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SYNTHESIS AND RING OPENING REACTIONS OF (3-ARYLOXIRAN-2-YL)(THIOPHEN-2-YL)METHANONES

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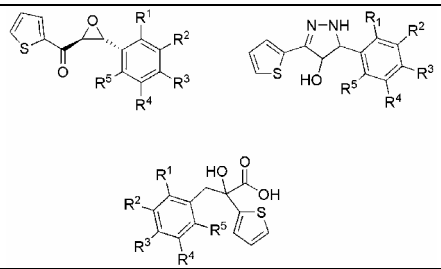
The Weitz-Scheffer epoxidation of thiophene-containing analogues of chalcone with hydrogen peroxide in the presence of NaOH has been used for the synthesis of the title oxiranes. Opening of the epoxide ring in these oxiranes using hydrazine afforded hydroxypyrazolines, whereas treatment with concentrated NaOH led to the isolation of thiophene-containing 2-hydroxypropionic acids.



INTRODUCTION

Chalcone and its analogues are valuable starting materials for the preparation of a large variety of derivatives through Michael additions or ring closure reactions.[1,2] Amongst the reactions in which chalcones are known to participate as substrates, epoxidation of the carbon–carbon double bond appears to be one of the most investigated transformation, and many variants for the asymmetric epoxidation of chalcones are available nowadays[3,4] owing to the significance of the resulting chiral epoxides as versatile building blocks for the synthesis of enantiomerically pure drugs and natural products. The synthetic utility of epoxides in the formation of more complex organic compounds relies heavily on their ability to undergo ring-opening reactions, very often with high (if not complete) regioselectivity and stereoselectivity. For example, chalcone epoxides have been recently employed as reagents in halogen-free (and sometimes metal-free) Friedel-Crafts alkylations of heteroaromatics. Thus, a series of reports have disclosed tris(4-bromophenyl)aminium hexachloroantimonate ($TBPA^{+}\cdot SbCl_6^{-}$) as a highly efficient non-metallic initiator of the ring-opening of chalcone epoxides to generate a distonic radical cation which subsequently acts as an alkylating agent. In the presence of this catalyst, chalcone epoxides react with anisole and 1-methoxynaphthalene to afford the normal alkylation products,[5] while the alkylation of 2-methoxynaphtalene or various 2-naphthols under the same conditions has led instead to naphtho[2,1-*b*]furans as a result of a cascade reaction comprising a Friedel-Crafts alkylation, followed by ring closure to 1,2-dihydro naphtho[2,1-*b*]furans and aromatisation.[5,6] The use of the same metal-free catalyst allowed the smooth reaction of chalcone epoxides with heteroaromatic substrates such as furans, pyrroles and indoles.[7] Through the same mechanism involving the epoxide opening as the first step, initiator $TBPA^{+}\cdot SbCl_6^{-}$ was also able to catalyze the cross

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cycloaddition of chalcone epoxides with alkenes[8] or with imines[9] to afford highly substituted tetrahydrofurans and 1,3-oxazolidines, respectively. In addition, three methodologies for the ring-opening of chalcone epoxides with indoles and pyrrole have been recently reported. The first of these synthetic approaches uses indium(III) chloride as catalyst in a regioselective process,[10] the second is an electrochemically-induced transformation catalyzed by a triarylimidazole redox mediator,[11] while the last is a green protocol that employs β-cyclodextrin in water.[12]

Besides the aforementioned ring-opening of chalcone epoxides based on the generation of cations for Friedel-Crafts alkylations, scarce examples of more classical approaches to ring-opening reactions of chalcone epoxides by nucleophiles are also available. Thus, thiolate anions that have been generated *in situ* by the indium(I) iodide-promoted cleavage of diaryl disulfides open the oxirane ring in chalcone epoxides in the presence of $InCl_3$ to give 3-arylthio-2-hydroxypropan-1-ones.[13] Aminolysis of chalcone epoxides with cyclic secondary aliphatic amines has been shown to depend strongly on the nature of the aryl substituent of the oxirane ring.[14] Despite the fact that chalcone epoxides have been known to undergo ring-opening with arylamines in the absence of catalysts,[15] a recent study has disclosed the use of sulfanilic acid as catalyst for the preparation of 3-arylamino-2-hydroxypropan-1-ones from chalcone epoxides.[16] Both 1,2- and 1,3-binucleophiles have been reported to participate in ring-opening reactions of chalcone epoxides, which usually occur with concomitant ring closure involving the neighbouring carbonyl function to yield hydroxyl-substituted heterocycles. Thus, hydrazine and its derivatives yielded 4-hydroxy-4,5-dihydropyrazoles,[15,17,18] hydroxylamine afforded 4-hydroxy-4,5-dihydroisoxazoles,[19,20] and thiourea led to 5,6-dihydro-5-hydroxypyrimidine-2(1*H*)-thione.[21]

