Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 49 (2008) 2254–2257
Tetrahedron Letters

Synthesis and reactions of hydroxyspiro[5.2]cyclooctenones based on the cyclization of the dianions of acetone and diethyl 2-oxopropylphosphonate with 1,1-diacylcyclopropanes

Nasir Rasool [a], Muhammad A. Rashid [a], Muhammad Adeel [a], Helmar Görls [c], Peter Langer [a,b,*]

[a] Institut für Chemie, Universität Rostock, Albert-Einstein-Str. 3a, 18059 Rostock, Germany
[b] Leibniz-Institut für Katalyse e. V.an der Universität Rostock, Albert-Einstein-Str. 29a, 18059 Rostock, Germany
[c] Institut für Anorganische und Analytische Chemie, Universität Jena, Lessingstraße 8, D-07743 Jena, Germany

Received 5 December 2007; revised 4 February 2008; accepted 6 February 2008
Available online 12 February 2008

Abstract

The cyclization of the dianions of diethyl 2-oxopropylphosphonate and of acetone with 1,1-diacylopropanes afforded hydroxyspiro[5.2]cyclooctenones which were transformed, by homo-Michael reactions with tetrabutylammonium halides, into various functionalized phenols or their dimers.

Keywords: Cyclizations; Cyclopropanes; Dianions; Regioselectivity; Spiro-compounds

Spirocyclopropanes are present in a number of pharmacologically interesting natural products, such as the cytotoxic illudins (Fig. 1),[1] CC-1065, or duocarmycin SA.[2] The illudins belong to the group of alkylating anticancer agents. The reaction of a nucleophile (such as glutathione) with the unsaturated ketone moiety results in the formation of a cyclohexadiene which rapidly undergoes an aromatization with concurrent ring opening of the cyclopropane moiety and alkylation of the DNA.[1] We have reported the $TiCl_4$-mediated domino '[3+3]-cyclization-homo-Michael' reaction of 1,3-bis(silyl enol ethers) with 1,1-diacylcyclopropanes.[3] These reactions proceed by in situ formation of spiro[2.5]cycloocta-4,7-dien-6-ones which are subsequently cleaved by the action of $TiCl_4$. In their pioneering work, Baird and Winstein studied the synthesis of spiro[2.5]cycloocta-4,7-dien-6-ones and their reaction with various nucleophiles.[4] Padwa and co-workers reported interesting cyclization reactions of diazo-compounds which allow a convenient synthesis of illudins.[5] Recently, we have reported[6] the synthesis of ester-substituted 1-hydroxyspiro[5.2]cyclooct-4-en-3-ones, precursors of spiro[2.5]cycloocta-4,7-dien-6-ones, based on cyclization reactions of 1,3-dicarbonyl dianions. The homo-Michael reaction of these highly activated[7,8] spirocyclopropanes, which exhibit a considerable anti-proliferative activity against human leukemia HL60 cells, with various nucleophiles results in the formation of functionalized phenols. This

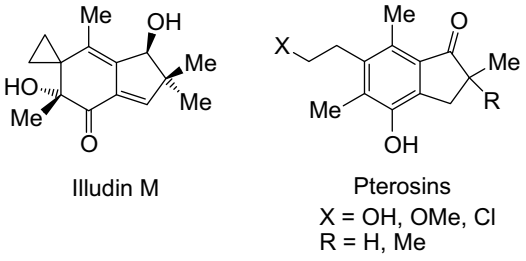


Fig. 1.

