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# Synthesis and reactivity of 1-hydroxyspiro[2.5]cyclooct-4-en-3-ones

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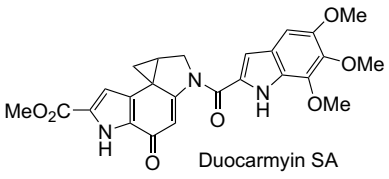
**Abstract**—The first 1-hydroxyspiro[2.5]cyclooct-4-en-3-ones were prepared by cyclization of free and masked 1,3-dicarbonyl dianions with 1,1-diacetylcyclopropane. 1-Hydroxyspiro[2.5]cyclooct-4-en-3-ones represent precursors of unstable spiro[5.2]cycloocta-4,7-dien-6-ones and reactions with a number of nucleophiles were studied. The reactions are enhanced by dynamic spiro-activation.


Acceptor substituted cyclopropanes represent important building blocks in homo Michael reactions with various nucleophiles.[1,2] In this context, spiro[2.5]cycloocta-4,7-dien-6-ones are of considerable interest; they can be regarded as vinylogous ketone substituted cyclopropanes. The rather unstable parent compound has been previously prepared, however, in only 2–4% yield.[3b,4c] In contrast, ether solutions ($10^{-3}$ M) proved to be more stable and reactions with HBr, $LiAlH_4$ or NaOMe have been reported to give phenols.[3] A number of substituted spiro[2.5]cycloocta-4,7-dien-6-one have been reported,[4a,b] which have been used for photochemical,[4c] electrochemical and other transformations.[4d] This includes mainly kinetically stabilized, sterically hindered compounds.[4c,d,5] Derivatives with aromatic rings fused to the double bonds represent an interesting subclass of spiro[2.5]cycloocta-4,7-dien-6-ones, which have been used during the synthesis of natural products, such as CC-1065 or duocarmycin SA.[6] In fact, the spiro[2.5]cycloocta-4,7-dien-6-one moiety plays an important role for the strong antitumour activity of these compounds.



Duocarmyin SA

We have recently reported the $TiCl_4$ mediated cyclization of 1,3-bis-silyl enol ethers with 1,1-diacetylcyclopropane.[7] This reaction proceeds by $TiCl_4$ mediated cyclization, subsequent $TiCl_4$ mediated cyclopropylcarbinyl → homoallyl rearrangement to give phenols with chlorinated side chain. Herein we report the synthesis of 1-hydroxyspiro[2.5]cyclooct-4-en-3-ones by cyclization of free and masked 1,3-dicarbonyl dianions with 1,1-diacetylcyclopropane. The reaction of 1-hydroxyspiro[2.5]cyclooct-4-en-3-ones, which represent stable precursors of (unstable) acceptor-substituted spiro[2.5]cycloocta-4,7-dien-6-ones, with a variety of nucleophiles was studied. The products, functionalized salicylates, are of considerable pharmacological relevance and occur in a variety of natural products and their analogues (e.g., salicylic acids, esters and glycosides) and in synthetic drugs (e.g., aspirin©).[8] These products are mostly not available by direct cyclization of bis-silyl enol ethers with 1,1-diacylcyclopropanes. The work reported herein offers a convenient approach to functionalized spiro[2.5]cyclooct-4-en-3-ones and represents a significant extension of known syntheses of functionalized salicylates.

The cyclization of the dianions of methyl acetoacetate and acetylacetone, generated by LDA,[9] with 1,1-diacetylcyclopropane (**3**)[10] afforded the 1-hydroxyspiro[5.2]cyclooct-4-en-3-ones **4b** and **4d**, respectively. During the optimization, the use of an excess of the dianion (2 equiv) proved to be an important parameter. The application of 1,3-bis-silyl enol ethers **2**, which can be regarded as masked dianions,[11,12] was studied next. The cyclization of **2a** with **3** in the presence of $TiCl_4$ (0.3–0.5 equiv) allowed the synthesis of 1-hydroxyspiro[5.2]cyclooct-4-en-3-one **4a** in 50% yield.[13] The use of more than 0.5 equiv of $TiCl_4$ resulted in cleavage of