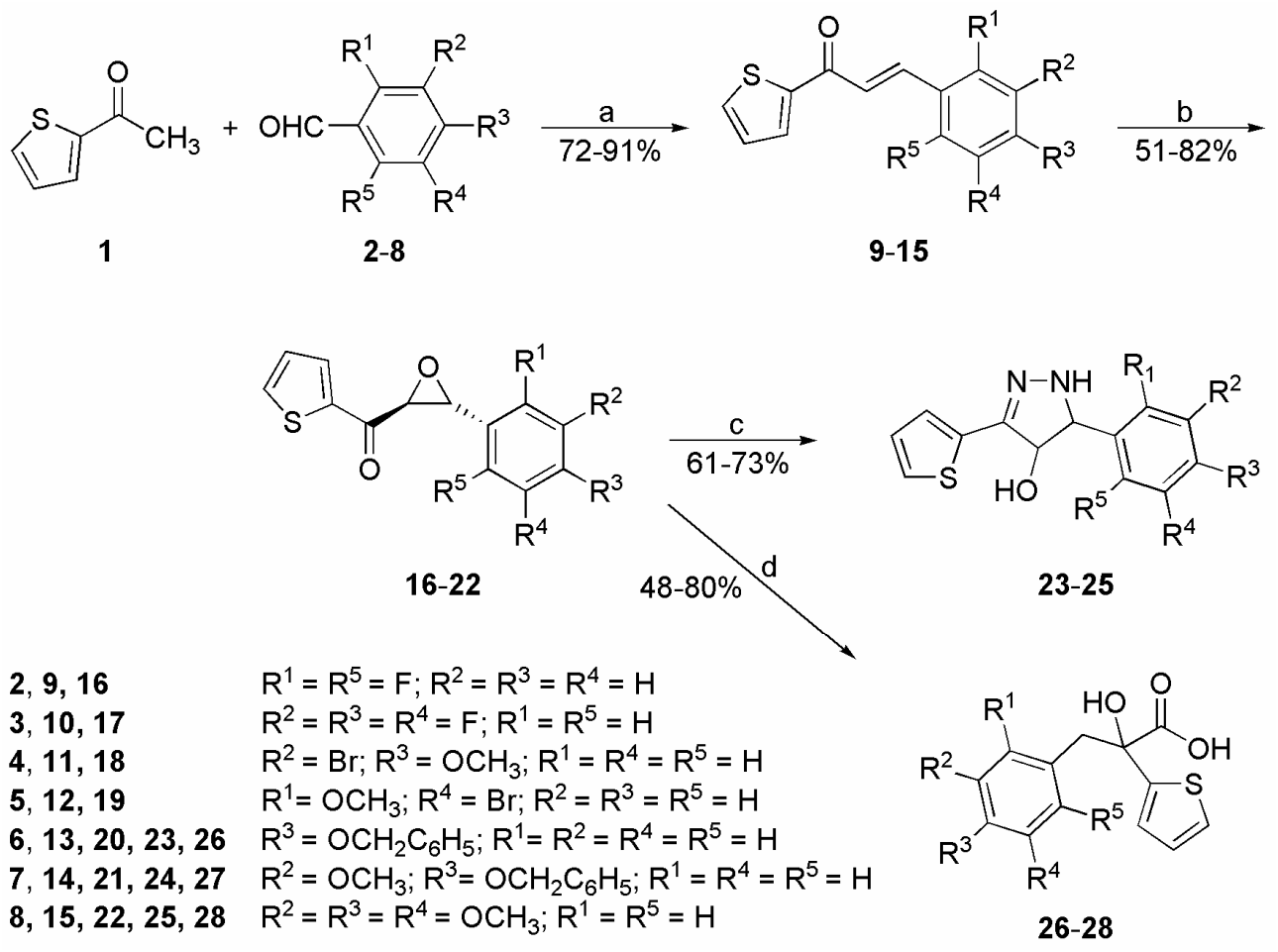
The current study, which is an extension of our previous work on the synthesis and chemistry of thiophene-substituted chalcone analogues,[22] reports the synthesis of novel thiophene-substituted α,β-unsaturated ketones, describes their conversion into the corresponding chalcone epoxides, and investigates the reaction of these oxiranes with hydrazine, as well as their transformation into α-hydroxy acids.

