Res Chem Intermed
DOI 10.1007/s11164-013-1101-8

Critical assessment of two classical synthetic methods for preparation of thiophene-substituted isoxazoles

Gheorghe Roman

Received: 10 December 2012 / Accepted: 4 February 2013

Abstract Formation of thiophene-substituted isoxazoles by reaction of chalcone dibromides and 1,3-diketones with hydroxylamine hydrochloride has been examined under different conditions. Use of KOH as base in the reaction of dibromide chalcone analogs with hydroxylamine hydrochloride yields mixtures of isomeric isoxazoles in modest yields. Replacement of KOH with pyridine affords negligible amounts of isoxazoles only, the intermediate 2-bromoprop-2-en-1-one being isolated from the reaction as the major product. Substitution of the β-bromine atom from a chalcone dibromides with a methoxy group by solvolysis occurred when no base was used. Mixtures of isomeric isoxazoles in which the isoxazole that had a 2-thienyl group at position 5 were always major components, were obtained in good yields from reaction of thiophene-containing 1,3-diketones with hydroxylamine hydrochloride, irrespective of reaction pH. At low pH, regioselectivity was poorer than that observed for reaction of chalcone dibromides with hydroxylamine hydrochloride, but yields were substantially better. At high pH, yields were comparable with those at low pH and regioselectivity for 3-aryl-5-(2-thiophenyl)isoxazole was slightly enhanced, but the dioxime corresponding to the initial 1,3-diketone was also produced in low yields as a mixture of stereoisomers.

Keywords Chalcone analogs · Chalcone dibromides · 1,3-Diketone · Isoxazole · Ring closure

Electronic supplementary material The online version of this article (doi: 10.1007/s11164-013-1101-8) contains supplementary material, which is available to authorized users.

G. Roman (✉)
Petru Poni Institute of Macromolecular Chemistry, 41A Aleea Gr. Ghica Vodă, 700487 Iaşi, Romania
e-mail: gheorghe.roman@icmpp.ro

Published online: 23 February 2013

Introduction

Isoxazoles are an important class of heterocyclic compounds because of their use as intermediates in organic synthesis and their numerous applications. In addition to their intrinsic value as structural units, isoxazoles are used in organic synthesis because of their versatility as synthons, primarily because they combine a potentially unlimited range of structural modification of their substituents with facile cleavage of the weak N–O bond [1, 2]. Isoxazoles also have a variety of technical applications in the production of dye-sensitized solar cells [3], fluorescent chemosensors for the fluoride anion [4], herbicides [5], and liquid crystals [6, 7]. In addition, isoxazole is a structure widely encountered in drug design, especially in the development of inhibitors of γ-aminobutyric acid (GABA) uptake [8], $GABA_A$ antagonists [9], or GABA agonists [10], but also in the structures of antibiotics [11], antithrombotic agents [12, 13], HIV infection inhibitors [14], antiviral candidates [15, 16], antifungals [17, 18], anticancer compounds [19–21], and antitubercular drugs [22–24].

A literature survey shows that 1,3-dipolar cycloaddition of nitrile oxides and alkynes and reaction of hydroxylamine with 1,3-dicarbonyl compounds are the most widely used synthetic methods for closure of the isoxazole ring [1, 25]. The shortcoming of both methods is the generation of a mixture of regioisomeric isoxazoles when asymmetrically substituted starting materials are used. Despite recent progress in the control of regioselectivity in cycloadditions of nitrile oxides and alkynes by use of copper(I) catalysts [26, 27], this approach remains unattractive for large-scale synthesis of 3,5-diarylisoxazoles, first because of the limited number and prohibitive cost of commercially available arylacetylenes, and, second, the difficult preparation of these alkynes by multi-step procedures that use expensive starting materials. In contrast, the latter strategy for construction of the isoxazole ring uses 1,3-dicarbonyl compounds or their synthetic equivalents which are readily accessible from inexpensive commercially available starting materials by two or three-step simple synthetic procedures. However, methods using this strategy usually yield a mixture of positional isomers in ratios that vary from one method to another. For example, synthesis of isoxazoles from α,β-dihalocarbonyl compounds (chalcone dibromides) as synthetic equivalents to 1,3-dicarbonyl compounds is usually regarded as highly selective, because only the isoxazole regioisomer derived from attack of hydroxylamine on the carbonyl function is usually formed. In contrast, oximation of unsymmetrical 1,3-diketones leads to both regioisomeric isoxazoles in the form of a mixture whose composition depends on the reaction conditions (solvent, temperature, pH) and on the nature of the aryl groups which, in turn, as a result of the steric and electronic properties, affects the equilibrium between the two possible tautomeric enol forms of the unsymmetrical 1,3-diketone [1].

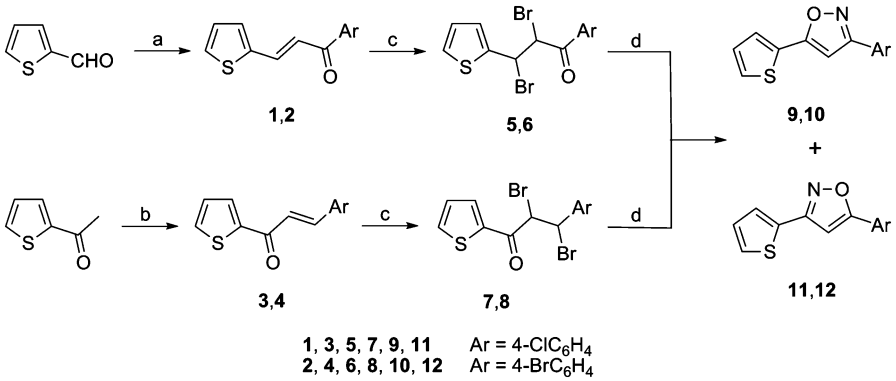
Easy access to large amounts of thiophene-substituted 3,5-diarylisoxazoles was required for a project in our laboratory. In an attempt to identify the best synthetic method for large-scale preparation of these compounds, we conducted a thorough investigation of the reaction of hydroxylamine with dibromides of

thienyl-containing chalcone analogs and the corresponding thienyl-containing 1,3-diketones. Our conclusions from this study are reported below.

Results and discussion

The four thienyl-containing chalcone analogs **1–4** required for this study were synthesized either by Claisen condensation of thiophene-2-carboxaldehyde with either 4′-chloroacetophenone or 4′-bromoacetophenone or by condensation of 2-acetylthiophene with either 4-chlorobenzaldehyde or 4-bromobenzaldehyde (Scheme 1). Compounds **1–4** were then transformed into the corresponding thienyl-containing chalcone dibromides **5–8** by treatment with bromine at room temperature [28]. On the basis of the value of the coupling constant (approximately 11 ppm) between the protons on the chiral carbon atoms, dibromides **5–8** exist in the *erythro* form in solution [29]. By diluting the reaction mixture with petroleum ether, compounds **5–8** were recovered in good yields and excellent purity, and were used as such in the subsequent step. Ring closure of these intermediates to thiophene-substituted isoxazoles **11–14** was initially performed by use of a reported procedure [30, 31] which entails slow addition of aqueous KOH to a suspension of the chalcone dibromide in hot ethanol containing hydroxylamine hydrochloride (Method A in the Experimental section). The solid isolated after work-up of the reaction mixture was subjected to ^{1}H NMR analysis, and the important signal of the proton at C4 in the isoxazole ring was monitored in the 6.5–7.0 ppm region. Despite previous reports which mention formation of only one of the two possible regioisomers, this reaction afforded both isomeric isoxazoles, as shown by the two singlets in the aforementioned region, which were always observed. Thus, dibromides **5** and **6** afforded isoxazoles **9** and **10**, respectively, as the major components in the mixture (94 %) whereas isoxazoles **11** and **12** amounted to approximately 6 % of the sample in each case. Isoxazoles **11** and **12** were obtained as the major components in the mixture (97 %) from dibromides **7** and **8**, respectively, whereas isoxazoles **9** and **10**, respectively, accounted for the remainder of the sample (3 %). As noted previously [32], repeated recrystallization from ethanol of mixtures of regioisomers **9** and **11** resulted in no variation in their ratio, as proved by NMR. The same behavior was noticed for mixtures of regioisomeric isoxazoles **10** and **12**. Use of different combinations of solvents in TLC analysis of the mixture on silica gel did not enable discrimination between the two regioisomers of each pair, making their separation by column chromatography virtually impossible. Nevertheless, the purity of isoxazoles **9–12** obtained by this method is acceptable for most intents and purposes. Unfortunately, yields of this synthetic method are low [31], and isoxazoles **9–12** have been obtained after one recrystallization in yields ranging from 38 to 24 %. Although yields can be improved slightly if the base is added very slowly to the reaction mixture, yields remain modest, rendering this method unattractive for large-scale synthesis.

