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Unusual behavior of 3-(dimethylamino)-1-(2-hydroxyphenyl)prop-2-en-1-one towards some phosphorus reagents: Synthesis of novel diethyl 2-phosphonochromone, diethyl 3-phosphonopyrone and 1,3,2-oxathiaphosphinines

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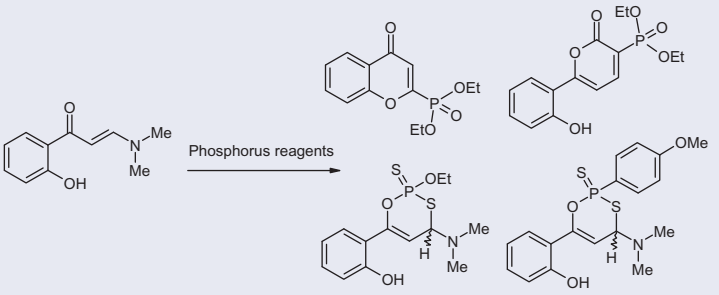
ABSTRACT

The chemical reactivity of 3-(dimethylamino)-1-(2-hydroxyphenyl)-prop-2-en-1-one (**1**) towards some phosphorus reagents was studied. The enaminone **1** was cyclized into diethyl 2-phosphonochromone **2** via its treatment with diethyl phosphite in basic medium. However, its reaction with triethoxy phosphonoacetate gave the substituted pyrone phosphonate **3**. In addition, two novel examples of 4-(dimethylamino)-6-(2-hydroxyphenyl)-2-sulfido-4*H*-1,3,2-oxathia-phosphinines **6** and **7** were obtained from treatment of enaminone **1** with *O,O*-diethyl dithiophosphoric acid and Lawesson's reagent. When enaminone **1** was also treated with phosphorus decasulfide, it was turned into 4*H*-thiochromene-4-thione while its treatment with phosphorus tribromide, phosphorus oxychloride, or phenylphosphonic dichloride, 4*H*-4-oxo-chromene was isolated in all cases. The possible reaction mechanisms of the formation of these products were discussed. The structures of newly isolated products were established by elemental analysis and spectral tools.

GRAPHICAL ABSTRACT



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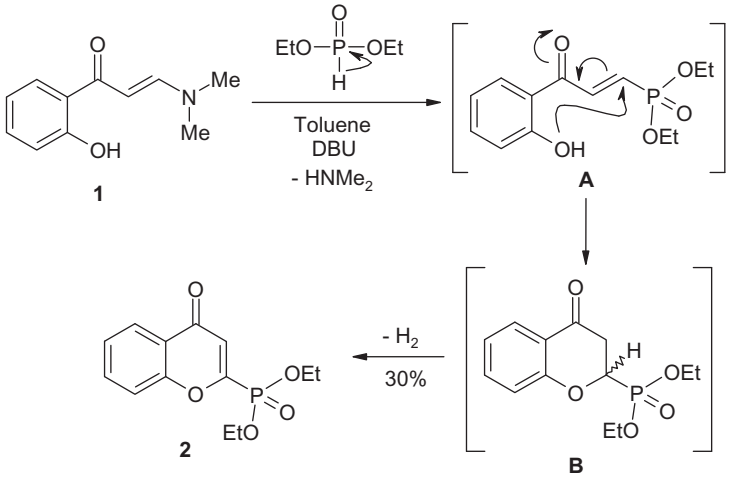
Introduction

Organophosphorus compounds are an important class of chemical substances with a variety of applications in biology, agriculture, and chemistry.[1–4] Phosphorus-containing heterocycles have been known since the late 19th century. However, a rapid development of studies, related to a variety of functionalized phosphorus heterocycles, especially structures having P–O, P–N, and P–S bonds,[5–7] began only in the middle of the last century, when the importance of phosphorus-containing substances in biological processes was fully recognized.[8–10] In addition, the phosphonate and thio-analog derivatives are usually more reactive and more toxic than the phosphate derivatives.[11] They have biological properties, which reflect many different aspects of their chemical structure.[12] Some recently discovered naturally-occurring phosphonates and thiophosphonates are described, together with some synthetic analogs. These synthetic analogs were utilized as tools for probing enzymic reaction[13] and inhibition of HIV virus by antisense oligonucleotides in patients suffering from AIDS.[14] On the other hand, enaminones are chemical compounds consisting of an amino group linked through a C=C to a carbonyl group. They are versatile synthetic intermediates that combine the ambident nucleophilicity of enamines with the ambident electrophilicity of enones.[15] The different chemical reactivities of the enaminones facilitated their reactions with a variety of electrophilic and nucleophilic reagents forming a series of the variable heterocycles.[16,17]