RESULTS AND DISCUSSION

The thiophene-containing chalcone analogues required as starting materials in this study have been obtained with very good yields through the NaOH-catalyzed Claisen condensation of 2-acetylthiophene **1** and a series of commercially available, less common, fluorine- and alkoxy-substituted aromatic aldehydes **2**–**8** (Scheme 1). Out of the seven synthesized chalcone analogues, compounds **10**, **12**, **13** and **14** were completely characterized for the first time. Chalcone analogue **9** has been previously reported,[23] and the recorded NMR spectra are identical to those given in the literature. Nonetheless, the physical and structural characterization of compound **9** has been amended in this paper by the addition of a melting point and the inclusion of the ^{13}C-^{19}F coupling in its ^{13}C NMR spectrum. Chalcone analogue **11** has been fully characterized by NMR spectroscopy in a previous report,[24] but its melting point was not given, and this omission has been corrected in this paper. Chalcone analogue **15** has been mentioned in several papers, and even though the proton spectrum reported in the literature[25] was identical to the one recorded for our compound, its ^{13}C NMR spectrum is reported for the first time in this paper. The characteristic signals in the ^{1}H NMR spectra of chalcone analogues **9**–**15** are the two doublets at chemical shifts situated between 7.30 and 7.70 for one olefinic proton, and between 7.70 and 8.00 ppm for the other. The 16 Hz coupling constant of these doublets supports the *E* geometry of these chalcone analogues **9**–**15**. The influence of fluorine substitution in compounds **9** and **10** has also been evidenced in the NMR spectra of these compounds through the splitting of the hydrogen and carbon signals in the fluorine-substituted phenyl ring.

Only a few chalcone epoxides have been so far obtained from 3-aryl-1-(thiophen-2-yl)prop-2-ene-1-ones through epoxidation under various conditions, but other synthetic approaches (such as the Darzens condensation[26] or the light-promoted Ru-catalyzed reaction of styrenes and benzaldehydes in the presence of an oxidant[27]) have been used to produce the known thiophene-substituted chalcone epoxides. The first known examples of thiophene-containing chalcone epoxides, which have been obtained using the classical Weitz-Scheffer reaction (hydrogen peroxide as oxidant in the presence of NaOH), emerged in the Russian literature.[28] Later, an asymmetric variant of the Weitz-Scheffer epoxidation was conducted on a thiophene-containing chalcone analogue in the presence of poly-L-lysine to afford the enantiomer of the epoxide with an (2*R*,3*S*) absolute configuration in an enantiomeric excess of 80%.[29] Since then,

several other systems that use different oxidants (NaOCl, *t*-butyl hydroperoxide) have been developed for the asymmetric epoxidation of thiophene-containing chalcone analogues in the presence of *Cinchona* alkaloids-derived phase transfer catalysts[30,31] or chiral monoaza-15-crown-5 macrocycles anellated to L-arabinose.[32] Because our aim was to obtain novel thiophene-containing chalcone epoxides irrespective of their enantiomeric content, a typical Weitz-Scheffer procedure that has been reported in recent literature[21] was employed to transform chalcone analogues **9**–**15** in chalcone epoxides **16**–**22** (Scheme 1). The yields were generally good, with the notable exception of compound **16** having a 2,6-difluorophenyl moiety, in which case the steric hindrance generated by the presence of two *ortho* substituents presumably limited the access of the oxidant species to the reaction site. In the same time, compound **19** that has in its structure a methoxy group *ortho* to the carbon atom in the phenyl ring that is involved in a bond with the oxirane was obtained with good yields. The characteristic signals in the proton NMR spectra of chalcone epoxides **16**–**22** are the two doublets in the range of 3.9–4.7 ppm and having the value of the coupling constants of approximately 2 Hz, which is indicative of the *trans* configuration of these compounds.[33] The two signals corresponding to the carbon atoms in the oxirane ring are located largely between 50 and 60 ppm in the carbon spectra of chalcone epoxides **16**–**22**. Again, the effect of the fluorine substituents in compounds **16** and **17** on the protons and carbon atoms of the phenyl ring has been evidenced through the multiplicity of the corresponding signals in the NMR spectra of these two compounds.