The identity of isoxazoles **9–12** could not be established solely by study of NMR data. Although reaction of chalcone dibromides with hydroxylamine is believed to be highly selective, because, usually, only the regioisomer formed by attack of the

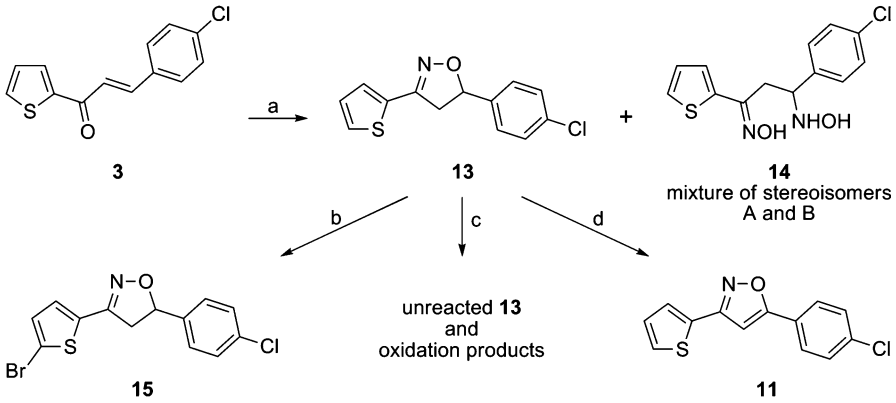


Scheme 1 Synthesis of thiophene-substituted isoxazoles from thienyl-containing chalcone dibromides. Reaction conditions: (*a*) 4′-chloroacetophenone or 4′-bromoacetophenone, ethanol, 40 % NaOH, rt, overnight; (*b*) 4-chlorobenzaldehyde or 4-bromobenzaldehyde, ethanol, 40 % NaOH, rt, overnight; (*c*) bromine, chloroform, rt, 2 h; (*d*) hydroxylamine hydrochloride, KOH, ethanol–water, 70–75 °C, 5–10 min

nitrogen atom of hydroxylamine on the carbonyl group of the chalcone dibromide is obtained, the method still is not entirely unequivocal [1]. Despite the wealth of information about assignment of the structures of isoxazoles resulting from reaction of chalcone dibromides with hydroxylamine, which supports the aforementioned conclusion, the structures of isoxazoles **9**–**12** ought to be proved beyond any doubt. Confirmation of their structure was finally achieved by corroborating the results from two different experiments, which led to the same conclusion. The first experiment was an attempt to synthesize one of the regioisomers of a pair via a different synthetic path that would indubitably lead to an isoxazole with a well-defined structure as the sole reaction product. To unambiguously obtain one regioisomer as the sole reaction product, the location of the aryl groups at C3 and C5 of the isoxazole ring in the starting material must be known precisely, and subsequent transformation of the starting material into the isoxazole should not affect the positions of these substituents. Brief examination of literature revealed that oxidation of isoxazolines to isoxazoles is a reaction that meets the latter criterium. The required starting material, isoxazoline **13**, was obtained first by oximation of chalcone analog **3**, by use of a literature method [33]; the by-product hydroxylamino oxime **14** was also isolated and characterized as a mixture of stereoisomers A and B in the relative ratio 1.4 to 1 (Scheme 2). A synthetic method [34], very similar to that described by Lesiak and Nielek, has recently been used to obtain isoxazoline **13**, but the appearance, melting point, and ^{1}H NMR spectrum reported by Ramiz et al. for the compound allegedly having the structure of **13** differ substantially from those of isoxazoline **13** obtained by us. Isoxazoline **13** has now been fully characterized, and correlation spectroscopy has been used to confirm the position of the 4-chlorophenyl and 2-thienyl substituents on the isoxazole ring. The 2D HMBC spectrum of compound **13** reveals strong correlation between C5 in the isoxazoline ring (82.1 ppm) and the protons of the 4-chlorophenyl moiety (7.30–7.37 ppm), and the proton at C5 in the isoxazoline ring (5.71 ppm) correlates

with the carbon atoms in the chlorophenyl substituent (127.4 ppm). Also, C3 in the isoxazoline ring (152.0 ppm) correlates strongly with one proton in the thiophene ring (7.19 ppm). Next, because the complex of 1,4-diazabicyclo[2.2.2]octane (DABCO) with bromine has recently been reported to cleanly and effectively oxidize isoxazolines to the corresponding isoxazoles [35], the experiment described by Azarifar et al. was repeated. However, in our hands, the reaction took a different course, and isoxazoline **15**, resulting from bromination of the thiophene ring of isoxazoline **13**, was obtained as the sole reaction product (Scheme 2). This is not surprising, because isoxazolines are known to resist oxidation to isoxazole by bromine [1]. The crude reaction mixture still contained approximately 20 % unreacted starting material, but no trace of either regioisomeric isoxazole **9** or **11** could be detected by NMR. Repeated recrystallization of the solid isolated from the reaction mixture yielded the pure isoxazoline **15** which melted sharply at 100–101 °C. Azarifar et al. reported a melting point of 191–193 °C for the compound they isolated from an identical experiment. In addition, the melting point of the product reported by Azarifar et al. is also different from the melting point of isoxazoles **9** or **11** reported in this paper; together this raises serious questions about the diligence of these authors. Next, oxidation of isoxazoline **13** was attempted by another method. Although chromium(VI) oxide in acetic acid has long been known as an oxidizing system able to dehydrogenate isoxazolines to isoxazoles [36], use of this method resulted in detection of only minute traces of isoxazole **11**, both in the solid isolated after work-up and in the chloroform extract of an aliquot of the filtrate obtained after isolation of the aforementioned solid. The isolated solid consisted mostly of unreacted isoxazoline **13**, whereas the residue obtained from the chloroform extract was a complex mixture of by-products most likely formed as a result of destructive oxidation of the isoxazoline ring. As this experiment was deemed inconclusive, we decided to use 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) as dehydrogenating agent. The residue obtained after processing the reaction mixture consisted of a mixture of unreacted starting material **13** and the expected isoxazole **11** in an approximate ratio of 9:11, according to NMR analysis. Isoxazole **11** was identified in the mixture on the basis of the presence of a singlet at 6.75 ppm in the ^{1}H NMR spectrum, assigned to the proton at C4 in the isoxazole ring, but no separation of a pure sample from the reaction mixture was attempted. Despite the fact that isoxazoline **13** was not completely converted to the corresponding isoxazole under these conditions, this experiment confirms that initial assignment of the structure of isoxazole **11** was correct. Taking into account that replacement of chlorine in **11** by bromine in **12** does not induce a significant change in the chemical shift of the proton at C4 in the isoxazole ring, and that the ^{1}H NMR spectrum of isoxazole **12** also contains a singlet at 6.75 ppm, isoxazole **12** must also be the regioisomer having the 2-thienyl substituent attached to C3 whereas the 4-bromophenyl moiety substitutes C5 of the isoxazole ring. The ^{1}H NMR spectra of isoxazoles **9** and **10** both contain a signal at 6.66 ppm for the proton at C4 in the isoxazole ring; they must, therefore, both have a 2-thienyl substituent at C5 and either a 4-chlorophenyl moiety or a 4-bromophenyl, respectively, at C3.