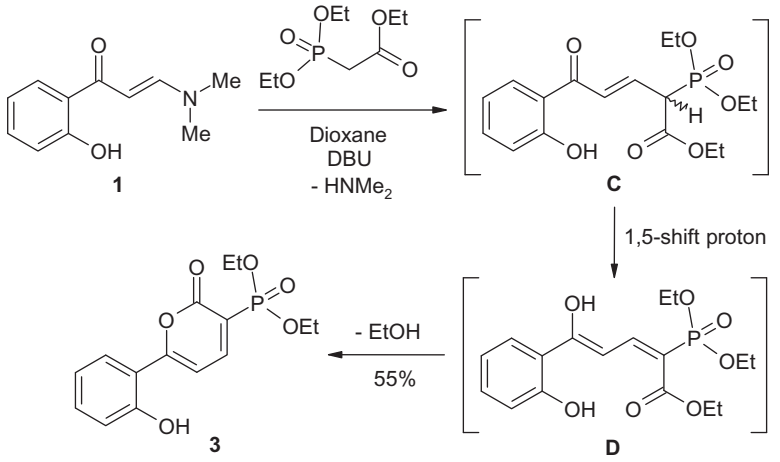
In this investigation, because of the importance of phosphonate and thio-analog derivatives, we studied the reactions of (2*E*)-3-(dimethylamino)-1-(2-hydroxyphenyl)-prop-2-en-1-one (**1**) towards some variable phosphorus reagents aiming to synthesize novel phosphonate or thiophosphonate containing heterocycles, which may be expected to be biologically active.

Results and discussion

The chemical reactivity of the enaminone **1**[18] towards diethyl phosphite and triethoxy phosphonoacetate as two examples of phosphorus esters was investigated. When compound **1** was allowed to react with diethyl phosphite in toluene containing a few drops of DBU as a basic catalyst, the reaction took place under the thermal condition and gave the novel diethyl (4-oxo-4*H*-chromen-2-yl)phosphonate (**2**) in low yield 30% (Scheme 1). The ^{31}P-NMR spectrum of product **2** had a singlet at δ 21.2 ppm.[19] Its ^{1}H-NMR spectrum exhibited a quartet at δ 4.18 (4 H, J = 7.2 Hz) and a triplet at δ 1.14 (6H, J = 7.2 Hz) assigned to the diethoxyphosphoryl group linked to the chromone ring. Moreover, the H–3 proton linked to the pyran ring appeared as a singlet at δ 6.51 ppm. The IR spectrum of **2** exhibited strong absorption bands at 1650 ($C{=}O_{pyrone}$), 1615 (C=C), 1228 (P=O), and 1026 (P–O–C) cm^{-1}. The chromonyl phosphonate **2** probably originated in a concerted nucleophilic addition of the diethyl phosphite to the enaminone via phospha-*Michael* addition reaction and removal of dimethylamine moiety to give the non-isolable intermediate **A**. The latter intermediate spontaneously underwent an intramolecular cycloaddition, followed by hydrogen elimination easily by air (Scheme 1).

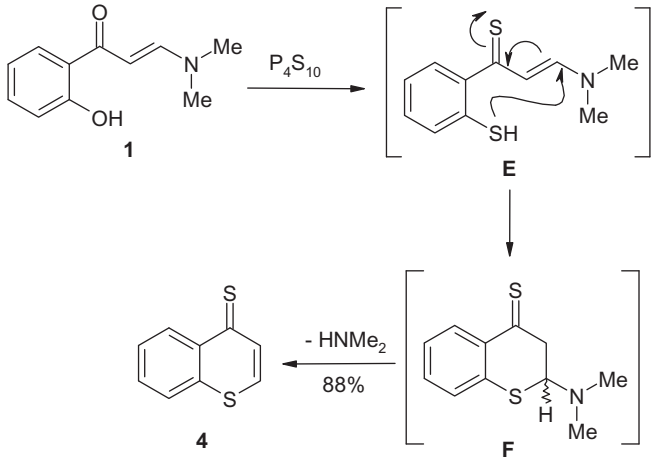


Scheme 1. Reaction of the enaminone **1** with diethyl phosphite.