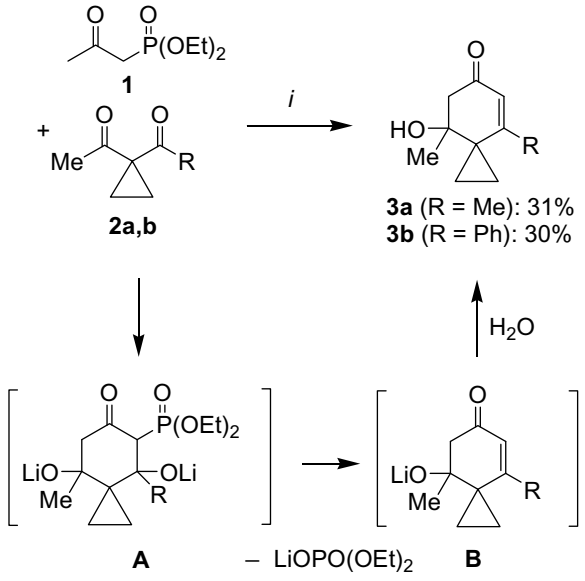
* Corresponding author. Tel.: +49 381 4986410; fax: +49 381 4986412.
E-mail address: peter.langer@uni-rostock.de (P. Langer).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.02.036

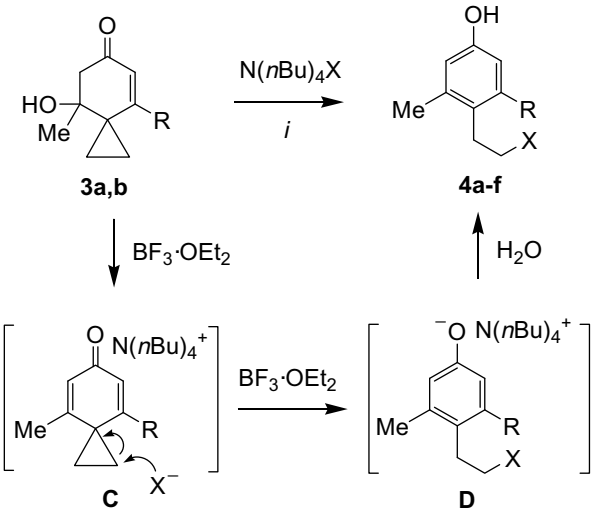
transformation is related to the biosynthesis of the carcinogenic pterosins (Fig. 1), which were isolated from the bracken fern *Pteridium aquilinium*.[9] It was shown earlier that the pterosins are formed from their direct biogenetic precursor, the spirocyclopropane ptaquilosin, by treatment with acid. It was proposed that the pterosins, ptaquilosin and illudin M are all formed from farnesyl phosphate via a common biosynthetic intermediate.[1,9] Herein, we report what are, to the best of our knowledge, the first cyclizations of the dianions of diethyl 2-oxopropylphosphonate and of acetone with 1,1-diacylcyclopropanes. These reactions provide a convenient access to hydroxyspiro[5.2]cyclooctenones. Homo-Michael reactions of these products with tetrabutylammonium halides allow for a convenient synthesis of functionalized phenols which are not readily available by other methods.

The cyclization[6] of the dianion[10,11] of diethyl 2-oxopropylphosphonate (**1**), generated by means of LDA, with 1,1-diacetylcyclopropane (**2a**) and 1-acetyl-1-benzoylcyclopropane (**2b**) afforded the 1-hydroxyspiro[5.2]cyclooct-4-en-3-ones **3a** and **3b**, respectively (Scheme 1). The formation of **3a**,**b** can be explained by cyclization (intermediate **A**), elimination of lithium diethylphosphate (intermediate **B**) and subsequent protonation upon the addition of water. The reaction can be regarded as a domino 'aldol/Horner–Wadsworth–Emmons (HWE)' reaction.

The $BF_3{\cdot}OEt_2$-mediated reaction of **3a**,**b** with tetrabutylammonium halides afforded the phenols **4a**–**f** containing a halogenated side chain (Scheme 2, Table 1). Products **4a**–**f** were presumably formed by $BF_3{\cdot}OEt_2$-mediated elimination of water to give a highly reactive spiro[2.5]cycloocta-4,7-dien-6-one (intermediate **C**). The cyclopropane moiety is subsequently cleaved by $BF_3{\cdot}OEt_2$-mediated attack of the halide ion to give a phenolate (intermediate **D**), which is protonated upon the addition of water (aqueous work-up).[6]



Scheme 1. Synthesis of spirocyclopropanes **3a**,**b**. Reagents and conditions: (i) (1) LDA (2.0 equiv), **1** (1.0 equiv), THF, 1 h, 0 °C; (2) **2a**,**b** (1.0 equiv), −78→20 °C, 14 h.