Scheme 1 – Synthesis and ring opening reactions of thiophene-containing chalcone epoxides. a) ethanol, NaOH, rt, overnight; b) 30% H_2O_2, 2N NaOH, methanol–acetone, 1 h; c) hydrazine hydrate, abs. ethanol, reflux, 6 h; d) NaOH, ethanol–water, reflux, 4 h.

The large number of literature reports that describe a wide range of reactions in which chalcone epoxides are starting materials proves the high reactivity of this class of compounds. The majority of the chalcone epoxides involved in these reactions derive rethrosynthetically from various carbocyclic analogues of chalcone, while the chemistry of chalcone epoxides featuring at least one heterocyclic moiety in their structure has been explored to a lesser extent. In particular, apart from a study dedicated to the reactions of (3-(4-chlorophenyl)oxiran-2-yl)(thiophen-2-yl)methanone with nucleophiles,[21] thiophene-containing chalcone epoxides have only sparingly been subjected to reactions such as reduction to the corresponding β-hydroxyketones,[34] or rearrangement to β-ketoaldehydes and their subsequent conversion into unsymmetrical benzils[35] or the related deoxybenzoins.[36] Because 4-hydroxypyrazolines are important intermediates for the synthesis of fully aromatized pyrazoles[15,37] and biologically active compounds,[17,38] the ring opening of chalcone epoxides **20**–**22** into hydroxypyrazolines **23**–**25** was investigated first (Scheme 1). The desired compounds were obtained with good yields when the starting materials and a slight excess of hydrazine hydrate were heated at reflux temperature in absolute ethanol for 6 h. The characteristic signals in the ^{1}H NMR spectra of hydroxypyrazolines **23**–**25** are those associated with the diastereotopic protons at C-4 and C-5 in the newly formed pyrazole ring. Since an extensive search of the literature revealed that no accurate NMR assignment for the protons and the carbon atoms in the pyrazole ring has been ever performed for 3,5-di(hetero)aryl-4,5-dihydro-1*H*-pyrazol-4-ols, we were unable to extrapolate the attribution for the protons at C-4 and C-5 in the pyrazole ring based on a precedent. Therefore, with a view to correctly assign the signals in the NMR spectra to the corresponding protons and carbon atoms in the pyrazole ring, 2D NMR spectra also were recorded for hydroxypyrazoline **23**. In the COSY spectrum, the doublet of doublets centered at 4.46 ppm correlates with the superimposed doublet of doublets at 4.89 ppm and with the doublet at 7.59 ppm, whereas the peaks centered at 4.89 ppm correlate with the signals at 4.46 ppm and with the doublet at 6.07 ppm. In addition, cross-peaks were noticed between the protons associated with the signals at 4.89 ppm and 6.07 ppm on one hand, and also between the protons associated with the signals at 4.46 ppm and 7.59 ppm on the other hand. Based on these observations, the signal centered at 4.46 ppm was assigned to the proton at C-5 of the pyrazole ring, while the signal at 4.89 ppm corresponds to the proton at C-4. The doublets at 6.07 ppm and 7.59 ppm were attributed to the protons in the OH group and pyrazole NH moiety, respectively, an assignment that was supported by the substantial decrease that was noticed for the integration values of these labile protons when the proton spectrum of compound **23** was retaken after the NMR sample had been treated with a drop of deuterium oxide. Moreover, no correlation was found in the ^{1}H-^{13}C HMQC spectrum of hydroxypyrazoline **23** for the doublets 6.07 ppm and 7.59 ppm, which proves that the protons associated with the protons associated with these signals are not directly linked to a carbon atom, but rather to heteroatoms. The cross-peaks involving the protons at C-5 (4.46 ppm) and at C-4 (4.89 ppm) allowed the indubitable assignment of the signal at 71.7 ppm to C-5, whereas the signal at 82.6 ppm was positively attributed to C-4. To complete the picture, the HMBC spectrum of compound **23** definitely indicated that the signal at 146.5 ppm belongs to C-3 in the pyrazole ring owing to the cross-peaks with the protons at C-4 and C-5.