Additional confirmation of the structures of isoxazoles **9**–**12** was obtained by use of mass spectroscopy. Isomer determination by mass spectroscopy relies on the



Scheme 2 Synthesis and reaction of 5-(4-chlorophenyl)-3-(thiophen-2-yl)-4,5-dihydroisoxazole **13** with different oxidizing agents. Reactions and conditions: (*a*) hydroxylamine hydrochloride, KOH, ethanol–water, reflux, 5 h; (*b*) DABCO–Br_2 complex, glacial acetic acid, rt, 5 h; (*c*) CrO_3, glacial acetic acid, 75–80 °C, 45 min; (*d*) DDQ, anhydrous dioxane, reflux, 6 h

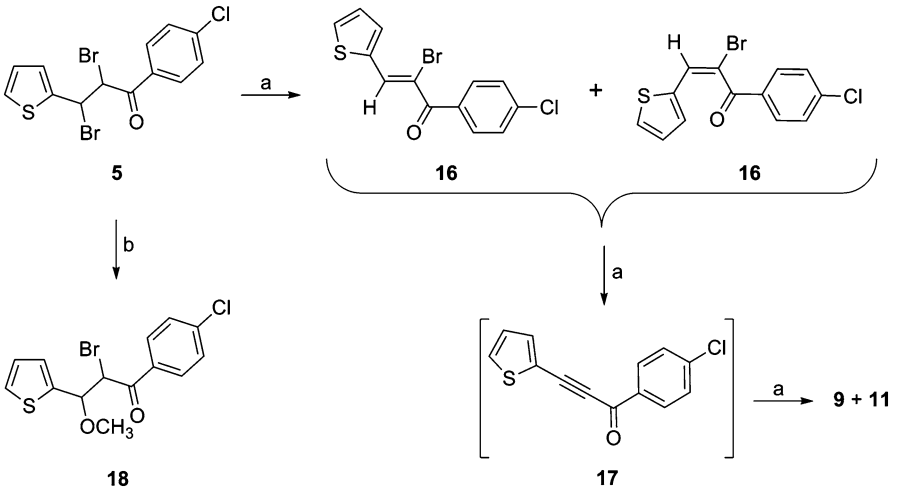
unique fragmentation pattern of 3,5-diarylisoxazoles, which very often gives as the base peak an acylium ion derived from the aromatic substituent at position 5 of the parent isoxazole, with other species [1]. The most intense peak in the MS–MS spectrum of isoxazole **9** was *m*/*z* 110.99, which is consistent with the *m*/*z* value for an acylium ion derived from thiophene, whereas the MS–MS analysis of the molecular ion of compound **11** resulted in a base peak at *m*/*z* 138.95 corresponding to the acylium ion derived from a chlorophenyl moiety. Therefore, the thienyl substituent is located at C5 in isoxazole **9** whereas the 4-chlorophenyl residue is located at C5 in regioisomer **11**.

It has been reported [37] that reaction of hydroxylamine hydrochloride with 2,3-dibromo-1-(5-chloro-2-hydroxyphenyl)-3-(2-furyl)propan-1-one in pyridine at reflux temperature yields the expected 3-(5-chloro-2-hydroxyphenyl)-5-(2-furyl)isoxazole whereas the same reactants produce the isomeric 5-(5-chloro-2-hydroxyphenyl)-3-(2-furyl)isoxazole in methanol at reflux temperature. Therefore, reaction of hydroxylamine hydrochloride with dibromide **5** was examined under these conditions also. Heating dibromide **5** with hydroxylamine hydrochloride in pyridine at reflux temperature for 3 h (Method B in the Experimental section) furnished a brown oil after work-up. ^{1}H NMR analysis showed that this oil contained both isoxazole **9** and isoxazole **11** in an approximate ratio of 2 to 1. These results suggest, at least for dibromide **5**, that this method is even less selective than that with KOH as base. Moreover, the isoxazoles seem to be minor components in the reaction mixture. Further work-up of the residue enabled isolation of modest amount of a solid, which was analyzed by NMR and shown to be a mixture of the *Z* and *E* isomers of 2-bromo-1-(4-chlorophenyl)-3-(2-thienyl)prop-2-en-1-one **16**. The approximate ratio of the *Z* and *E* isomers of compound **16** was determined to be approximately 4 to 1 on the basis of the ratio of the signals of the ethylenic proton for each stereoisomer (peaks with δ 7.75 and 7.99 ppm in Fig. 1S in the Supplementary Material). Isolation from the reaction mixture of the unsaturated

bromo ketone **16** (Scheme 3), an intermediate in the synthesis of isoxazole **9** from dibromide **5**, suggests that pyridine is not a strong enough base to promote conversion of **16** into acetylenic ketone **17**. This is in agreement with previous results showing that dehydrohalogenation of dibromides similar to **5** in the presence of triethylamine affords α-bromo ketones in excellent yields [38], but further loss of hydrogen bromide from unsaturated bromo ketones to yield acetylenic ketones requires use of a stronger base, such as KOH [39].

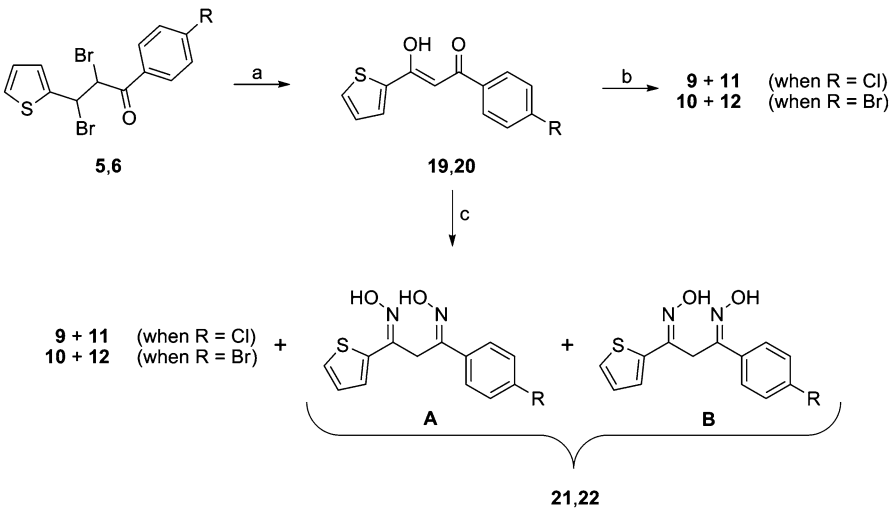
Reaction of dibromide **5** with hydroxylamine hydrochloride in the absence of a base (Method C in the Experimental section) afforded no isoxazole (shown by NMR analysis of the crude reaction mixture). The product of the reaction is, instead, 2-bromo-1-(4-chlorophenyl)-3-methoxy-3-(2-thienyl)propan-1-one **18**, which arises from nucleophilic substitution of the reactive bromine in the position β to the carbonyl function with a methoxy group by solvolysis (Scheme 3). Similar behavior has been reported [40] for dibromides of analogs of chalcone derived from 4-methoxybenzaldehyde, which exchange the bromine in the position β to the carbonyl with an alkoxy group when heated with alcohols for a short time. The structure of compound **18** was established on the basis of several NMR experiments including 2D homonuclear and heteronuclear correlation spectroscopy (Figs. 2S, 3S, 4S, 5S in the Supplementary Material). These experiments confirm that the methoxy group is located on the carbon atom adjacent to the thiophene ring.

Reaction of hydroxylamine hydrochloride with thiophene-containing 1,3-diketones was also investigated (Scheme 4). The intermediate dicarbonyl compounds **19** and **20** were obtained in excellent yield by reaction of dibromides **5** and **7**, respectively, with sodium methoxide in methanol and subsequent hydrolysis [41]. The equilibrium between the diketo and keto–enol forms of these compounds is strongly shifted toward the latter in deuterated chloroform (98 % keto–enol form for