Scheme 2. Reaction of **3a**,**b** with nBu$_4$NX. Reagents and conditions: (i) nBu$_4$NX (1.0 equiv), $BF_3{\cdot}OEt_2$(0.5 equiv), −78→20 °C, 12 h.

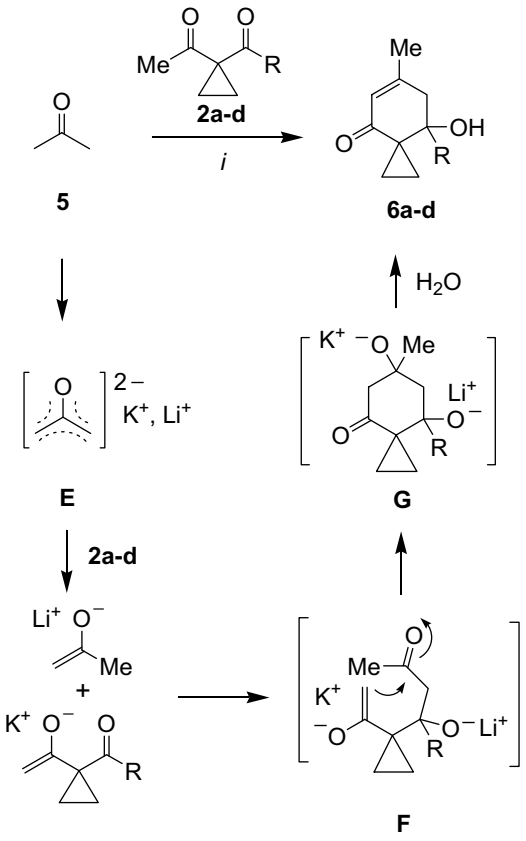
Table 1
Synthesis of phenols **4a**–**f**

4	R	X	Yield[a] (%)
a	Me	Cl	73
b	Me	Br	68
c	Me	I	63
d	Ph	Cl	70
e	Ph	Br	75
f	Ph	I	81

[a] Isolated products.

The cyclization of 1,1-diacylcyclopropanes **2a**–**d** with the dianion[11,12] of acetone (**5**), generated by the addition of **5** to a THF-suspension of potassium hydride and subsequent addition of TMEDA and nBuLi, afforded the 1-hydroxyspiro[5.2]cyclooct-3-en-5-ones **6a**–**d** (Scheme 3, Table 2). The unexpected formation **6a**–**d**, which are regioisomers of products **3a**,**b**, can be explained as follows: the reaction of dianion **E** with **2a**–**d** resulted in internal protonation. The attack of the monoanion of acetone onto the enolate of **2a**–**d** afforded intermediate **F**. The latter underwent a cyclization to give **G** which afforded **6a**–**d** upon aqueous work-up. Products **6b**–**d** were formed by regioselective attack of dianion **E** onto the aroyl rather than the acetyl group of **2b**–**d**. This result can be explained based on the mechanism suggested. Alternatively, a direct attack of dianion **E** onto **2a**–**d** can be discussed. However, this mechanism is less likely as the first attack of **E** should occur onto the more reactive acetyl rather than the benzoyl group.

The $BF_3{\cdot}OEt_2$-mediated reaction of **6a** with tetrabutylammonium halides afforded the phenols **7a**–**c** (Scheme 4, Table 3).[13] Their formation can be explained by a

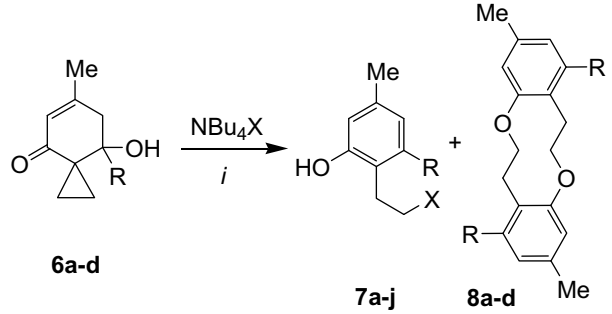


Scheme 3. Synthesis of **6a–d**. Reagents and conditions: (i) (1) KH, THF, 0 °C; (2) *n*BuLi, TMEDA, −20 °C; (3) **2a–d** −30→15 °C, 15 h.