Scheme 2. Reaction of the enaminone **1** with triethoxy phosphonoacetate.

In the same manner, the enaminone **1** reacted with triethoxy phosphonoacetate in toluene under the basic condition. On the basis of spectral data, the structure of the isolated product was identified as diethyl [6-(2-hydroxyphenyl)-2-oxo-2*H*-pyran-3-yl]phosphonate (**3**) in moderate yield (Scheme 2). Compound **3** showed the absorption bands at 1679 ($C{=}O_{pyrone}$), 1252 (P=O), and 1036 (P–O–C). Furthermore, the ^{31}P-NMR spectrum of compound **3** recorded a singlet at δ 22.8 ppm due to a phosphonate group. In its ^{1}H-NMR, the diethoxy moiety was displayed at δ 1.06 and 1.37 (t, J = 7.2 Hz, 6H, CH_3) and 3.76–3.82, 4.13–4.19 (m, 4H, CH_2) ppm, while the H–5 proton of pyrone ring was exhibited as a doublet at δ 6.66 ppm, with coupling constant 5.6 Hz. Moreover, the ^{13}C-NMR spectrum of **3** showed among others a doublet (J_{PC} = 174 Hz) at δ 119.6 ppm due to the C–P, whereas the $C{=}O_{pyrone}$ appeared at δ 167.7 ppm.

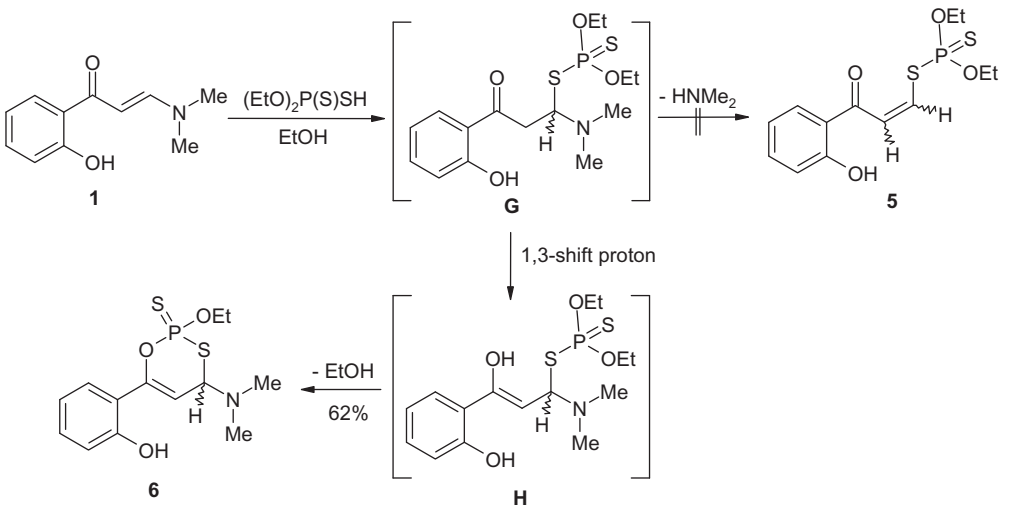


Scheme 3. Reaction of the enaminone **1** with P4S10 in toluene.

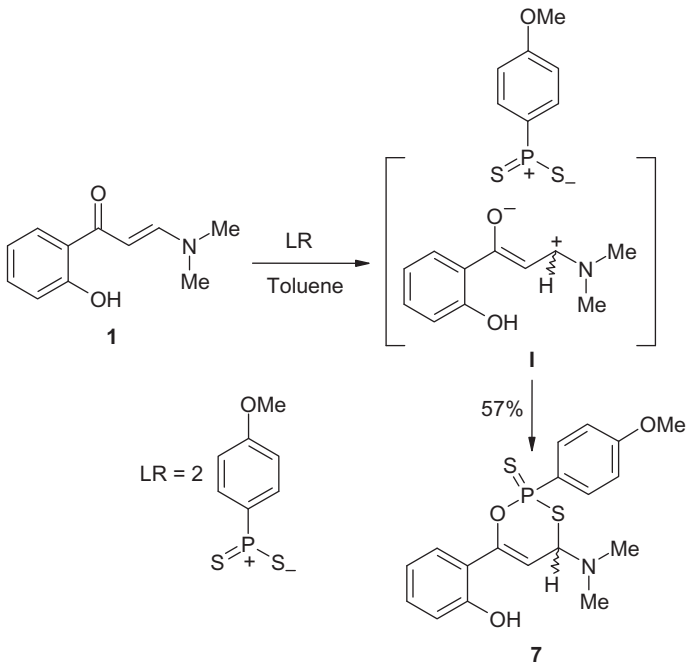
Compound **3** was properly formed through an initial attack of the carbanion *C*–atom of P-reagent on the *β*-carbon atom of allylic system of enaminone **1** in tandem loss of dimethylamine moiety forming the intermediate **C**. This intermediate underwent 1,5-proton shift, followed by further elimination of the ethyl alcohol molecule via an intramolecular cyclization (Scheme 2).[20]