Scheme 3 Reaction of dibromide **5** with hydroxylamine hydrochloride at high and low pH. Reaction conditions: (*a*) hydroxylamine hydrochloride, pyridine, reflux, 3 h; (*b*) hydroxylamine hydrochloride, methanol, reflux, 5 h

compound **19**; 95 % keto–enol form for compound **20**), as determined by NMR. On the basis of information available in the literature, this type of compound enolizes at the carbonyl neighboring the thiophene moiety [42]. Oximation of unsymmetrical 1,3-diketones **19** and **20** was conducted in alcoholic solvents at reflux at either low pH (hydroxylamine hydrochloride only) or high pH (in the presence of pyridine). At low pH (Method D in the Experimental section), oximation of **19** led to a mixture of isoxazole **9** (86 %), isoxazole **11** (10 %), and unreacted starting material (4 %). A first recrystallization from ethanol removed the unreacted diketone **19**, and yielded a mixture of isoxazoles **9** (89 %) and **11** (11 %); the ratio of these isomers remained the same after a second recrystallization from ethanol. Reaction of **20** with hydroxylamine hydrochloride under the same conditions afforded a mixture of isoxazole **10** (80 %), isoxazole **12** (9 %), and unreacted starting material (11 %). Because of the large amount of unreacted diketone **20** in the crude reaction mixture, its complete removal required three recrystallizations from ethanol, and the final ratio of isoxazole **10** to isoxazole **12** was 9:1. Conversion of **19** and **20** into the corresponding isoxazoles was, in both cases, 60–70 % after purification, which makes this synthetic approach more efficient than reaction of dibromides **5–8** with hydroxylamine. However, the regioselectivity of the reaction was, in each case, slightly poorer than that obtained from reaction of the dibromides **5–8** with hydroxylamine hydrochloride in the presence of KOH, so the purity of isoxazoles **9** and **10** obtained by use of this method qualifies them as technical grade materials only. Furthermore, this method leads predominantly to isoxazoles with a 2-thienyl substituent at position 5, presumably because of the direction of enolization of the substrate. Similar results have previously been reported for 1-phenyl-3-(2-thienyl)propane-1,3-dione [43].



Scheme 4 Synthesis and reaction of 1,3-diketones **16** and **17** with hydroxylamine hydrochloride at low and high pH. Reaction conditions: (*a*) MeONa, methanol, reflux, 1 h, then 36 % HCl, reflux, 5 min; (*b*) hydroxylamine hydrochloride, methanol, reflux, 7 h; (*c*) hydroxylamine hydrochloride, pyridine, ethanol, reflux, 5 h

At high pH (Method E in the Experimental section), transformation of 1,3-diketone **19** by reaction with hydroxylamine was complete, also affording a mixture of isoxazoles **9** and **11** and a by-product which was easily separated from the isomeric isoxazoles on the basis of its limited solubility in chloroform (Scheme 4). The mixture of isomeric isoxazoles recovered from the chloroform extract was indicative of 65 % conversion of starting material **19**, and contained 93 % isoxazole **9** and 7 % isoxazole **11**; its composition remained unchanged after one recrystallization from ethanol. 1,3-Diketone **20** behaved similarly under the same reaction conditions, and an isolation procedure identical with that used for processing the crude reaction mixture obtained from diketone **19** afforded a mixture of isoxazoles **10** (93.5 %) and **12** (6.5 %) whose composition was not altered by recrystallization from ethanol. The purity of isoxazoles **9** and **10** obtained by use of this approach is comparable with that of the same isoxazoles obtained from dibromides using KOH as base, but the yields were significantly better. Again, one should note that only isoxazoles having a 2-thienyl substituent at position 5 are available by use of this approach.

NMR analysis of the fraction insoluble in chloroform from reaction of 1,3-diketone **19** with hydroxylamine hydrochloride in the presence of pyridine showed that, apart from the signals in the aromatic region (Fig. 6S in the Supplementary Material), the proton spectrum of the by-product contained one pair of singlets in the aliphatic region and two distinct pairs of singlets in the off-set (Fig. 7S in the Supplementary Material). Integration of these peaks clearly showed that one signal of each of these pairs is associated with one compound, and that a different compound is responsible for the other signal in each of these pairs. The close chemical shift values of the signals in each pair suggest that the structures of these two compounds are very similar. The ratio of the signal in the aliphatic region to the corresponding signals in the pairs in the off-set is 2:1:1. Taking into consideration other possible interactions between the starting materials in addition to that leading to isoxazoles, the two compounds in the by-product from oximation of 1,3-diketone **19** are most likely stereoisomers of 1-(4-chlorophenyl)-3-(thiophen-2-yl)propane-1,3-dione dioxime **21**. Of the four possible stereoisomers of this dioxime, the (1*E*,3*Z*) and (1*Z*,3*E*) isomers **A** and **B** (Scheme 4) are the most plausible candidates for the two components of the by-product, because both isomers are stabilized by an intramolecular hydrogen bond. Because the ratio of these two stereoisomers is approximately 1:7, the signals in the proton spectrum of their mixture can be tentatively assigned. Inspection of the ^{13}C NMR spectrum confirmed the presence of the aliphatic carbon atom of the methylene group, and the absence of any carbonyl functions in the structure of the compounds in the fraction insoluble in chloroform. The molecular formula for the compound in this fraction was also supported by results obtained from mass spectrometry (Fig. 8S in the Supplementary Material). The ESI–MS spectrum of the fraction insoluble in chloroform was recorded in methanol, and the peak for the most abundant singly charged species at *m*/*z* 293.0855 can be assigned to the deprotonated compound $[M - H]^-$. Results from elemental analysis were also consistent with the values calculated for dioxime **21**. The fraction insoluble in chloroform obtained from processing the crude reaction mixture resulting from reaction of diketone **20** was also investigated, and the presence of a mixture of stereoisomeric dioximes **22** was corroborated by results from NMR

analysis, mass spectrometry, and elemental analysis. The ratio of the two stereoisomers of dioxime **22** is approximately 1:1.3. As a consequence, accurate assignment of the peaks in the proton spectrum of their mixture is more difficult, and the ^{13}C NMR spectrum of **22** is reported as the sum of peaks for both stereoisomers.

Conclusions

Reaction of two pairs of thienyl-containing chalcone dibromides with hydroxylamine hydrochloride in the presence of KOH was investigated, and shown to lead to modest yields of mixtures of isomeric isoxazoles in which the isomer resulting from oximation of the carbonyl function in the starting chalcone dibromide is the major component. No pure product could be obtained by repeated recrystallization of these mixtures. In the presence of pyridine, an intermediate in the synthesis of isoxazoles, the unsaturated bromoketone resulting from dehydrobromination of the starting chalcone dibromide, was isolated. In the absence of the base, replacement of the bromine atom at the position β to the carbonyl function with a methoxy group from the solvent occurred. Good yields of 3-aryl-5-(2-thienyl)isoxazoles (also as mixtures with their regioisomers) were obtained from the reaction of thienyl-containing 1,3-diketones with hydroxylamine hydrochloride, irrespective of the pH of the reaction mixture. The regioselectivity of the reaction improved slightly at high pH, but yields of isoxazoles decreased to some extent because of formation of the dioximes of the starting 1,3-diketones as by-products.

Experimental

All chemicals were purchased from commercial suppliers and used without further purification. Melting points were taken on a Mel-Temp II apparatus and are uncorrected. Elemental analysis was conducted in-house, on a PerkinElmer 2400 Series II CHNS/O system. Analytical TLC was performed on pre-coated plates (Merck silica gel 60, F_{254}); spots were visualized by UV illumination. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400-MHz spectrometer. The signals from residual protons in the deuterated solvents were used as internal standards for the ^{1}H NMR spectra. The chemical shifts for carbon atoms are given relative to $CDCl_3$ ($\delta = 77.16$ ppm) or d_6-DMSO ($\delta = 39.52$ ppm). Mass spectrometry data were obtained on an Agilent 6520 Series Accurate-Mass Quadrupole Time-of-Flight (Q-TOF) LC–MS using electrospray ionization (negative-ion mode for the analysis of compound **21**, and positive-ion mode for compounds **9** and **11**). For isoxazoles **9** and **11**, fragmentation of the molecular ion (*m*/*z* 262) was performed in MS–MS mode at a collision energy of 40 eV.

General procedure for synthesis of chalcones **1**–**4**

A solution of the required ketone (20 mmol) and aldehyde (20 mmol) in ethanol (20 mL) was treated at room temperature with efficient stirring with 40 % NaOH

(5–7 drops). The mixture was kept at room temperature overnight, then the solid was isolated by filtration, washed thoroughly with small volumes of cold 2-propanol, air-dried, and recrystallized from methanol.

*1-(4-Chlorophenyl)-3-(thiophen-2-yl)prop-2-en-1-one (**1**)*

Yellowish crystals, yield 82 %, mp 121–122 °C (lit. mp 118–120 °C [44]; lit. mp 121–122 °C [45]).