Table 2
Synthesis of spirocyclopropanes **6a–d**

6	R	Yield[a] (%)
a	Me	41
b	Ph	33
c	4-ClC_6H_4	31
d	4-FC_6H_4	30

[a] Isolated products.



Scheme 4. Reaction of **6a–d** with nBu_4NX. Reagents and conditions: (i) nBu_4NX (1.0 equiv), $BF_3{\cdot}OEt_2$ (0.5 equiv), −78→20 °C, 12 h.

mechanism related to the one discussed for **4a–f** (vide supra). The structure of **7a** was independently confirmed by X-ray crystal structure analysis (Fig. 2).[14] The $BF_3{\cdot}OEt_2$-mediated reaction of **6b** with tetrabutylammonium chloride resulted in the formation of the halogen-free 10-membered cyclic diether **8b** in 66% yield. The employment of tetrabutylammonium bromide and iodide afforded **8b** in 63% and 79% yield, respectively. The formation of **8b** can be explained by direct opening of the cyclopropane moiety of one molecule of **6b** with the oxygen of another molecule, followed by cyclization. The reaction of spirocyclopropane **6c** with tetrabutylammonium bromide afforded a separable mixture of phenol **7g** (30%) and dimer **8c** (51%). The employment of tetrabutylammonium iodide resulted in the formation of phenol **7h** and dimer **8c** in 33% and 59% yield, respectively. The reaction of spirocyclopropane **6d** with tetrabutylammonium chloride gave exclusively dimer **8d** (50%), whereas phenol **7j** (41%) was isolated when tetrabutylammonium iodide was used. This result can be explained by the higher nucleophilicity of iodide compared to chloride. The attack of the iodide ion onto the cyclopropane moiety is more rapid than the attack of the oxygen atom of another molecule. In conclusion, the product distribution seems to depend on the substituent R and on the tetraammonium halide employed.

Table 3
Synthesis of phenols **7** and their dimers **8**

7	8	R	X	Yield (%) (**7**)[a]	Yield (%) (**8**)[a]
a	**a**	Me	Cl	65	0
b	**a**	Me	Br	77	0
c	**a**	Me	I	81	0
d	**b**	Ph	Cl	0	66
e	**b**	Ph	Br	0	63
f	**b**	Ph	I	0	79
g	**c**	4-ClC_6H_4	Br	30	51
h	**c**	4-ClC_6H_4	I	33	59
i	**d**	4-FC_6H_4	Cl	0	50
j	**d**	4-FC_6H_4	I	41	0

[a] Isolated products.

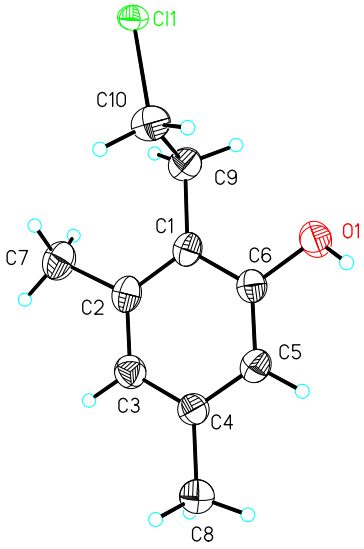


Fig. 2. Ortep plot of **7a**.

In conclusion, the cyclization of 1,1-diacylopropanes with the dianions of diethyl 2-oxopropylphosphonate and acetone afforded hydroxyspiro[5.2]cyclooctenones which were transformed, by homo-Michael reactions, into functionalized phenols or their dimers. The preparative scope and applications of the methodology reported is currently being studied.

Acknowledgement

Financial support by the State of Pakistan (scholarships for M.A.R. and N.R.) is gratefully acknowledged.