We have decided to investigate next the reaction of thiophene-containing chalcone epoxides with concentrated NaOH. Despite having been known for more than a century, there is a surprisingly small number of reports in the literature on this transformation leading primarily to 2,3-diaryl-2-hydroxypropionic acids besides variable amounts of other by-products. Moreover, to the best of our knowledge, this reaction seems to have never been applied to chalcone epoxides featuring heteroaromatic rings in their structure. The transformation comprises as its first step the ring-opening of the oxirane ring in chalcone epoxide by the hydroxide anion; the resulting 1,2-diketone intermediate subsequently undergoes a benzilic-type rearrangement in the second step to afford the α-hydroxy acid. This reaction mechanism is supported by the isolation of the intermediate 1,2-diketone in a small number of cases, especially after short reaction times. Other synthetic methods, such as the alkylation of methyl mandelate,[39,40] the alkylation of a protected mandelate followed by deprotection,[41] or the addition of Grignard reagents to α-keto esters[40,42] have been also used for the preparation of 2,3-diaryl-2-hydroxypropionic acids, but these methods require the use of more expensive and more difficult to handle reagents compared to the

synthetic approach described herein. Typically, heating at reflux temperature of thiophene-containing chalcone epoxides **20**–**22** in the presence of excess NaOH in a mixture of ethanol and water afforded the hitherto unknown 3-aryl-2-hydroxy-2-(thiophen-2-yl)propionic acids **26**–**28** (Scheme 1). The crude compounds were obtained in good yields after filtration and treatment of the solution with dilute HCl, but recrystallization from aqueous ethanol was accompanied by a poor recovery of the pure α-hydroxy acids. The characteristic signals in the ^{1}H NMR spectra of compounds **26**–**28** are the two doublets at approximately 3.1 and 3.3 ppm, corresponding to the diastereotopic protons in the methylene group adjacent to the chiral carbon atom. Also, two very broad peaks, each integrating for one proton, were noticed in the ^{1}H NMR spectra of α-hydroxy acids **27** and **28**. The labile nature of the protons associated with these peaks was proven by the significant decrease of their integrating value (or even the flattening of the signals in a manner that made them indiscernible from the baseline of the spectrum) when the ^{1}H NMR spectrum was recorded again after the sample had been shaken with a drop of deuterium oxide. The peaks, which have been attributed to the protons in the hydroxyl and carboxyl functions in α-hydroxy acids **27** and **28**, appeared in the proton spectra at approximately 5.9 and 13.1 ppm, respectively. The typical signals in the ^{13}C NMR spectra of α-hydroxy acids **26**–**28** are the peak near 77 ppm, which corresponds to the quaternary chiral carbon atom, and the peak in the range of 45 to 47 ppm, attributed to the carbon atom in the methylene group adjacent to the quaternary chiral carbon atom.

As it has been mentioned above, 1,2-diketones are intermediates in the synthesis of α-hydroxy acids from chalcone epoxides, and ring opening of chalcone epoxides in the presence of NaOH has been known to lead to mixtures of structurally related α-hydroxy acid and 1,2-diketone.[15,43] However, a report[44] describing the rearrangement of chalcone epoxides to 1,2-ketones on silica gel has drawn our attention. This synthetic methodology seemed to be an extremely useful entry towards otherwise difficult to obtain 1,2-ketones, as this straightforward transformation entails inexpensive and affordable starting materials, occurs with excellent yields, and apparently yields no by-products (including the related α-hydroxy acid) that require subsequent separation. Unfortunately, in our hands, the attempted rearrangement of thiophene-containing chalcone epoxide **20** over silica gel under the conditions reported in this procedure led to the isolation of 4-(benzyloxy)benzaldehyde **6**, a product that presumably arises from the splitting of the epoxide ring in a manner that resembles the recently reported oxidative cleavage of epoxides in the presence of vanadyl acetylacetonate.[45] According to the NMR analysis of the crude product isolated from this reaction, benzaldehyde **6** was accompanied only by traces of impurities, which were probably derived from the thiophene-containing part of the chalcone epoxide **20** (based on signals that were barely noticeable in the proton spectrum and were tentatively attributed to the protons in the thiophene ring). Because no significant amount of compounds containing a thiophene ring has been retrieved from the combined mixture of non-polar solvents used as reaction medium and in the work-up, it can be hypothesized that the thiophene-containing part of reactant **20** was transformed into polar compound (or compounds), which remained preferentially adsorbed onto silica rather than pass into the dichloromethane washings.