Next, we studied the behavior of the enaminone **1** towards some phosphorus sulfides. The interaction of phosphorus decasulfide with compound **1** in dry toluene resulted in the formation of red crystals of the known 4*H*-thiochromene-4-thione (**4**) in high yield 88% yield (Scheme 3).[21–23] The reaction mechanism that outlined in Scheme 3 showed that compound **4** was formed through the thionation of carbonyl and hydroxyl groups, followed by an intramolecular cyclization and removal of dimethylamine molecule.

In addition, the interesting novel 1,3,2-oxathiaphosphinine derivative **6** was smoothly obtained in 62% yield from the reaction of enaminone **1** with *O,O*-diethyl dithiophosphoric acid (formed in *situ*) in absolute ethanol under thermal condition (Scheme 4). Obviously, the initial nucleophile attacks the thiol group of phosphorus reagent on *β*-carbon atom of the allylic system, forming the intermediate **G** without the elimination of dimethylamine molecule as an unusual behavior.[24] This latter intermediate underwent 1,3-proton shift, followed by elimination of ethanol molecule through the attack of enolic OH at the phosphonate moiety (Scheme 4). The structure of 1,3,2-oxathiaphosphinine **6** was supported by elemental analysis and spectral tools. The ^{1}H-NMR spectrum of **6** showed the OH proton at δ 10.10 ppm and two types of the methyl protons at δ 1.14 (3H, t, EtO) and 2.91, 2.94 (6H, s, NMe_2). In addition, the two protons of 1,3,2-oxathiaphosphinine ring appeared as two doublets at δ 6.02 and 6.68 ppm with coupling constant 7.2 Hz that indicated to their presence in *cis*-form. Besides, its ^{13}C-NMR spectrum displayed the characteristic carbon atoms of NMe_2 (43.2 and 44.2) and EtO (12.8 and 60.9) ppm, whereas the carbon atoms of 1,3,2-oxathiaphosphinine appeared at δ 68.3 (C–4), 93.6 (C–5), and 153.0 (C–6) ppm.

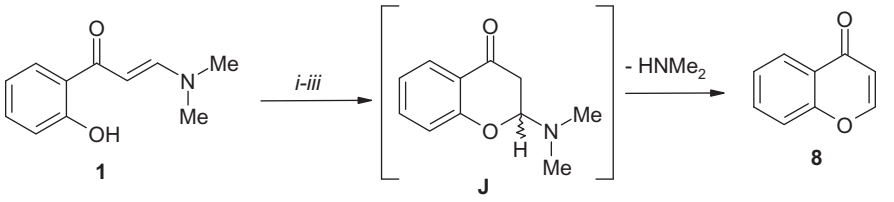


Scheme 4. Reaction of the enaminone **1** with P4S10 in absolute ethanol.



Scheme 5. Reaction of the enaminone **1** with LR in toluene.

Interestingly, the reaction of enaminone **1** with Lawesson's reagent (LR) in dry toluene, did not give the product **4** but it afforded 4-(dimethylamino)-6-(2-hydroxyphenyl)2-(4-methoxyphenyl)-2-sulfido-4*H*-1,3,2-oxathiaphosphinine (**7**) advantageously in 57% yield (Scheme 5). Compound **7** was regarded to be formed via one-step [4 + 2] cycloaddition mechanism as shown in Scheme 5. The ^{1}H-NMR spectrum of **7** showed that the protons of methyl groups at δ 2.94, 3.00 (NMe_2), and 3.89 (OMe) ppm.



Scheme 6. Reaction of the enaminone **1** with phosphorus halides in toluene.

The presence of a methoxy group in **7** was also attested by a signal at δ 54.9 ppm in its ^{13}C-NMR spectrum, whereas the dimethylamino group appeared at δ 43.4 and 44.2 ppm. The product **7** also showed a signal at δ 51.6 ppm in its ^{31}P-NMR spectrum.