References and notes

1. (a) Saever, F. J. *J.N.Y. Bot. Garden* **1938**, 263; (b) Seaver, F. J. *J.N.Y. Bot. Garden* **1939**, 236; (c) Nakanishi, K.; Tada, M.; Yamada, Y.; Ohashi, M.; Komatsu, N.; Terekawa, H. *Nature* **1963**, *197*, 292; (d) Anchel, M.; Hervey, A.; Robbins, W. J. *Proc. Natl. Acad. Sci. U.S.A.* **1950**, *36*, 300; (e) McMorris, T. C.; Anchel, M. *J. Am. Chem. Soc.* **1963**, *85*, 831; (f) McMorris, T. C.; Anchel, M. *J. Am. Chem. Soc.* **1965**, *87*, 1594; (g) Ayer, W. A.; Browne, L. M. *Tetrahedron* **1981**, *37*, 2199; (h) McMorris, T. C.; Kelner, M. J.; Wang, W.; Estes, L. A.; Montoya, M. A.; Taetle, R. *J. Org. Chem.* **1992**, *57*, 6876; for the synthesis of an illudinoid library see: (i) Pirrung, M. C.; Liu, H. *Org. Lett.* **2003**, *5*, 1983.
2. (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; (f) Tietze, L. F.; Hannemann, R.; Buhr, W.; Lögers, M.; Menningen, P.; Lieb, M.; Starck, D.; Grote, T.; Döring, A.; Schuberth, I. *Angew. Chem., Int. Ed.* **1996**, *35*, 2674; (g) Tietze, L. F.; Buhr, W.; Looft, J.; Grote, T. *Chem. Eur. J.* **1998**, *4*, 1554.
3. (a) Langer, P.; Bose, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4033; (b) Bose, G.; Nguyen, V. T. H.; Ullah, E.; Lahiri, S.; Görls, H.; Langer, P. *J. Org. Chem.* **2004**, *69*, 9128.
4. (a) Baird, R.; Winstein, S. *J. Am. Chem. Soc.* **1957**, *79*, 4238; (b) Baird, R.; Winstein, S. *J. Am. Chem. Soc.* **1963**, *85*, 574; (c) Woolhouse, A. D. *Aust. J. Chem.* **1977**, *30*, 1145; (d) Schuster, D. I.; Polowczyk, C. J. *J. Am. Chem. Soc.* **1966**, *88*, 1722; (e) 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; (f) Ward, R. S.; Thatcher, K. S. *Tetrahedron Lett.* **1981**, *22*, 4831; (g) Kende, A. S.; Hebeisen, P.; Sanfilippo, P. J.; Toder, B. H. *J. Am. Chem. Soc.* **1982**, *104*, 4244; (h) Schultz, A. G.; Taveras, A. G. *Tetrahedron Lett.* **1996**, *37*, 5853.
5. Padwa, A.; Curtis, E. A.; Sandanayaka, V. P. *J. Org. Chem.* **1996**, *61*, 73.
6. (a) Bose, G.; Bracht, K.; Bednarski, P. J.; Lalk, M.; Langer, P. *Bioorg. Med. Chem.* **2006**, *14*, 4694; (b) for the synthesis of **4a–c**, see: Rasool, N.; Rashid, M. A.; Reinke, H.; Fischer, C.; Langer, P. *Tetrahedron* **2008**, in print.
7. (a) Houben-Weyl, Methoden der Organischen Chemie, In *Carbocyclic Three-Membered Ring Compounds*, 4th ed.; de Meijere, A., Ed.; Thieme: Stuttgart, 1996; Vol. E17; (b) Houben-Weyl, *The Chemistry of the Cyclopropyl Group*, Rappoport, Z., Ed.; Wiley: Chichester, 1987.
8. Reactions of acceptor-substituted cyclopropanes have been classified by Danishefsky in terms of 'strictly nucleophilic ring openings', 'electrophilically assisted ring openings' and 'spiro-activations': Danishefsky, S. J. *Acc. Chem. Res.* **1979**, 66. In the domino '[3+3]-cyclization-homo-Michael' reaction reported herein two effects are operating: (a) a 'dynamic spiro-activation' and (b) activation by an electrophile. For a dynamic spiro activation, see: Zefirov, N. S.; Kozhushkov, S. I.; Kuznetsova, T. S. *Tetrahedron* **1982**, *38*, 1693.
