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6-Chloro-2(2*H*)-pyranone: a new 2(2*H*)-pyranone synthon

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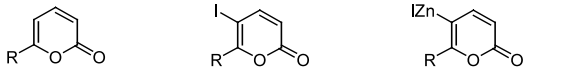
Abstract—6-Chloro-2(2*H*)-pyranone, which can be prepared in high yield from commercially available *trans*-glutaconic acid, undergoes facile Pd/Cu-catalyzed reaction with various 1-alkynes to give rise to the corresponding 6-(1-alkynyl)-2(2*H*)-pyranones in moderate to good yields. These last hitherto unknown compounds have been used as direct precursors to 6-alkyl- and 6-[(*Z*)-1-alkenyl]-2(2*H*)-pyranones. © 2002 Elsevier Science Ltd. All rights reserved.

6-Substituted 2(2*H*)-pyranones with no substituent at the 3-, 4- or 5-position are a restricted class of natural products responsible for an intriguing and diversified spectrum of biological activities[1] and only a few general methods have been described for their synthesis.[2–4] Recently, we reported that hydrolysis of 6-alkyl- and 6-[(*E*)-1-alkenyl]-5-iodozinc-2(2*H*)-pyranones, **3a** and **3b**, which are available by insertion of activated zinc metal on the carbon–iodine bond of iodides **2a** and **2b**, gives rise to the corresponding 6-substituted 2(2*H*)-pyranones, **1a** and **1b**, respectively, in satisfactory yields.[2] We also reported that a representative 6-aryl-2(2*H*)-pyranone, i.e. **1c**, can be prepared in high yield by Pd-catalyzed triethylammonium formate reduction of the corresponding 6-aryl-5-iodo-2(2*H*)-pyranone **2c**.[2]



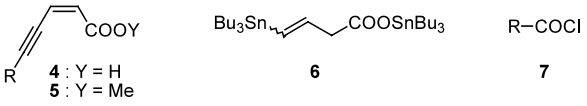
1a : R = alkyl
1b : R = (*E*)-1-alkenyl
1c : R = Ph

2a : R = alkyl
2b : R = (*E*)-1-alkenyl
2c : R = Ph

3a : R = alkyl
3b : R = (*E*)-1-alkenyl

The 6-substituted 5-iodo-2(2*H*)-pyranones used in this study were prepared in modest selectivity (pyranone/furanone ratio = 1.9–3.8) by iodolactonization of the corresponding (*Z*)-2-en-4-ynoic acids **4**,[5] but, very recently, we synthesized iodides **2a** in good yields and very high selectivity by iodolactonization of methyl (*Z*)-2-en-4-ynoates **5** with ICl in CH_2Cl_2.[6,7]

Very recently, two other methods for the synthesis of 6-substituted 2(2*H*)-pyranones have been described.[3,4]



4 : Y = H
5 : Y = Me

6

7

Parrain, Duchêne and co-workers[3] efficiently synthesized 6-alkyl-, 6-[(*E*)-1-alkenyl]- and 6-aryl-2(2*H*)-pyranones by Pd-catalyzed stereoselective annulation of tributylstannyl 4-(tributylstannyl)-3-butenoate (**6**) by acyl chlorides **7**. On the other hand, Negishi and co-workers[4] prepared compound **1c** and some 2(2*H*)-pyranones of general formula **1a** by $ZnBr_2$-catalyzed annulation of the corresponding carboxylic acids **4**. However, the method of Parrain, Duchêne and co-workers,[3] although it has the virtue of simplicity, suffers from the disadvantage that the preparation of compound **6**, which is not commercially available, involves the use of more than 2 equiv. of Bu_3SnH, a toxic reagent. Moreover, this method is far from meeting the atom economy requirement. On the other hand, the procedure of Negishi and co-workers[4] is not superior to those involving the use of compounds **2**[2] or **6**.[3] In fact, it proved to be highly selective only for carboxylic acids **4** in which the substituent at the 5-position is hexyl, isopropyl or cyclohexyl (pyranone/furanone ratio = 15.7–24.0), but when this substituent was *tert*-butyl or phenyl the selectivity of the $ZnBr_2$-catalyzed reaction was modest (pyranone/furanone = 1.85) and null, respectively.[4]

Motivated by our interest for biologically active 6-substituted 2(2*H*)-pyranones, we considered the possibility to concisely synthesize 6-(1-ynyl)-2(2*H*)-pyranones **8** by a methodology complementary with those involving the preparation and use of compounds **2**,[2] **6**,[3] and **4**.[4] We also felt that compounds **8**, which include naturally-occurring substances[8] sometimes characterized by inter-

Keywords: pyrones; Sonogashira reaction; palladium catalysis; selectivity; hydrogenation.

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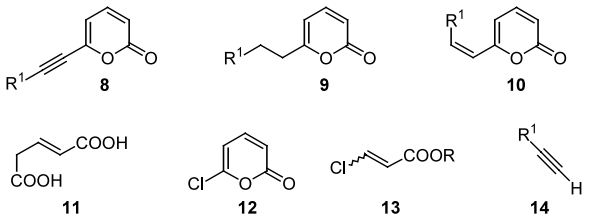
esting biological properties,[1e] might be valuable precursors to 6-alkyl- and 6-[(*Z*)-1-alkenyl]-2(2*H*)-pyranones of general formula **9** and **10**, respectively.

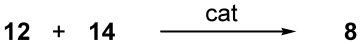


We envisaged that 6-chloro-2(2*H*)-pyranone (**12**) should be of particular interest for the synthesis of compounds **8** via a Pd-catalyzed reaction. In fact, it is a substrate which can be easily prepared from commercially available *trans*-glutaconic acid (**11**)[9] and, due to the chlorine atom at its 6-position, it can be regarded as a cyclic vinylogous compound of alkyl 3-chloropropenoates (**13**), which are activated alkenyl chlorides able to undergo Pd-catalyzed reactions.[10] Thus, compound **12** might be a convenient precursor to 6-(1-ynyl)-2(2*H*)-pyranones **8** by procedures involving Pd-catalyzed reactions with 1-ynylmetals or, more conveniently, with 1-alkynes **14**.

We were gratified to find that the Sonogashira reaction[11] between **12**, which we prepared in 82% yield from **11** using a modification of the procedure reported in the literature,[9,12] and 2.0 equiv. of 1-alkynes **14** in benzene or toluene at room temperature in the presence of 3.0 equiv. of Et_3N, 5 mol% $PdCl_2(PPh_3)_2$ and 15 mol% CuI provided the required 2(2*H*)-pyranone derivatives **8** in moderate to good yields (Table 1).[13–15]

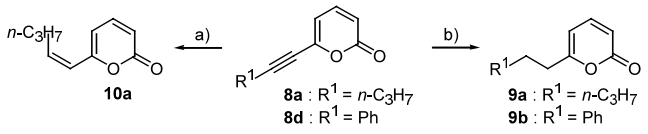
The 1-alkynes, which were successfully used, included 1-pentyne (**14a**), 1-hexyne (**14b**), 3,3-dimethyl-1-butyne (**14c**), phenylacetylene (**14d**), trimethylsilylacetylene (**14e**), 1-(tetrahydropyranyloxy)-4-pentyne (**14f**), and 3,3-dimethylamino-1-propyne (**14g**) (entries 1–7, Table 1). On the contrary, the reaction of **12** with 1-phenyl-2-propyn-1-ol (**14h**) (entry 8, Table 1), which was performed for 3 h at room temperature and then for 12 h under reflux, did not produce either the desired 6-(1-ynyl)-2(2*H*)-pyranone **8h** or ketone **15**, which might derive from a coupling–isomerization sequence similar to that which occurs when electron-deficient aryl

Table 1. Synthesis of 6-(1-ynyl)-2(2*H*)-pyranones **8** from **12** and 1-alkynes (**14**)[a]



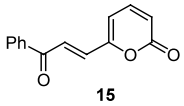
Entry	1-Alkyne		Product		Yield
	14	R^1	**8**		(%)
1	**14a**	*n*-C_3H_7		(**8a**)	85
2[b]	**14b**	*n*-C_4H_9		(**8b**)	69
3	**14c**	*t*-C_4H_9		(**8c**)	81
4	**14d**	Ph		(**8d**)	59
5	**14e**	Me_3Si		(**8e**)	85
6	**14f**	$THPO(CH_2)_3$		(**8f**)	71
7	**14g**	Me_2NCH_2		(**8g**)[c]	35
8[d]	**14h**	PhCH(OH)		(**8h**)	——

a) The reactions were carried out at room temperature for 21 h in benzene or toluene solutions in the presence of 5 mol % $PdCl_2(PPh_3)_2$, 15 mol % CuI and 3.0 equiv of Et_3N. A 2 : 1 molar ratio between **14** and **12** was used. b) This reaction was carried out using crude **12**. c) This compound was contaminated by ca. 15 % of 1,6-di(N,N-dimethylamino)2,4-hexadiyne. d) This reaction was carried out for 3 h at rt and for 12 h under reflux.