*1-(4-Bromophenyl)-3-(thiophen-2-yl)prop-2-en-1-one (**2**)*

Yellow crystals, yield 84 %, mp 130–131 °C (lit. mp 133–135 °C [44]).

*3-(4-Chlorophenyl)-1-(thiophen-2-yl)prop-2-en-1-one (**3**)*

Light yellow crystals, yield 79 %, mp 132–133 °C (lit. mp 133 °C [46]; lit. mp 132–133 °C [47]).

*3-(4-Bromophenyl)-1-(thiophen-2-yl)prop-2-en-1-one (**4**)*

Yellow crystals, yield 66 %, mp 136–137 °C (lit. mp 131–133 °C [48]).

General procedure for synthesis of thienyl-containing chalcone dibromides **5**–**8**

A solution of bromine (1.6 g, 10 mmol) in chloroform (5 mL) was added dropwise to a solution of chalcone analog **1**–**4** (10 mmol) in the smallest volume of chloroform (10–15 mL) at room temperature. The reaction mixture was stirred at room temperature for 2 h then diluted with petroleum ether (bp 40–60 °C, 50 mL) and refrigerated for 3 h. The solid was isolated by filtration, washed with petroleum ether, and air-dried.

*2,3-Dibromo-1-(4-chlorophenyl)-3-(thiophen-2-yl)propan-1-one (**5**)*

Colorless solid, yield 75 %, mp 144–145 °C; lit. mp 144–145 °C [28]; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.72 (d, $J = 10.8$ Hz, 1H), 5.97 (d, $J = 10.8$ Hz, 1H), 7.01 (dd, $J = 3.6$ and 5.2 Hz, 1H), 7.27 (dd, $J = 0.8$ and 3.6 Hz, 1H), 7.45 (d, $J = 5.2$ Hz, 1H), 7.53 (d, $J = 8.8$ Hz, 2H), 8.03 (d, $J = 8.8$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 44.7, 48.3, 127.0, 127.6, 128.7, 129.6, 130.5, 132.7, 141.1, 142.1, 189.9.

*2,3-Dibromo-1-(4-bromophenyl)-3-(thiophen-2-yl)propan-1-one (**6**)*

Colorless solid, yield 73 %, mp 138–139 °C (dec); lit. mp 131–134 °C [28]; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.71 (d, $J = 11.2$ Hz, 1H), 5.97 (d, $J = 11.2$ Hz, 1H), 7.01 (dd, $J = 3.6$ and 5.2 Hz, 1H), 7.27 (dd, $J = 0.8$ and 3.6 Hz, 1H), 7.45 d, $J = 5.2$ Hz, 1H), 7.70 (d, $J = 8.4$ Hz, 2H), 7.95 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR

($CDCl_3$, 100 MHz): δ 44.7, 48.2, 127.0, 127.7, 128.7, 129.9, 130.5, 132.6, 133.1, 142.1, 190.1.

*2,3-Dibromo-3-(4-chlorophenyl)-1-(thiophen-2-yl)propan-1-one (**7**)*

Colorless solid, yield 78 %, mp 188–189 °C; lit. mp 189–198 °C [28]; ^{1}H NMR (d_6-DMSO, 400 MHz): δ 5.78 (d, $J = 11.2$ Hz, 1H), 6.56 (d, $J = 11.2$ Hz, 1H), 7.40 (dd, $J = 4.0$ and 4.8 Hz, 1H), 7.52 (d, $J = 8.4$ Hz, 2H), 7.85 (d, $J = 8.4$ Hz, 2H), 8.23 (dd, $J = 0.8$ and 4.8 Hz, 1H), 8.55 (dd, $J = 0.8$ and 4.0 Hz, 1H); ^{13}C NMR (d_6-DMSO, 100 MHz): δ 47.0, 49.4, 128.7, 129.3, 130.7, 133.7, 135.8, 137.6, 138.1, 140.8, 184.8.

*2,3-Dibromo-3-(4-bromophenyl)-1-(thiophen-2-yl)propan-1-one (**8**)*

Colorless solid, yield 86 %, mp 191–192 °C (dec); ^{1}H NMR (d_6-DMSO, 400 MHz): δ 5.77 (d, $J = 11.2$ Hz, 1H), 6.56 (d, $J = 11.2$ Hz, 1H), 7.40 (dd, $J = 4.0$ and 4.8 Hz, 1H), 7.66 (d, $J = 8.4$ Hz, 2H), 7.79 (d, $J = 8.4$ Hz, 2H), 8.23 (dd, $J = 0.8$ and 4.8 Hz, 1H), 8.55 (dd, $J = 0.8$ and 4.0 Hz, 1H); ^{13}C NMR (d_6-DMSO, 100 MHz): δ 47.0, 49.4, 122.4, 129.3, 130.9, 131.6, 135.9, 138.0, 138.1, 140.8, 184.8.

Oximation of chalcone **3**

A mixture of 3-(4-chlorophenyl)-1-(thiophen-2-yl)prop-2-en-1-one **3** (1.245 g, 5 mmol) and hydroxylamine hydrochloride (1.38 g, 20 mmol) in methanol (20 mL) was treated with a solution of KOH (1.98 g, 30 mmol, purity 85 %) in water (7 mL). The mixture was heated at reflux temperature for 5 h, then the solvent was removed under reduced pressure. The residue was stirred with water (100 mL) for 30 min, then the solid was isolated by filtration and washed with water (2 × 15 mL). The dry solid (1 g) was suspended in chloroform (15 mL), and the suspension was filtered to remove a small amount of insoluble material. The residue obtained after removal of the chloroform under reduced pressure was recrystallization from ethanol to afford the analytical sample (315 mg) of isoxazoline **13**. The aqueous filtrate from isolation of the crude isoxazoline was treated, with efficient stirring, with 10 % HCl until pH 5–6. The solid was then isolated by filtration, air-dried, and recrystallized from 2-propanol to give the analytical sample of hydroxylamino oxime **14**.

*5-(4-Chlorophenyl)-3-(thiophen-2-yl)-4,5-dihydroisoxazole (**13**)*

Colorless solid, yield 24 %, mp 88–89 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.30 (dd, $J = 8.0$ and 16.4 Hz, 1H), 3.79 (dd, $J = 11.2$ and 16.4 Hz, 1H), 5.71 (dd, $J = 8.0$ and 11.2 Hz, 1H), 7.06 (dd, $J = 4.0$ and 5.0 Hz, 1H), 7.19 (dd, $J = 0.4$ and 3.6 Hz, 1H), 7.30–7.37 (m, 4H), 7.41 (dd, $J = 0.4$ and 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 44.1, 82.1, 127.4, 127.5, 128.6, 128.7, 129.1, 131.8, 134.3, 139.3, 152.0.

*3-(4-Chlorophenyl)-3-(hydroxyamino)-1-(thiophen-2-yl)propan-1-one oxime (**14**), mixture of stereoisomers A and B*

Off-white solid, yield 10 %, mp 171–172 °C (softening at 148 °C); ^{1}H NMR (d_6-DMSO, 400 MHz): δ 2.77 (dd, $J = 8.4$ and 14.4 Hz, 1H, stereoisomer A), 2.93 (dd, $J = 8.4$ and 12.8 Hz, 1H, stereoisomer B), 3.07 (dd, $J = 6.8$ and 13.2 Hz, 1H, stereoisomer B), 3.21 (dd, $J = 5.6$ and 14.4 Hz, 1H stereoisomer A), 4.23 (d, $J = 5.2$ Hz, 1H, stereoisomers A and B), 5.95 (s, 1H, stereoisomer B, exchangeable with D), 6.00 (s, 1H, stereoisomer A, exchangeable with D), 7.00 (dd, $J = 4.0$ and 5.2 Hz, 1H, stereoisomer B), 7.16 (dd, $J = 4.0$ and 5.2 Hz, 1H, stereoisomer A), 7.21 (d, $J = 4.0$ Hz, 1H, stereoisomer B), 7.25–7.37 (m, 5H, stereoisomers A and B, 1H exchangeable with D), 7.40 (d, $J = 5.2$ Hz, 1H, stereoisomer B), 7.62 (d, $J = 4.0$ Hz, 1H, stereoisomer A), 7.73 (d, $J = 5.2$ Hz, 1H, stereoisomer A), 11.17 (s, 1H, stereoisomer B, exchangeable with D), 11.68 (s, 1H, stereoisomer A, exchangeable with D).