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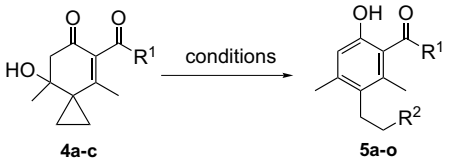
the cyclopropane moiety and formation of salicylate **5d** (vide infra). The yield significantly decreased when less than 0.3 equiv of $TiCl_4$ or a different Lewis acid was employed. Spiro[5.2]cyclooctenones **4b** and **4c** were prepared in 55% and 57% yield, respectively. The acetylacetone derived product **4d** was obtained in 15% yield. Our preliminary results show that the use of dianions is particularly useful for 1,3-diketones whereas the use of bis-silyl enol ethers are more suitable for β-ketoesters (Scheme 1).

Treatment of **4a** with trifluoroacetic acid (TFA) resulted in formation of the trifluoroacetate **5a**.[14] The formation of **5a** can be explained by elimination of water to give a spiro[2.5]cycloocta-4,7-dien-6-one, followed by attack of TFA onto the cyclopropane moiety (Scheme 2). Despite the poor nucleophilicity of TFA, **5a** was isolated in 95% yield. All attempts to directly prepare **5a** by TFA-mediated cyclization of **2a** with **3** were unsuccessful and resulted in the formation of complex mixtures.

The reaction of 1-hydroxyspiro[2.5]cyclooct-4-en-3-ones **4** with other nucleophiles was studied (Scheme 3, Table 1). Treatment of a $CH_2Cl_2$ solution of **4b** with $TiF_4$ afforded the fluoride **5b**. Likewise, treatment of **4a** with $TiCl_4$ afforded the chloride **5d** in moderate yield. The reaction of **4c** and **4a** with $TiBr_4$ and $TiI_4$ afforded the halides **5f** and **5h**, respectively. The chlorination of **4c** with $Bu_4NCl$ in the presence of calalytic amount of $BF_3{\cdot}OEt_2$ afforded **5e** in very good yield. Likewise, the reaction of **4c** and **4b** with $Bu_4NBr$ and $Bu_4NI$ afforded **5f** and **5h** in high yields, respectively. The reaction of **4c** with $Bu_4NF$ in presence of $BF_3{\cdot}OEt_2$, however, failed to give the desired product **5c**. Treatment of a $CH_2Cl_2$ solution of **4c** with *p*-toluenesulfonic acid (TsOH) afforded the tosylate **5i**. The reaction of **4c** with glacial acetic acid (AcOH) afforded the acetate **5j**. The addition of $BF_3{\cdot}OEt_2$ was required, presumably due to the relatively low acidity of AcOH. The reaction of a methanol solution of **4b** with sulfuric acid afforded the alcohol **5k** rather than the expected methyl ether. In contrast, the ethyl ether **5l** was obtained by reaction of **4a** with ethanol in the presence of $BF_3{\cdot}OEt_2$. The replacement of the latter by TFA resulted in formation of **5l**, however, in low yield. In contrast, the TFA-mediated reaction of **4b** with hydroxybenzene gave the ether **5m**. Likewise, the TFA-mediated reaction of **4a** with thiohydroxybenzene afforded the sulfide **5n**. The $BF_3{\cdot}OEt_2$ mediated

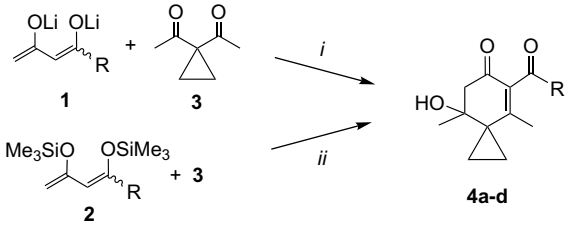



**Scheme 3.** Synthesis of functionalized salicylates **5**.

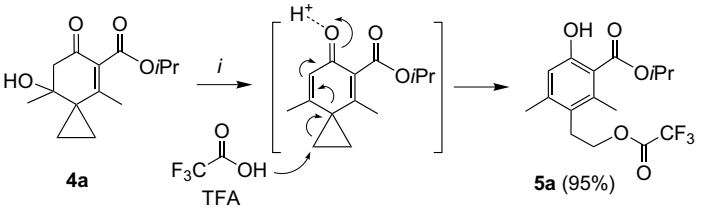
**Table 1.** Reactions of spiro[5.2]cyclooctenones **4**