EXPERIMENTAL

Materials and methods

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. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400-MHz spectrometer. The signals owing to residual protons in the deuterated solvents were used as internal standards for the ^{1}H NMR spectra. The chemical shifts for the carbon atoms are given relative to deuteriochloroform (δ = 77.16 ppm) and d_6-dimethyl sulfoxide (δ = 39.52 ppm).[46] The chemical reagents were obtained from Sigma–Aldrich and were used without prior purification. Silica gel 60 (for column chromatography, 0.040–0.063 mm) was supplied by Merck.

Synthesis of thiophene-containing chalcone analogues – General procedure

To a solution of the aldehyde (5 mmol) in ethanol (minimum volume required to solve the aldehyde at room temperature) was added 2-acetylthiophene **1** (630 mg, 5 mmol) followed by 3–4 drops of 10% aq. NaOH. The mixture was stirred at room temperature overnight, then it was refrigerated for 2 h. The solid was filtered, washed with cold ethanol (5 mL), and recrystallized from the appropriate solvent.

(E)-3-(2,6-Difluorophenyl)-1-(thiophen-2-yl)-2-propen-1-one (**9**)

This compound was obtained from 2-acetylthiophene **1** and 2,6-difluorobenzaldehyde **2** as off-white crystals (905 mg, 72%), mp 114–115 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 6.93–

7.01 (m, 2H), 7.19 (dd, *J* = 3.6 and 5.2 Hz, 1H), 7.29–7.37 (m, 1H), 7.70 (dd, *J* = 1.2 and 5.2 Hz, 1H), 7.73 (d, *J* = 16.0 Hz, 1H), 7.86 (dd, *J* = 1.2 and 3.6 Hz, 1H), 7.92 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 112.1 (dd, *J* = 5.4 and 20.2 Hz), 113.0 (t, *J* = 14.7 Hz), 127.3, (t, *J* = 8.4 Hz), 128.5, 130.0, 131.4 (t, *J* = 11.0 Hz), 132.3, 134.4, 145.5, 162.2 (dd, *J* = 6.8 and 256.0 Hz), 182.3; *Anal*. $C_{13}H_8F_2OS$: C, 62.39; H, 3.22. Found: C, 62.55; H, 3.07.

(E)-1-(Thiophen-2-yl)-3-(3,4,5-trifluorophenyl)-2-propen-1-one (**10**)

This compound was obtained from 2-acetylthiophene **1** and 3,4,5-trifluorobenzaldehyde **3** as colorless crystals (980 mg, 73%), mp 185–186 °C (acetone); ^{1}H NMR ($CDCl_3$): δ 7.20 (dd, *J* = 3.6 and 4.8 Hz, 1H), 7.22–7.30 (m, 2H), 7.32 (d, *J* = 15.6 Hz, 1H), 7.66 (d, *J* = 15.6 Hz, 1H), 7.72 (dd, *J* = 1.2 and 4.8 Hz, 1H), 7.87 (dd, *J* = 1.2 and 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 112.4 (dd, *J* = 5.9 and 15.8 Hz), 123.8, 128.6, 130.9–131.3 (m), 132.4, 134.8, 140.7, 141.0 (dt, *J* = 15.5 and 255.4 Hz), 145.1, 151.5 (ddd, *J* = 4.1, 10.2 and 251.5 Hz), 181.3; *Anal*. Calcd. for $C_{13}H_7F_3OS$: C, 58.21; H, 2.63. Found: C, 58.44; H, 2.80.