Attempted oxidation of isoxazoline **13** with DABCO–Br_2 complex

5-(4-Chlorophenyl)-3-(thiophen-2-yl)-4,5-dihydroisoxazole **13** (422 mg, 1.6 mmol) was added in one portion to a suspension of DABCO–Br_2 complex (503 mg, 3.2 mmol) in glacial acetic acid (5 mL), and the mixture was stirred at room temperature for 6 h. The mixture was treated with aqueous 20 % Na_2CO_3 until the pH reached 8, and the solid was then isolated by filtration, air-dried, and recrystallized repeatedly from ethanol.

*3-(5-Bromothiophen-2-yl)-5-(4-chlorophenyl)-4,5-dihydroisoxazole (**15**)*

Colorless crystals, yield 45 %, mp 100–101 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.24 (dd, $J = 8.4$ and 16.4 Hz, 1H), 3.73 (dd, $J = 10.8$ and 16.4 Hz, 1H), 5.70 (dd, $J = 8.4$ and 10.8 Hz, 1H), 6.90 (d, $J = 4.0$ Hz, 1H), 7.01 (d, $J = 4.0$ Hz, 1H), 7.30 (d, $J = 8.4$ Hz, 2H), 7.35 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 43.4, 82.3, 116.4, 127.4, 128.8, 129.2, 130.3, 133.4, 134.4, 139.0, 151.4.

Attempted oxidation of isoxazoline **13** with CrO_3

A solution of 5-(4-chlorophenyl)-3-(thiophen-2-yl)-4,5-dihydroisoxazole **13** (711 mg, 2.7 mmol) and CrO_3 (540 mg, 5.4 mmol) in glacial acetic acid (20 mL) was heated in an oil bath at 90 °C for 45 min. The mixture was poured into water (300 mL), and left at room temperature for 24 h. The solid (203 mg) was isolated by filtration, air-dried, and analyzed by NMR. An aliquot of the filtrate (100 mL) was extracted with chloroform (2 mL × 25 mL), and the combined extracts were washed with water (2 × 15 mL), and dried over anhydrous Na_2SO_4. The residue obtained after removal of chloroform under reduced pressure was analyzed by NMR.

Oxidation of isoxazoline **13** with DDQ

A mixture of 5-(4-chlorophenyl)-3-(thiophen-2-yl)-4,5-dihydroisoxazole **13** (527 mg, 2 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (908 mg, 4 mmol) in anhydrous 1,4-dioxane (10 mL) was heated at reflux temperature for 6 h. The mixture was left at room temperature overnight. It was then filtered, the solvent was removed under reduced pressure, and the residue was analyzed by ^{1}H NMR.

General procedure for synthesis of 1,3-diketones **19** and **20**

A solution of sodium methoxide (prepared from sodium (575 mg, 25 at-gr) and 15 mL methanol) was added dropwise to a suspension of either dibromide **5** or dibromide **7** (10 mmol) in methanol (15 mL) at room temperature. The reaction mixture was then heated at reflux temperature for 1 h, left to cool to 40–50 °C, treated dropwise with 36 % HCl (2.5 mL), then heated again at reflux temperature for 5 min. The reaction mixture was then diluted with water (60 mL), and stirred for 1 h at room temperature. The solid was isolated by filtration, air-dried, and recrystallized from ethanol.

*1-(4-Chlorophenyl)-3-hydroxy-3-(thiophen-2-yl)prop-2-en-1-one (**19**)*

Yellow crystals, yields 86 %, mp 128–129 °C (lit. mp 130–131 °C [49]); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.64 (s, 1H), 7.17 (dd, $J = 4.0$ and 4.8 Hz, 1H), 7.45 (d, $J = 8.4$ Hz, 2H), 7.65 (dd, $J = 0.8$ and 4.8 Hz, 1H), 7.81 (dd, $J = 0.8$ and 4.0 Hz, 1H), 7.88 (d, $J = 8.4$ Hz, 2H), 16.29 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 93.2, 128.3, 128.5, 129.1, 130.7, 133.0, 133.1, 138.6, 142.1, 179.7, 183.1.

*1-(4-Bromophenyl)-3-hydroxy-3-(thiophen-2-yl)prop-2-ene-1-dione (**20**)*

Yellow crystals, yield 87 %, mp 142–143 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.64 (s, 1H), 7.17 (dd, $J = 4.0$ and 4.8 Hz, 1H), 7.61 (d, $J = 8.8$ Hz, 2H), 7.65 (dd, $J = 0.8$ and 4.8 Hz), 7.77–7.83 (m, 3H), 16.26 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 93.2, 127.2, 128.4, 128.5, 130.7, 132.1, 133.0, 133.5, 142.1, 179.7, 183.2.

General procedures for synthesis of isoxazoles **9–12**

*Method A (from chalcone dibromides **5–8** in the presence of KOH)*

A suspension of dibromide **5–8** (3 mmol) in ethanol (30 mL) was heated to a gentle boiling then a solution of hydroxylamine hydrochloride (417 mg, 6 mmol) in water (1.5 mL) was added. The mixture was treated dropwise with a solution of KOH (990 mg, 85 % purity, 15 mmol) in water (2 mL), and, after heating to near boiling point for 5–10 min, the mixture was cooled to room temperature, gradually diluted

with water (70 mL), and kept overnight at room temperature. The solid was isolated by filtration, washed thoroughly with water and recrystallized from ethanol.

*3-(4-Chlorophenyl)-5-(thiophen-2-yl)isoxazole (**9**)*

Off-white crystals, yield 32 %, mp 129–131 °C (lit. mp 127–128 °C [50]); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.66 (s, 1H), 7.15 (dd, $J = 3.6$ and 4.8 Hz, 1H), 7.42–7.50 (m, 3H), 7.56 (dd, $J = 0.8$ and 3.6 H, 1H), 7.78 (d, $J = 8.8$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 97.2, 127.3, 127.5, 128.2, 128.3, 128.4, 129.2, 129.4, 136.3, 162.1, 165.8.

*3-(4-Bromophenyl)-5-(thiophen-2-yl)isoxazole (**10**)*

Off-white crystals, yield 24 %, mp 141–143 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.66 (s, 1H), 7.15 (dd, $J = 4.0$ and 5.2 Hz, 1H), 7.47 (dd, $J = 1.2$ and 5.2 Hz, 1H), 7.56 (dd, $J = 1.2$ and 4.0 Hz, 1H), 7.60 (d, $J = 8.4$ Hz, 2H), 7.71 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 97.2, 124.6, 127.4, 128.0, 128.3, 128.4, 128.5, 129.2, 132.3, 162.2, 165.8.

*5-(4-Chlorophenyl)-3-(thiophen-2-yl)isoxazole (**11**)*

Off-white crystals, yield 38 %, mp 160–162 °C (lit. mp 191–193 °C [35]); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.74 (s, 1H), 7.14 (dd, $J = 3.6$ and 4.8 Hz, 1H), 7.42–7.49 (m, 3H), 7.51 (d, $J = 3.6$ Hz, 1H), 7.75 (d, $J = 8.8$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 98.0, 125.8, 127.3, 127.6, 127.8, 127.9, 129.5, 130.8, 136.6, 158.4, 169.4.

*5-(4-Bromophenyl)-3-(thiophen-2-yl)isoxazole (**12**)*

Off-white crystals, yield 32 %, mp 164–165 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.75 (s, 1H), 7.14 (dd, $J = 3.6$ and 5.2 Hz, 1H), 7.44 (dd, $J = 1.2$ and 5.2 Hz, 1H), 7.51 (d, $J = 1.2$ and 3.6 Hz, 1H), 7.62 (d, $J = 8.4$ Hz, 2H), 7.68 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 98.0, 124.9, 126.2, 127.5, 127.6, 127.8, 127.9, 130.7, 132.5, 158.4, 169.4.

*Method B (from chalcone dibromide **5** in the presence of pyridine)*

A mixture of dibromide **5** (2 mmol) and hydroxylamine hydrochloride (167 mg, 2.4 mmol) in pyridine (5 mL) was heated at reflux temperature for 3 h. The reaction mixture was diluted with water (15 mL), and treated, with efficient stirring, with dilute HCl (36.5 % HCl–water 1:4 *v*/*v*) until pH 4. The supernatant was decanted, and the reddish oil was then dissolved in ethyl acetate (20 mL). The organic phase was washed thoroughly with water, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was triturated with 2-propanol (10 mL). The solid was filtered and recrystallized from 2-propanol.