As an extension of this study, the behavior of enaminone **1** towards some phosphorus halides was also investigated. Thus, the reaction of enaminone **1** with phosphorus tribromide, phosphorus oxychloride, or phenylphosphonic dichloride in dry toluene containing triethylamine did not give any phosphorylated product (Scheme 6). Instead the simple 4*H*-chromone (**8**) was formed in all cases.[18] The formation of compound **8** might be due to the preference of enaminone **2** to cyclize than to react with the phosphorus reagent that facilitated the cyclization process (Scheme 6).

Conclusion

In summary, we studied the interaction of 3-(dimethylamino)-1-(2-hydroxyphenyl)-prop-2-en-1-one (**1**) with some examples of phosphorus esters and sulfides. These reactions afforded novel phosphorus compounds such as chromonyl and pyranyl phosphonates as well as 1,3,2-oxathiaphosphinine derivatives. However, 4*H*-chromone and full thia analog were isolated when enaminone was treated with phosphorus halides and phosphorus decasulfide, respectively.

Experimental

The melting points were determined in an open capillary tube on a digital Stuart SMP-3 apparatus. Infrared spectra were measured on Perkin–Elmer 293 spectrophotometer using KBr disks. ^{1}H- and ^{13}C-NMR spectra were measured on Gemini-300BB spectrometer (400 and 100 MHz), using DMSO-d_6 as a solvent and TMS (δ) as an internal standard. ^{31}P-NMR spectra were measured on a Bruker (162 MHz) spectrophotometer using DMSO-d_6 as a solvent, TMS as an internal standard and 85% H_3PO_4 as an external reference. Mass spectra were recorded on direct probe controller inlet part to single quadropole mass analyzer in (thermo scientific GCMS). Elemental microanalysis was performed on Perkin–Elmer 2400II at the Chemical War department, Ministry of Defense. The purity of the synthesized compounds was checked by thin layer chromatography (TLC) and elemental microanalysis. 3-(Dimethylamino)-1-(2-hydroxyphenyl)-prop-2-en-1-one (**1**) was prepared according to the reported method rported in the literature.[18]

Synthesis of diethyl (4-oxo-4H-chromen-2-yl)phosphonate (2)

A mixture of 3-(dimethylamino)-1-(2-hydroxyphenyl)prop-2-en-1-one (**1**) (0.95 g, 5 mmol) and diethyl phosphite (0.7 mL, 5 mmol) in dry toluene (30 mL) containing a few drops of DBU as a catalyst, was heated under reflux for 10 hours. The solvent was concentrated into one-third of the volume. After adding petroleum ether (15 ml), the formed solid was filtered off, washed with ether and crystallized from diluted methanol to give pale yellow solid in 30% yield; mp 98 − 100 °C. IR (KBr), (ν max, cm^{-1}): 3055 (C−H_{arom}), 2950 (C−H_{aliph}), 1650 (C=O), 1615 (C=C), 1228 (P=O), 1026 (P−O−C). ^{1}H-NMR (400 MHz, DMSO-d_6): 1.14 (t, 6H, J = 7.2 Hz, CH_3), 4.18 (q, 4H, J = 7.2 Hz, OCH_2), 6.51 (s, 1H, H−3), 7.19 (t, 1H, J = 8 Hz, H−6), 7.47 (t, 1H, J=7.6 Hz, H−8), 7.59 (t, 1H, J=7.6 Hz, H−7), 7.89 (d, 1H, J=8.0 Hz, H−5). ^{13}C-NMR (100 MHz, DMSO-d_6): 16.4 (CH_3), 63.5 (OCH_2), 114.0 (C−3), 118.9 (C−8), 123.8 (C−6), 125.2 (C−4a), 129.6 (C−5), 134.8 (C−7), 156.9 (d, J=152 Hz, C − 2), 159.0 (C−8a), 177.5 (C−4). ^{31}P-NMR (162 MHz, DMSO-d_6): 21.8 ppm. MS (m/z, I%): 282 (M^+, 10%). Anal. Calcd for $C_{13}H_{15}O_5P$ (282.24): C, 55.32%; H, 5.36%. Found: C, 55.01%; H, 5.03%.