| 5 | $R^1$ | $R^2$ | Conditions | % (5)[a] |
|---|---|---|---|---|
| **a** | O*i*Pr | $O_2CCF_3$ | TFA, $CH_2Cl_2$ | 95 |
| **b** | OMe | F | $TiF_4$, $CH_2Cl_2$ | 26 |
| **c** | OEt | F | $Bu_4NF$, $CH_2Cl_2$, $BF_3{\cdot}OEt_2$ | 0 |
| **d** | O*i*Pr | Cl | $TiCl_4$, $CH_2Cl_2$ | 53 |
| **e** | OEt | Cl | $Bu_4NCl$, $CH_2Cl_2$, $BF_3{\cdot}OEt_2$ | 84 |
| **f** | OEt | Br | $TiBr_4$ | 94 |
| **f** | OEt | Br | $Bu_4NBr$, $CH_2Cl_2$, $BF_3{\cdot}OEt_2$ | 96 |
| **g** | O*i*Pr | I | $TiI_4$, $CH_2Cl_2$ | 47 |
| **h** | OMe | I | $Et_4NI$, $CH_2Cl_2$, $BF_3{\cdot}OEt_2$ | 96 |
| **i** | OEt | OTos | TsOH, $CH_2Cl_2$ | 61 |
| **j** | OEt | OAc | AcOH, $CH_2Cl_2$, $BF_3{\cdot}OEt_2$ | 79 |
| **k** | OMe | OH | $H_2SO_4$, MeOH | 40 |
| **l** | O*i*Pr | OEt | $BF_3{\cdot}OEt_2$, EtOH | 61 |
| **m** | OMe | OPh | PhOH, TFA, $CH_2Cl_2$ | 57 |
| **n** | O*i*Pr | SPh | PhSH, TFA | 70 |
| **o** | OEt | CH=$CH_2$ | BrMgCH=$CH_2$, THF, $BF_3{\cdot}OEt_2$, $CH_2Cl_2$ | 33 |

[a] Yield of isolated product.




**Scheme 1.** Synthesis of 1-hydroxyspiro[2.5]cyclooct-4-en-3-ones; (i) **1** (2 equiv), **3** (1 equiv), THF, $-78 \rightarrow 20$ °C, 12 h, 20 °C, 12 h, yields: **4b** (R = OMe): 16%, **4d** (R = Me): 36%; (ii) $TiCl_4$ (0.3 equiv), $CH_2Cl_2$, molecular sieves (4 Å), $-78 \rightarrow 20$ °C, 12 h, yields: **4a** (R = O*i*Pr): 50%, **4b** (R = OMe): 55%, **4c** (R = OEt): 57%, **4d** (R = Me): 15%.




**Scheme 2.** Reaction of **4a** with TFA; (i) TFA, $CH_2Cl_2$, 20 °C, 4 h.

reaction of **4c** with vinyl magnesium bromide afforded **5o**.

Reactions of acceptor substituted cyclopropanes have been discussed by Danishefsky in terms of 'strictly nucleophilic ring openings', 'electrophilically assisted ring openings' and 'spiro-activation'.[2] According to Zefirov et al.[15] the reactions reported herein can be classified as being enhanced by 'dynamic spiro-activation', which allows a rationale of the unusually[15] mild cyclopropane ring opening.