*(2-Bromo-1-(4-chlorophenyl)-3-(2-thienyl)prop-2-en-1-one (**16**) (mixture of Z and E isomers)*

Tan crystals, yield 19 %, mp 119–120 °C (lit. mp 120–121 °C [50]); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.14–7.21 (m, 1H), 7.44–7.53 (m, 2H), 7.65–7.74 (m, 2H), 7.75 (s, 0.2H), 7.99 (s, 0.8H).

*Method C (from chalcone dibromide **5** at low pH)*

A mixture of dibromide **5** (2 mmol) and hydroxylamine hydrochloride (167 mg, 2.4 mmol) in methanol (10 mL) was heated at reflux temperature for 5 h. The solvent was removed under reduced pressure, and the residue was dissolved in warm 2-propanol (5 mL), diluted with petroleum ether (bp 40–60 °C, 25 mL), and refrigerated overnight at −20 °C, when a solid separated. The solid was isolated by filtration to give compound **18**.

*2-Bromo-1-(4-chlorophenyl)-3-methoxy-3-(2-thienyl)propan-1-one (**18**)*

Tan crystals, yield 52 %, mp 49–50 °C (2-propanol–petroleum ether); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.27 (s, 3H), 5.09 (d, $J = 9.6$ Hz, 1H), 5.13 (d, $J = 10.0$ Hz, 1H), 7.05 (dd, $J = 3.6$ and 4.8 Hz, 1H), 7.20 (d, $J = 3.6$ Hz, 1H), 7.40 (d, $J = 4.8$ Hz, 1H), 7.49 (d, $J = 8.4$ Hz, 2H), 7.98 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 47.8, 58.0, 79.4, 126.5, 126.8, 128.6, 129.3, 130.4, 133.5, 140.5, 141.6, 191.7.

*Method D (from 1,3-diketones **19** and **20** at low pH)*

A mixture of 1,3-diketone (3 mmol) and hydroxylamine hydrochloride (417 mg, 6 mmol) was heated at reflux temperature in a mixture of methanol (15 mL) and water (1 mL) for 7 h. The mixture was left to cool to room temperature, then the solid formed on dilution with water (35 mL) was isolated by filtration and analyzed by ^{1}H NMR spectroscopy. Repeated recrystallization of the crude reaction mixture from ethanol afforded a mixture of isoxazoles, as evidenced by NMR.

*3-(4-Chlorophenyl)-5-(thiophen-2-yl)isoxazole (**9**) and 5-(4-chlorophenyl)-3-(thiophen-2-yl)isoxazole (**11**)*

Yield 76 %, ratio between **9** and **11** approximately 8 to 1, mp 128–133 °C.

*3-(4-Bromophenyl)-5-(thiophen-2-yl)isoxazole (**10**) and 5-(4-bromophenyl)-3-(thiophen-2-yl)isoxazole (**12**)*

Yield 61 %, ratio between **10** and **12** approximately 9 to 1, mp 137–141 °C.

*Method E (from 1,3-diketones **19** and **20** at high pH)*

A mixture of 1,3-diketone (3 mmol), hydroxylamine hydrochloride (313 mg, 4.5 mmol), and pyridine (3 mL) in ethanol (10 mL) was heated at reflux temperature for 5 h. After being kept at room temperature for 24 h, the mixture was poured on to water (75 mL), and the resulting solid was isolated by filtration and air-dried. The solid was extracted with chloroform (2 × 25 mL), then the solvent was removed from the extract under reduced pressure to afford a mixture of isomeric isoxazoles. The fraction insoluble in chloroform was collected by filtration to give the dioximes **21** or **22**.

*3-(4-Chlorophenyl)-5-(thiophen-2-yl)isoxazole (**9**) and 5-(4-chlorophenyl)-3-(thiophen-2-yl)isoxazole (**11**)*

Yield 61 %, ratio between **9** and **11** approximately 12 to 1, mp 130–132 °C.

*1-(4-Chlorophenyl)-3-(thiophen-2-yl)propane-1,3-dione dioxime (**21**), mixture of stereoisomers A and B*

Colorless solid, yield 10 %, mp 178–179 °C; ^{1}H NMR (d_6-DMSO, 400 MHz): δ 4.23 (s, 2H), 7.00 (dd, J = 4.0 and 4.8 Hz, 1H), 7.31 (d, J = 3.6 Hz, 1H), 7.32–7.43 (m, 3H), 7.58 (d, J = 8.4 Hz, 2H), 11.60 (s, 1H), 11.79 (s, 1H) (for the major stereoisomer); 4.19 (s, 2H), 7.15 (dd, J = 4.0 and 4.8 Hz, 1H), 7.32–7.43 (m, 2H), 7.64 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 4.0 Hz, 1H), 7.74 (d, J = 4.8 Hz, 1H), 11.62 (s, 1H), 11.84 (s, 1H) (for the minor stereoisomer); ^{13}C NMR (d_6-DMSO, 100 MHz): δ 22.5, 125.9, 126.8, 127.2, 127.7, 128.2, 133.5, 134.3, 139.4, 148.7, 152.2 (for the major stereoisomer); Anal. Calcd. for $C_{13}H_{11}ClN_2O_2S$: C, 52.97; H, 3.76; N, 9.50. Found: C, 52.61; H, 3.95; N, 9.22.

*3-(4-Bromophenyl)-5-(thiophen-2-yl)isoxazole (**10**) and 5-(4-bromophenyl)-3-(thiophen-2-yl)isoxazole (**12**)*

Yield 59 %, ratio between **10** and **12** approximately 14 to 1, mp 142–144 °C.

*1-(4-Bromophenyl)-3-(thiophen-2-yl)propane-1,3-dione dioxime (**22**), mixture of stereoisomers A and B*

Colorless solid, yield 13 %, mp 184–185 °C; ^{1}H NMR (d_6-DMSO, 400 MHz): δ 4.23 (s, 2H), 6.97–7.03 (m, 1H), 7.31 (d, J = 3.6 Hz, 1H), 7.39 (d, J = 5.2 Hz, 1H), 7.47–7.61 (m, 4H), 11.61 (s, 1H), 11.82 (s, 1H) (for the major stereoisomer); 4.18 (s, 2H), 7.12–7.18 (m, 1H), 7.47–7.61 (m, 4H), 7.68 (d, J = 3.6 Hz, 1H), 7.74 (d, J = 5.2 Hz, 1H), 11.65 (s, 1H), 11.85 (s, 1H) (for the minor stereoisomer); ^{13}C NMR (d_6-DMSO, 100 MHz): δ 22.5, 28.9, 121.9, 122.2, 124.0, 125.7, 125.9, 126.8, 127.3, 128.0, 128.1, 128.6, 130.9, 131.1, 134.7, 135.4, 139.4, 144.4, 148.8, 149.6, 152.3, 152.4 (for both stereoisomers). Anal. Calcd. for $C_{13}H_{11}BrN_2O_2S$: C, 46.03; H, 3.27; N, 8.26. Found: C, 45.74; H, 3.51; N, 8.03.

Acknowledgments The research leading to these results has received funding from the European Union's Seventh Framework Programme (FP7/2007-2013) under grant agreement no. 264115—STREAM. The assistance of Miss Mihaela Bălan with the 2D NMR experiments is gratefully acknowledged. The author thanks Dr Mihaela Silion for her valuable help with the mass spectrometry experiments.