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References

[1] Holla, B. S.; Ashok, M. *Phosphorus, Sulfur Silicon Relat. Elem.* **2007**, *182*, 981–991. DOI: 10.1080/10426500601088853.
[2] Eugenia, F. C.; Laichici, M.; Gheorghe, F. C.; Vlascici, D. *J. Serb. Chem. Soc.* **2006**, *71*, 1031–1038. DOI: 10.2298/JSC0610031F.
[3] He, L.-N.; Zhou, R.-X.; Chen, R.-Y.; Li, K.; Zhang, Y.-J. *Heteroatom Chem.* **1999**, *10*, 105–111. DOI: 10.1002/(SICI)1098-1071(1999)10:2<105::AID-HC3>3.0.CO;2-V.
[4] Ali, T. E. *Eur. J. Med. Chem.* **2009**, *44*, 4539–4546. DOI: 10.1016/j.ejmech.2009.06.022
[5] Chen, R. Y.; Mao, L. J.; Chen, X. *Phosphorus SulfurSilicon Relat. Elem.* **2000**, *165*, 91–97. DOI: 10.1080/10426509608054794.
[6] Ali, T. E.; Hassan, M. M. *Res. Chem. Intermed.* **2018**, *44*, 173–189. DOI: 10.1007/s11164-017-3096-z.
[7] Lonnecke, P.; Meisel, M. *Phosphorus Sulfur Silicon Relat. Elem.* **1997**, *124*, 401–405. DOI: 10.1080/10426509708046798.
[8] Abdou, W. M.; Ganoub, N. A.; Sabry, E. *Monatsh. Chem.* **2016**, *147*, 619–626. DOI: 10.1007/s00706-015-1542-4.
[9] Misiura, K.; Szymanowicz, D.; Kuśnierczyk, H. *Bioorg. Med. Chem.* **2001**, *9*, 1525–1532. DOI: 10.1016/S0968-0896(01)00025-6
[10] Feng, W.; Novera, W.; Peh, K.; Neo, D.; Ramanujulu, P. M.; Moore, P. K.; Deng, L.-W.; Dymock, B. W. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 967–972. DOI: 10.1016/j.bmcl.2016.12.079
[11] Schultz, C. *Bioorg. Med. Chem.* **2003**, *11*, 885–898. DOI: 10.1016/S0968-0896(02)00552-7
[12] Corbridge, D. E. C. *Phosphorus. An Outline of Its Chemistry, Biochemistry, and Technology*; Elsevier: Amsterdam, **1985**.
[13] De Clercq, E.; Walker, R. T. *Targets for the Design of Antiviral Agents*; Plenum Press: New York, **1984**.

[14] Nawrot, B.; Sipa, K. *Curr. Top. Med. Chem.* **2006**, *6*, 913–925. DOI: 10.2174/156802606777303658
[15] Pahovnik, D.; Ursic, U.; Groselj, U.; Meden, A.; Svete, J.; Stanovnik, B. Z. *Naturforsch.* **2008**, *63b*, 407–414. DOI: 10.1515/znb-2008-0407.
[16] Ali, T. E.; Ibrahim, M. A.; El-Gendy, Z. M.; El-Amin, E. M. *Synth. Commun.* **2013**, *43*, 3329–3341. DOI: 10.1080/00397911.2013.783074.
[17] Elkholy, Y. M.; Erian, A. W. *Heteroatom Chem.* **2003**, *14*, 503–508. DOI: 10.1002/hc.10178.
[18] Pleier, Glas, A.-K.; H.; Grosche, M.; Sirsch, P.; Thiel, W. *Synthesis.* **2001**, 55–62. DOI: 10.1055/s-2001-9761
[19] Kazmierczak, M.; Kubicki, M.; Koroniak, H. *J. Fluorine Chem.* **2014**, *167*, 128–134. DOI: 10.1016/j.jfluchem.2014.06.008.
[20] Abdou, W. M.; Shaddy, A. A.; Kamel, A. A. *Chem. Pap.* **2017**, *71*, 1961–1973. DOI: 10.1007/s11696-017-0190-z.
[21] Chauhan, M. S.; Still, I. W. J. L. *Can. J. Chem.* **1975**, *53*, 2880–2890. DOI: 10.1139/v75-408.
[22] Guillouzo, G. P.; Lozach, N. *Bull. Soc. Chim. Fr.* **1962**, 1624–1633.
[23] Mayer, R. *Chem. Ber.* **1957**, *90*, 2362–2369. DOI: 10.1002/cber.19570901035.
[24] Shawali, A. S. *Arkivoc.* **2012**, *i*, 383–431.