## Acknowledgements

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## References and notes

1. (a) Houben-Weyl In *Carbocyclic Three-Membered Ring Compounds,* 4th ed.; de Meijere, A., Ed.; *Methoden der Organischen Chemie*; Thieme: Stuttgart, 1996; Vol. E17; (b) *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley: Chichester, 1987.
2. Danishefsky, S. J. *Acc. Chem. Res.* **1979**, 66.
3. (a) Baird, R.; Winstein, S. *J. Am. Chem. Soc.* **1957**, *79*, 4238; (b) Baird, R.; Winstein, S. *J. Am. Chem. Soc.* **1963**, *85*, 574.
4. (a) Woolhouse, A. D. *Aust. J. Chem.* **1977**, *30*, 1145; (b) Schuster, D. I.; Polowczyk, C. J. *J. Am. Chem. Soc.* **1966**, *88*, 1722; (c) Phillips, J. P.; Gillmore, J. G.; Schwartz, P.; Brammern, L. E., Jr.; Berger, D. J.; Tanko, J. M. *J. Am. Chem. Soc.* **1998**, *120*, 195; (d) for matrix isolation of tetrafluorospiro[2.5]cycloocta-4,7-dien-6-one: Sander, W.; Koetting, C.; Huebert, R. *J. Phys. Org. Chem.* **2000**, *13*, 561.
5. (a) Ward, R. S.; Thatcher, K. S. *Tetrahedron Lett.* **1981**, *22*, 4831; (b) Kende, A. S.; Hebeisen, P.; Sanfilippo, P. J.; Toder, B. H. *J. Am. Chem. Soc.* **1982**, *104*, 4244; (c) Schultz, A. G.; Taveras, A. G. *Tetrahedron Lett.* **1996**, *37*, 5853.
6. (a) Bryson, T. A.; Roth, G. A. *Tetrahedron Lett.* **1988**, *29*, 2167; (b) Boger, D. L.; Johnson, D. S. *J. Am. Chem. Soc.* **1990**, *112*, 5832; (c) Boger, D. L.; Garbaccio, R. M.; Jin, Q. *J. Org. Chem.* **1997**, *62*, 8875; (d) Boger, D. L.; Boyce, C. W.; Carpaccio, R. M.; Goldberg, J. A. *Chem. Rev.* **1997**, *97*, 787; (e) Tietze, L. F.; Hannemann, R.; Buhr, W.; Lögers, M.; Menningen, P.; Lieb, M.; Starck, D.; Grote, T.; Döring, A.; Schuberth, I. *Angew. Chem.* **1996**, *108*, 2840; *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2674; (f) Tietze, L. F.; Buhr, W.; Looft, J.; Grote, T. *Chem. Eur. J.* **1998**, *4*, 1554.
7. Langer, P.; Bose, G. *Angew. Chem.* **2003**, *115*, 4165; *Angew. Chem. Int. Ed.* **2003**, *42*, 4033.
8. *Römpp Lexikon Naturstoffe*; Steglich, W., Fugmann, B., Lang-Fugmann, S., Eds.; Thieme: Stuttgart, 1997.
9. Weiler, L. *J. Am. Chem. Soc.* **1970**, *92*, 6702.
10. The starting materials were prepared according to a known procedure: Zefirov, N. S.; Kuznetsova, T. S.; Kozhushkov, S. I.; Surmina, L. S.; Rakina, Z. A. *Zh. Org. Khim.* **1983**, *19*, 541.
11. (a) Chan, T.-H.; Brownbridge, P. *J. Chem. Soc., Chem. Commun.* **1979**, 578; (b) Chan, T.-H.; Brownbridge, P. *J. Am. Chem. Soc.* **1980**, *102*, 3534; (c) Molander, G. A.; Cameron, K. O. *J. Am. Chem. Soc.* **1993**, *115*, 830.
12. For a review of 1,3-bis-silyl enol ethers, see: Langer, P. *Synthesis* **2002**, 441.