9. (a) McMorris, T. C.; Voeller, B. *Phytochemistry* **1971**, *10*, 3253; (b) Yoshishira, K.; Fukuoka, M.; Kuroyanagi, M.; Natori, S. *Chem. Pharm. Bull.* **1971**, *19*, 1491; (c) Bardouille, V.; Mootoo, B. S.; Hirotsu, K.; Clardy, J. *Phytochemistry* **1978**, *17*, 275; (d) Sengupta, P.; Sen, M.; Niyogi, S. K.; Pakrashi, S. C.; Ali, E. *Phytochemistry* **1976**, *15*, 995; (e) Yoshihira, K.; Fukuoka, M.; Kuroyanagi, M.; Natori, S.; Umeda, M.; Morohoshi, T.; Enomoto, M.; Saito, M. *Chem. Pharm. Bull.* **1978**, *26*, 2346.
10. Grieco, P. A.; Pogonowski, C. S. *J. Am. Chem. Soc.* **1973**, *95*, 3071.
11. For a review of ketone dianion chemistry, see: (a) Ryu, I.; Nakahira, H. In *The Chemistry of Organolithium Compounds*; Rappoport, A., Marek, I., Eds.; Wiley: West Sussex, 2006; Vol. 2. For a review of cyclization reactions of dianions, see: (b) Langer, P.; Freiberg, W. *Chem. Rev.* **2004**, *104*, 4125 and references cited therein.
12. Hubbard, J. S.; Harris, T. M. *J. Am. Chem. Soc.* **1980**, *102*, 2111.
13. *Typical procedure for the synthesis of functionalized phenols from spirocyclopropanes*: To a CH_2Cl_2 solution (15 mL) of 8-hydroxy-6,8-dimethylspiro[2.5]oct-5-en-4-one (**6a**) (334 mg, 2.0 mmol) and of nBu$_4$NCl (554 mg, 2.0 mmol) was dropwise added $BF_3{\cdot}OEt_2$ (0.24 mL, 2.0 mmol) at −78 °C under argon atmosphere. The solution was allowed to warm to 20 °C over 6 h and was stirred for additional 6 h at 20 °C. The solution was filtered and the filtrate was poured into hydrochloric acid (1.0 M). The organic and the aqueous layer were separated and the latter was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, hexane–EtOAc) to give **7a** as a colourless solid (242 mg, 65%). *2-(2-Chloroethyl)-3,5-dimethylphenol* (**7a**): ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.24 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.11 (t, 2H, $J = 8.0$ Hz, CH_2), 3.67 (t, 2H, $J = 7.4$ Hz, CH_2), 6.44 (s, 1H, ArH), 6.61 (s, 1H, ArH). ^{13}C NMR (62 MHz, $CDCl_3$): δ 19.4 (CH_3), 19.5 (CH_3), 30.2 (CH_2), 43.2 (CH_2), 113.8 (CH), 120.0 (C), 123.8 (CH), 137.5, 138.2, 153.8 (C). IR (KBr): $\tilde{\nu} = 3350$ (m), 3453 (S), 2870 (m), 1716 (s), 1632 (s), 1562 (m), 1439 (s), 1325 (m), 1142 (m), 1152 (s), 1122 (w), 834 (m), cm^{-1}. GC–MS (EI, 70 eV): m/z (%): 186 (M^+, ^{37}Cl, 9), 184 (M^+, ^{35}Cl, 21), 148 (6), 135 (100), 105 (11), 91 (13), 77 (14). HRMS (EI): calcd for $C_{10}H_{13}OCl$ [M^+, ^{35}Cl]: 184.06494, found: 184.06527.
14. CCDC-676879 contains all crystallographic details of this publication and are available free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or can be ordered from the following address: Cambridge Crystallographic Data Centre, 12 Union Road, GB-Cambridge CB21EZ; Fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk.