dimethylpyrano[4,3-d]1,3-dioxin-4,5-dione (2, Scheme 1), prepared by Elvidge and co-workers[4] in the early 1950's, reacted readily at C-7 with heteroatom nucleophiles to form substituted heterocycles 3. The reactivity of the chloro substituent was evaluated extensively as was the reactivity and stability of both ring systems. The properties of 2 described by Elvidge demonstrated that the reactivity of this material was analogous to that of an acid chloride. While reactions with carbon based nucleophiles were not described, we envisioned this substrate as being an excellent candidate for a transition metal mediated cross coupling reaction, therefore providing a suitable manifold for SAR at the 6-position of this system. If successful, the resulting dioxinones 4 would later serve as masked ketenes[5] which would react with amines or alcohols under thermal conditions to form the desired 4-hydroxy-3-carboxamides and esters 1.

Reaction between malonyl dichloride and acetone under reflux according to the literature procedure[4a] afforded after recrystallization a moderate yield of 2 as a highly crystalline material (Scheme 2). In the initial experiment, treatment of 2 with phenyl tributyltin in the presence of *trans*-benzyl(chloro) bis(triphenylphosphine) palladium (II)[6] under reflux in $CHCl_3$ resulted in a slow conversion to 4a.[7] The generality of this method was demonstrated through the reaction of 2 with a variety of aromatic and alkyl tributyltin reagents (4a-i). It was discovered early in this work that implementation of bis(triphenylphosphine) palladium(II) chloride[8] in THF instead of the *trans*-benzyl(chloro) bis(triphenylphosphine)palladium(II) catalyst above, resulted in cleaner reaction mixtures and shorter times to completion.

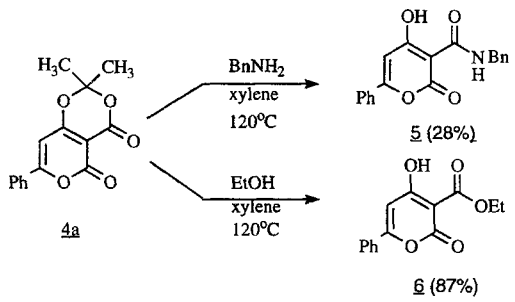


Scheme 1



Scheme 2

The substituted dioxinones (e.g., 4a, Scheme 3) readily reacted with amines or alcohols in hot xylene to afford, upon cooling, analytically pure amides or esters (e.g. 5 or 6).[9]



Scheme 3

In conclusion, we have described a concise two step preparation of novel 6-substituted-4-hydroxy-2*H*-pyran-2-one-3-carboxamides and esters from previously described 7-chloro-2,2-dimethylpyrano[4,3-

d]1,3-dioxin-4,5-dione 2. The methodology offers a significant improvement over the previous synthesis of these types of compounds by allowing for facile introduction of substituents at the 6-position of the pyrone nucleus.

Acknowledgement: The authors would like to thank the Structural, Physical, and Analytical Chemistry Unit at Pharmacia and Upjohn for analytical spectra and elemental analyses.