13. Synthesis of **4b**: $TiCl_4$ (0.05 mL in 1 mL $CH_2Cl_2$, 0.45 mmol) was added dropwise at −78 °C under argon atmosphere to a stirred solution of **3** (0.190 g, 1.5 mmol) and **2b** (0.580 g, 2.2 mmol) in $CH_2Cl_2$ (100 mL) in the presence of molecular sieves (4 Å; 1.0 g). The reaction mixture was allowed to warm to 20 °C over 6 h, was stirred for additional 6 h at 20 °C and was then filtered. The filtrate was poured into an aqueous solution of HCl (1.0 M, 100 mL). The organic layer was collected, and the aqueous was extracted with $CH_2Cl_2$ (3 × 100 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane–ethylacetate = 1:4 → 1:1) to give **4b** (0.186 g, 55%) as a colourless solid; mp 108–109 °C; $R_f = 0.13$ (ethylacetate–hexane 1:4); $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 3.81$ (s, 3H, $CH_3$), 2.72 (d, 1H, $J = 15.6$ Hz, $CH_2$), 2.62 (d, 1H, $J = 15.6$ Hz, $CH_2$), 2.24 (s, 1H, OH), 1.69 (s, 3H, $CH_3$), 1.50–1.43 (m, 1H, $CH_2$), 1.26 (s, 3H, $CH_3$), 1.17–1.06 (m, 2H, $CH_2$), 0.89–0.85 (m, 1H, $CH_2$); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 194.06$, 167.61, 161.79, 132.61, 70.36 (C), 52.24 ($CH_3$), 51.29 ($CH_2$), 32.16 (C), 25.26, 17.04 ($CH_3$), 10.98, 9.54 ($CH_2$); IR (KBr): $\tilde{\nu} = 2950$ (w), 1715 (s), 1669 (s), 1606 (w), 1439 (m), 1383 (m), 1248 (m), 1160 (w) cm$^{-1}$; MS (EI, 70 eV): $m/z$ (%): 224.1 ($M^+$, 40), 209.0 (30), 177 (48), 164.1 (69), 148.3 (48), 79.2 (30), 43.1 (100), 28.0 (37); elemental analysis calcd (%) for $C_{12}H_{16}O_4$ (224.25): C 64.27, H 7.19; found: C 63.74, H 7.71.
14. Synthesis of **5a**: TFA (0.04 mL, 0.52 mmol) was added dropwise at 20 °C to a stirred solution of **4a** (0.064 g, 0.25 mmol) in $CH_2Cl_2$ (1.0 mL) and the reaction mixture was stirred for 4 h (monitored by TLC). The solvent and TFA were removed in vacuo and the residue was purified by column chromatography (silica gel, hexane/ethylacetate = 1:19) to give **5a** (0.084 g, 95%) as a colourless solid; mp 32–33 °C; $R_f = 0.58$ (ethylacetate–hexane 1:9); $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 10.77$ (s, 1H, OH), 6.71 (s, 1H, ArH), 5.32 (sep, 1H, $J = 6.3$ Hz, OCH), 4.37 (t, 2H, $J = 8.1$ Hz, $CH_2F$), 3.08 (t, 2H, $J = 8.1$ Hz, $CH_2$), 2.53 (s, 3H, $CH_3$), 2.35 (s, 3H, $CH_3$), 1.40 (d, 3H, $J = 6.3$ Hz, $CH_3$), 1.39 (d, 3H, $J = 6.3$ Hz, $CH_3$); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 170.79$ (2C), 160.33, 157.47 (q, $J = 42.1$ Hz, $CF_3$), 144.09, 139.25, 124.54 (C), 117.33 (CH), 112.53 (C), 69.80 (CH), 66.27, 27.93 ($CH_2$), 21.89 (2C), 20.93, 18.61 ($CH_3$); IR (KBr): $\tilde{\nu} = 2959$ (s), 1786 (m), 1657 (s), 1453 (s), 1375 (s), 1166 (s), 1105 (m) cm$^{-1}$; MS (EI, 70 eV): $m/z$ (%): 348.6 ($M^+$, 68), 306.4 (41), 288.6 (100), 161.2 (93), 91.1 (31), 43.1 (34); the exact molecular mass for $C_{16}H_{19}O_5F_3$; $m/z = 348.1185 \pm 2$ mD ($M^+$) was confirmed by HRMS (EI, 70 eV).
15. Zefirov, N. S.; Kozhushkov, S. I.; Kuznetsova, T. S. *Tetrahedron* **1982**, *38*, 1693.