Scheme 1. *Reagents and conditions*: (a) H_2 (1 atm), 10% $Pd/BaSO_4$ (cat.), pyridine (cat.), toluene, rt (94%); (b) H_2 (1 atm), 10% $Pd/BaSO_4$ (cat.), toluene, rt (91% for **9a**; 71% for **9b**).

halides are reacted with 1-(hetero)aryl-2-propyn-1-ols in THF under reflux in the presence of Et_3N and catalytic quantities of $PdCl_2(PPh_3)_2$ and CuI.[16]



This last result, however, was not unexpected. In fact, it has been reported that **12** is able to react with *N*- or *O*-nucleophiles and that alcohols such as methanol cause ring opening of **12**.[17] On the other hand, we observed that compound **12** was completely consumed in the Pd/Cu-catalyzed reaction with **14h**, even though we were unable to isolate and identify the product(s) derived from the nucleophilic attack of **14h** on **12**.

Having secured good access to compounds **8** we next demonstrated their synthetic utility by their conversion into 6-alkyl-2(2*H*)-pyranones **9** and 6-[(*Z*)-1-alkenyl]-2(2*H*)-pyranones **10** (Scheme 1). Thus, hydrogenation of **8a** in toluene at room temperature using pyridine-poisoned 10% palladium on $BaSO_4$ selectively gave **10a** in 94% yield. Compound **10a** is the (*Z*)-stereoisomer of a substance extracted from *Solenopsis invicta*.[1c]

On the other hand, when toluene solutions of **8a** and **8b** were hydrogenated at room temperature in the presence of 10% palladium on $BaSO_4$, chemically pure **9a** and **9b** were selectively obtained in 91 and 71% yield, respectively. Compound **9a** is a fungal metabolite of *Trichoderma viride*[18] and a pheromone component of ants.[19]

In conclusion, we developed an efficient and convenient synthesis of 6-(1-ynyl)-2(2*H*)-pyranones **8** through Pd/Cu catalyzed reaction of 1-alkynes with easily available 6-chloro-2(2*H*)-pyranone (**12**). Moreover, we demonstrated the synthetic utility of compounds **8** by their conversion into 6-alkyl-2(2*H*)-pyranones **9** and 6-[(*Z*)-1-alkenyl]-2(2*H*)-pyranones **10**. A study on the use of **12** and 6-(trimethylsilylethynyl)-2(2*H*)-pyranone (**8e**) as direct precursors to 6-(hetero)aryl- and 6-(1,3-diynyl)-2(2*H*)-pyranones, respectively, is in progress.

Acknowledgements

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12. Compound **12** was prepared according to this procedure: Phosphorous pentachloride (32.0 g, 153.7 mmol) was added portionwise to **11** (techn. 90%, 10.0 g, 76.9 mmol) cooled in an ice bath. The mixture was heated to 100°C for 10 min and then cooled to 0°C, poured into ice water (100 ml) and extracted with CH_2Cl_2 (3×80 ml), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was fractionally distilled to give **12** (8.2 g, 82% yield) as a colourless solid. Mp 27°C (lit.[8] mp 27°C).
13. It should be noted that, due to the high reactivity of Et_2NH towards **14**, the Sonogashira reaction between **14** and 1-alkynes **16** could not be performed in the presence of this secondary amine.
14. All new compounds were obtained in analytically pure form if not otherwise noted. Selected spectral properties of compounds **8a–g** are as follows.
Compound **8a**: IR (film): 2227, 1736, 1620, 1541, 1324, 1097, 801 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.03 (3H, t, $J=7.5$ Hz), 1.62 (2H, *pseudo*-sext., $J=7.5$ Hz), 2.40 (2H, t, $J=7.0$ Hz), 6.29 (1H, dd, $J=9.0$ and 1.0 Hz), 6.30 (1H, dd, $J=7.0$ and 1.0 Hz), 7.28 ppm (1H, dd, $J=9.0$ and 7.0 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.4, 21.2, 21.3, 73.7, 97.9, 109.1, 116.0, 142.9, 145.3, 161.3 ppm.