References and Notes

1. a) Tominaga, Y; Ushirogochi, A.; Matsuda, Y; *J.Heterocycl. Chem.* **1987**, *24*, 1557-1567. and references cited therein. b) Mustafa, A. "Furopyrans and Furopyrones" in Heterocyclic Compounds Interscience Publishers, London **1967**, 2-11.
2. Tominaga, Y; Ushirogochi, A.; Matsuda, Y, and Kobayashi, G. ; *Chem. Pharm. Bull.* **1984**, *32*, 3384-3395 and references cited therein.
3. a) Hormi, O.E.O; Paakkanen, A.M. *J. Org. Chem.* **1987**, *52*, 5275-5276 . b) Takeuchi, N.; Nakagawa, H.; Kamisato, M.; Tobinaga, S.; *Chem. Pharm. Bull.* **1980**, *28*, 2460-2467.
4. A series of three papers pertaining to this chemistry were reported by Elvidge a) Davis, S.J.; Elvidge, J.A.; *J. Chem. Soc.* **1952**, 4109-4114. b) Davis, S.J.; Elvidge, J.A.; *J. Chem. Soc.* **1953**, 2251-2257. c) Elvidge, J.A.; *J. Chem. Soc.* **1962**, 2606-2611. Preliminary investigations in our laboratory involving the reactions of 2 with organometallic reagents resulted in multicomponent mixtures of ring opened products.
5. Sato, M. Ogasawara, H., Oi, K, Kato, K. *Chem. Pharm. Bull.* **1983**, *31*, 1896-1901.
6. Milstein, D., Stille, J.K. *J.Org. Chem.* **1979**, *44*, 1613-1618.
7. Typical procedure: To a stirring mixture of 2 (1.0 g, 4.33 mmol) and phenyltributylstannane (1.75 g, 4.77 mmol) in THF (12 ml) was added bis(triphenylphosphine) palladium(II) chloride (150 mg, 0.20 mmol). The mixture was heated at 80°C for 16 h, cooled to ambient temperature, and treated with a saturated aqueous solution of KF (15 ml). TLC indicated that in each case starting material was consumed with a single non-polar component evident. The mixture was stirred vigorously for 20 min, the solids filtered through celite and washed with additional THF (25 ml). The organic layers were combined, diluted with EtOAc (25 ml), and washed with water (2 x 50 ml). The organics were dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The residue was purified via SiO_2 flash column chromatography (eluant 2% $MeOH/CH_2Cl_2$) to afford 0.39 g 4a (33%) as a bronze solid. m.p. >300°C. ^1H NMR ($CDCl_3$) δ 1.81 (s, 6 H), 6.51 (s, 1 H), 7.55 (m, 3 H), 7.89 (d, *J* = 8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 25.6, 92.0, 95.3, 108.3, 126.7, 129.2, 129.9, 133.0, 156.0, 156.7, 167.2, 172.1. IR (mull) 1774 (s), 1717, 1707, 1620 (s), 1579, 1550 (s), 1497, 1435 (s), 1393, 1276 (s), 1228, 1183 (s), 1151, 1019, 771, MS (EI) *m/z* (rel. intensity) 272 (M+, 8), 272 (8), 215 (11), 214 (56), 147 (5), 146 (45), 106 (8), 105 (99), 77 (35), 69 (5), 51 (9). Anal. Calcd for $C_{15}H_{12}O_5$. 0.28 H_2O: C, 64.95; H, 4.56. Found: C, 64.96; H, 4.58.
8. Labadie, J.W., Stille, J.K. *J.Am. Chem. Soc.* **1983**, *105*, 6129-6137.
9. General procedure for reaction of dioxinones with amines or alcohols: The appropriate dioxinone (1 eq) and amine (1 eq) or alcohol (3 eq) were heated at reflux in xylene (.04 M) for 2 h at which time TLC indicated complete comsumption of starting material (eluant 1:1 EtOAc/ hexane). If the resulting mixtures remained heterogeneous at reflux a small quantity of dimethylformamide was added to homogenize. The reaction mixture was allowed to cool to ambient temperature, and the solid which precipitated from solution was filtered, and dried *in vacuo* to afford analytically pure material.
Benzyl amide 5: 0.051 mg, (28% from 0.15 g, 0.55 mmol of **1a**). m.p. 195-196°C. ^1H NMR ($CDCl_3$) δ 4.62 (d, *J* = 6 Hz, 2 H), 6.61 (s, 1 H), 7.31 (m, 5 H), 7.50 (m, 3 H), 7.85 (d, J = 6 Hz, 2 H) 9.35 (brs, 1 H) (OH absent); IR (mull) 3295, 1704 (s), 1631, 1580 (s), 1550 (s), 1498 (s), 1439 (s), 1429, 842, 771, 750, 695, 683, 647, 600 cm^{-1}; MS (EI) m/z (rel. intensity) 321 (M+, 62), 322 (13), 321 (62), 107 (30), 106 (99), 105 (31), 91 (54), 79 (11), 77 (32), 69 (19), 65 (13). Anal. Calcd for $C_{19}H_{15}NO_4$: C, 71.02; H, 4.70; N, 4.36. Found: C, 70.87; H, 4.71; N, 4.38.
Ethyl ester 6: 0.082 g (87% from 0.10 g 0.36 mmol of **1a**). m.p.130-131°C (m.p.lit 132°C)[3a] ^1H NMR ($CDCl_3$) δ 1.44 (t, J = 6 Hz, 3 H), 4.47 (q, J = 6 Hz, 2 H),6.56 (s, 1 H), 7.52 (m, 3 H), 7.87 (d, J = 6 Hz, 2 H), 14.05 (s, 1 H); IR (mull) 1748 (s), 1714, 1633 (s), 1581, 1564 (s), 1498, 1424 (s), 1342 (s), 1270 (s), 1227, 1115, 1054, 828, 774, 692 cm^{-1}; MS (EI) m/z (rel. intensity) 260 (M+, 66), 260 (66), 214 (29), 188 (45), 147 (26), 146 (39), 105 (99), 102 (18), 77 (54), 69 (49), 51 (16). Anal. Calcd for $C_{14}H_{12}O_5$: C, 64.61; H, 4.65. Found: C, 64.64; H, 4.72.