References

1. P. Grünanger, P. Vita-Finzi, in *The Chemistry of Heterocyclic Compounds,* vol. 49, *Part 1*, ed. by E.C. Taylor (Wiley, New York, 1991)
2. D. Giomi, F.M. Cordero, F. Machetti, in *Comprehensive Heterocyclic Chemistry III*, vol. 4, ed. by A.R. Katritzky, C.A. Ramsden, E.F.V. Scriven, R.J.K. Taylor (Elsevier, Oxford, 2008), pp. 365–485
3. Y.-T. Li, C.-L. Chen, Y.-Y. Hsu, H.-C. Hsu, Y. Chi, B.-S. Chen, W.-H. Liu, C.-H. Lai, T.-Y. Lin, P.-T. Chou, Tetrahedron **66**, 4223–4229 (2010)
4. Z. Yang, K. Zhang, F. Gong, S. Li, J. Chen, J.S. Ma, L.N. Sobenina, A.I. Mikhaleva, G. Yang, B.A. Trofimov, Beilstein J. Org. Chem. **7**, 46–52 (2011)
5. K.E. Pallett, S.M. Cramp, J.P. Little, P. Veerasekaran, A.J. Crudace, A.E. Slater, Pest Manag. Sci. **57**, 133–142 (2001)
6. D.R. dos Santos, A.G. Silva de Oliveira, R.L. Coelho, I.M. Begnini, R.F. Magnago, L. da Silva, ARKIVOC (xvii), 157–166 (2008)
7. A.A. Vieira, F.R. Bryk, G. Conte, A.J. Bortoluzzi, H. Gallardo, Tetrahedron Lett. **50**, 905–908 (2009)
8. R.P. Clausen, E.K. Moltzen, J. Perregaard, S.M. Lenz, C. Sanchez, E. Falch, B. Frølund, T. Bolvig, A. Sarup, O.M. Larsson, A. Schousboe, P. Krogsgaard-Larsen, Bioorg. Med. Chem. **13**, 895–908 (2005)
9. B. Frølund, L.S. Jensen, L. Guandalini, C. Canillo, H.T. Vestergaard, U. Kristiansen, B. Nielsen, T.B. Stensbøl, C. Madsen, P. Krogsgaard-Larsen, T. Liljefors, J. Med. Chem. **48**, 427–439 (2005)
10. P. Krogsgaard-Larsen, B. Frølund, T. Liljefors, B. Ebert, Biochem. Pharmacol. **68**, 1573–1580 (2004)
11. E. Nakayama, K. Watanabe, M. Miyauchi, K. Fujimoto, J. Ide, J. Antibiot. (Tokyo) **43**, 1122–1130 (1990)
12. S. Batra, T. Srinivasan, S.K. Rastogi, B. Kundu, A. Patra, A.P. Bhaduri, M. Dixit, Bioorg. Med. Chem. Lett. **12**, 1905–1908 (2002)
13. S. Batra, A.K. Roy, A. Patra, A.P. Bhaduri, W.R. Surin, S.A.V. Raghavan, P. Sharma, K. Kapoor, M. Dikshit, Bioorg. Med. Chem. **12**, 2059–2077 (2004)
14. B. Loh, L. Vozzolo, B.J. Mok, C.C. Lee, R.J. Fitzmaurice, S. Caddick, A. Fassati, Chem. Biol. Drug Des. **75**, 461–474 (2010)
15. Y.S. Lee, S.M. Park, B.H. Kim, Bioorg. Med. Chem. Lett. **19**, 1126–1128 (2009)
16. V.E. Kuz'min, A.G. Artemenko, E.N. Muratov, I.L. Volineckaya, V.A. Makarov, O.B. Riabova, P. Wutzler, M. Schmidtke, J. Med. Chem. **50**, 4205–4213 (2007)
17. F. Chevreuil, A. Landreau, D. Séraphin, G. Larcher, S. Mallet, J.-P. Bouchara, P. Richomme, J. Enzyme Inhib. Med. Chem. **22**, 563–569 (2007)
18. M. Tomishima, H. Ohki, A. Yamada, K. Maki, F. Ikeda, Bioorg. Med. Chem. Lett. **18**, 2886–2890 (2008)
19. X. Han, C. Li, M.D. Mosher, K.C. Rider, P. Zhou, R.L. Crawford, W. Fusco, A. Paszczynski, N.R. Natale, Bioorg. Med. Chem. **17**, 1671–1680 (2009)
20. M.W. Amolins, L.B. Peterson, B.S.J. Blagg, Bioorg. Med. Chem. **17**, 360–367 (2009)
21. S.F.M. Tohid, N.I. Ziedan, F. Stefanelli, S. Fogli, A.D. Westwell, Eur. J. Med. Chem. **56**, 263–270 (2012)
22. J. Mao, H. Yuan, Y. Wang, B. Wan, M. Pieroni, Q. Huang, R.B. van Breemen, A.P. Kozikowski, S.G. Franzblau, J. Med. Chem. **52**, 6966–6978 (2009)
23. C. Changtam, P. Hongmanee, A. Suksamrarn, Eur. J. Med. Chem. **45**, 4446–4457 (2010)
24. M. Pieroni, A. Lilienkampf, Y. Wang, B. Wan, S. Cho, S.G. Franzblau, A.P. Kozikowski, ChemMedChem **5**, 1667–1672 (2010)
25. T.M.V.D. Pinho e Melo, Curr. Org. Chem. **9**, 925–958 (2005)

26. F. Himo, T. Lovell, R. Hilgraf, V.V. Rostovtsev, L. Noodleman, K.B. Shapless, V.V. Fokin, J. Am. Chem. Soc. **127**, 210–216 (2005)
27. T.V. Hansen, P. Wu, V.V. Fokin, J. Org. Chem. **70**, 7761–7764 (2005)
28. F.G. Weber, Z. Chem. **10**, 143–144 (1970)
29. F.G. Weber, Tetrahedron **26**, 2507–2514 (1970)
30. A.L. Baumstark, D.R. Chrisope, R.A. Keel, D.W. Boykin, J. Heterocycl. Chem. **17**, 1719–1721 (1980)
31. C.E. Stephens, R.K. Arafa, J. Chem. Educ. **83**, 1336–1340 (2006)
32. J. Larkin, M.G. Murray, D.C. Nonhebel, J. Chem. Soc. C 947–949 (1970)
33. T. Lesiak, S. Nielek, Chem. Heterocycl. Compd. **11**, 137–140 (1975)
34. M.M.M. Ramiz, W.A. El-Sayed, A.I. El-Tantawy, A.A.-H. Abdel-Rahman, Arch. Pharm. Res. **33**, 647–654 (2010)
35. D. Azarifar, K. Khosravi, R.-A. Veisi, ARKIVOC (ix), 178–184 (2010)
36. R.P. Barnes, T.C. Goodwin Jr, T.W. Cotton Jr, J. Am. Chem. Soc. **69**, 3135–3138 (1947)
37. S.S. Thakare, A.G. Doshi, Asian J. Chem. **13**, 780–782 (2000)
38. Y. Budak, M. Ceylam, Chin. J. Chem. **27**, 1575–1581 (2009)
39. C.L. Bickel, J. Am. Chem. Soc. **69**, 2134–2136 (1947)
40. W.B. Black, R.E. Lutz, J. Am. Chem. Soc. **77**, 5134–5140 (1955)
41. G.E. Southard, G.M. Murray, J. Org. Chem. **70**, 9036–9039 (2005)
42. Yu.K. Yur'ev, N.V. Magdesieva, V.V. Titov, Zh. Obshch. Khim. **34**, 1078–1081 (1964)
43. E. Belgodere, R. Bossio, F. De Sio, S. Marcaccini, R. Pepino, Heterocycles **20**, 501–504 (1983)
44. C.-J. Zheng, S.-M. Jiang, Z.-H. Chen, B.-J. Ye, H.-R. Piao, Arch. Pharm. (Weinheim) **344**, 689–695 (2011)
45. R. Laliberté, J. Manson, H. Warwick, G. Medawar, Can. J. Chem. **46**, 1952–1956 (1968)
46. L. Greiner-Bechert, H.-H. Otto, Arch. Pharm. (Weinheim) **324**, 563–572 (1991)
47. G. Dannhardt, W. Kiefer, G. Krämer, S. Maehrlein, U. Nowe, B. Fiebich, Eur. J. Med. Chem. **35**, 499–510 (2000)
48. S.A. Basaif, T.R. Sobahi, A.K. Khalil, M.A. Hassan, Bull. Korean Chem. Soc. **26**, 1677–1681 (2005)
49. J.K. Sneed, R. Levine, J. Am. Chem. Soc. **72**, 5219–5220 (1950)
50. N. Latif, N. Mishriky, N.S. Girgis, Indian J. Chem. **15B**, 118–120 (1977)