Compound **8b**: IR (film): 2228, 1735, 1619, 1542, 1324, 1096, 801 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.93 (3H, t, $J=7.0$ Hz), 1.35–1.65 (4H, m), 2.43 (2H, t, $J=7.0$ Hz), 6.28 (1H, d, $J=9.5$ Hz), 6.30 (1H, d, $J=7.0$ Hz), 7.28 ppm (1H, dd, $J=9.5$ and 7.0 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.4, 19.0, 21.9, 29.8, 73.6, 98.1, 109.1, 116.0, 142.9, 145.3, 161.3 ppm.

Compound **8c**: mp 70–72°C. IR (KBr): 2227, 1728, 1619, 1539, 1090, 918, 800 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.30 (9H, s), 6.27 (1H, dd, $J=9.1$ and 1.0 Hz), 6.30 (1H, dd, $J=6.5$ and 1.0 Hz), 7.28 ppm (1H, dd, $J=9.0$ and 6.5 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 28.0, 30.1 (3C), 72.2, 105.2, 109.0, 115.8, 142.9, 145.3, 161.3 ppm.

Compound **8d**: mp 82–84°C. IR (KBr): 2213, 1730, 1717, 1620, 1536, 1089, 806 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 6.32 (1H, dd, $J=9.5$ and 1.0 Hz), 6.46 (1H, dd, $J=7.0$ and 1.0 Hz), 7.30 (1H, dd, $J=9.5$ and 7.0 Hz), 7.32–7.54 ppm (5H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ 81.4, 95.3, 110.0, 116.5, 120.4, 128.4 (2C), 129.9, 131.8 (2C), 142.7, 144.9, 161.0 ppm.

Compound **8e**: mp 63–65°C. IR (KBr): 2161, 1723, 1619, 1611, 1540, 1090, 844 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.25 (9H, s), 6.33 (1H, dd, $J=9.5$ and 1.0 Hz), 6.40 (1H, dd, $J=7.0$ and 1.0 Hz), 7.28 ppm (1H, dd, $J=9.5$ and 7.0 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 0.7 (3C), 95.5, 102.8, 110.2, 117.1, 142.6, 144.3, 160.8 ppm.

Compound **8f**: IR (film): 2228, 1735, 1619, 1541, 1323, 1034, 802 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.47–1.80 (6H, m), 1.89 (2H, *pseudo*-quint., $J=6.5$ Hz), 2.57 (2H, t, $J=7.0$ Hz), 3.43–3.58 (2H, m), 3.77–3.94 (2H, m), 4.59 (1H, br s), 6.30 (1H, d, $J=9.0$ Hz), 6.30 (1H, d, $J=7.0$ Hz), 7.28 ppm (1H, dd, $J=9.0$ and 7.0 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.3, 19.5, 25.3, 28.1, 30.5, 62.2, 65.5, 73.7, 97.3, 98.7, 109.1, 116.1, 142.8, 145.1, 161.1 ppm.

Compound **8g**: IR (film): 2219, 1732, 1620, 1541, 1324, 1095, 804 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.35 (6H, s), 3.51 (2H, s), 6.33 (1H, d, $J=9.5$ Hz), 6.38 (1H, d, $J=6.5$ Hz), 7.29 ppm (1H, dd, $J=9.5$ and 6.5 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 43.9 (2C), 48.0, 77.9, 91.7, 109.8, 116.7, 142.7, 144.5, 160.9 ppm.

15. Very recently, it has been reported that 3,5-dibromo-2(2*H*)-pyranone undergoes facile Sonogashira reaction with various 1-alkynes to give rise to the corresponding 3-(1-alkynyl)-5-bromo-2(2*H*)-pyranones with good to excellent chemical yields and selectivity. See: Lee, J.-H.; Park, J.-S.; Cho, C.-G. *Org. Lett.* **2002**, *4*, 1171–1173.
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