(E)-3-(3-Bromo-4-methoxyphenyl)-1-(thiophen-2-yl)-2-propen-1-one (**11**)

This compound was obtained from 2-acetylthiophene **1** and 3-bromo-4-methoxybenzaldehyde **4** as yellow crystals (1390 mg, 86%), mp 133–134 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 3.94 (s, 3H), 6.92 (d, *J* = 8.4 Hz, 1H), 7.18 (dd, *J* = 4.0 and 4.8 Hz, 1H), 7.29 (d, *J* = 15.6 Hz, 1H), 7.53 (dd, *J* = 2.0 and 8.4 Hz, 1H), 7.68 (dd, *J* = 1.2 and 4.8 Hz, 1H), 7.73 (d, *J* = 15.6 Hz, 1H), 7.85–7.90 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 56.5, 112.0, 112.5, 120.5, 128.4, 128.9, 130.0, 131.9, 132.7, 134.0, 142.4, 145.7, 157.8, 181.9; *Anal*. Calcd. for $C_{14}H_{11}BrO_2S$: C, 52.03; H, 3.43. Found: C, 51.84; H, 3.40.

(E)-3-(5-Bromo-2-methoxyphenyl)-1-(thiophen-2-yl)-2-propen-1-one (**12**)

This compound was obtained from 2-acetylthiophene **1** and 5-bromo-2-methoxybenzaldehyde **5** as yellow crystals (1350 mg, 84%), mp 111–112 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 3.90 (s, 3H), 6.82 (d, *J* = 8.8 Hz, 1H), 7.18 (dd, *J* = 4.0 and 4.8 Hz, 1H), 7.45 (dd, *J* = 2.4 and 8.8 Hz, 1H), 7.46 (d, *J* = 16.0 Hz, 1H), 7.68 (dd, *J* = 1.2 and 4.8 Hz, 1H), 7.72 (d, *J* = 2.4 Hz, 1H); 7.86 (dd, *J* = 1.2 and 3.6 Hz, 1H), 8.05 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 56.0, 113.1, 123.4, 125.9, 128.4, 131.4, 132.0, 134.0, 134.2, 138.0, 145.7, 157.9, 182.3; *Anal*. Calcd. for $C_{14}H_{11}BrO_2S$: C, 52.03; H, 3.43. Found: C, 51.72; H, 3.17.

(E)-3-(4-Benzyloxyphenyl)-1-(thiophen-2-yl)-2-propen-1-one (**13**)

This compound was obtained from 2-acetylthiophene **1** and 4-(benzyloxy)benzaldehyde **6** as light yellow crystals (1455 mg, 91%), mp 142–143 °C (ethyl acetate); ^{1}H NMR ($CDCl_3$): δ 5.12 (s, 2H), 7.02 (dd, *J* = 2.8 and 8.8 Hz, 2H), 7.18 (dd, *J* = 4.0 and 4.8 Hz, 1H), 7.31 (d, *J* = 15.2 Hz, 1H), 7.33–7.47 (m, 4H), 7.60 (d, *J* = 2.8 and 8.8 Hz, 2H), 7.66 (dd, *J* = 1.2 and 4.8 Hz, 1H), 7.83 (d, *J* = 15.2 Hz, 1H), 7.85 (dd, *J* = 0.8 and 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 70.3, 115.5, 119.6, 127.6, 127.8, 128.3, 128.8, 130.4, 131.6, 133.6, 136.5, 144.0, 145.9, 161.0, 182.2; *Anal*. Calcd. for $C_{20}H_{16}O_2S$: C, 74.97; H, 5.03. Found: C, 75.22; H, 4.87.

(E)-3-(4-Benzyloxy-3-methoxyphenyl)-1-(thiophen-2-yl)-2-propen-1-one (**14**)

This compound was obtained from 2-acetylthiophene **1** and 4-benzyloxy-3-methoxybenzaldehyde **7** as light yellow crystals (1560 mg, 89%), mp 116–117 °C (ethanol); ^{1}H NMR (d_6-DMSO): δ 3.88 (s, 3H), 5.16 (s, 2H), 7.12 (d, *J* = 8.4 Hz, 1H), 7.29–7.49 (m, 7H), 7.55 (d, *J* = 2.0 Hz, 1H), 7.68 (d, *J* = 15.6 Hz, 1H), 7.77 (d, *J* = 15.6 Hz, 1H), 8.04 (d, *J* = 4.8 Hz, 1H), 8.33 (d, *J* = 3.6 Hz, 1H); ^{13}C NMR (d_6-DMSO): δ 55.8, 69.9, 111.3, 113.2, 119.6, 123.7, 127.6, 127.9, 128.0, 128.4, 128.8, 133.3, 135.2, 136.7, 143.5, 149.3, 150.3, 181.6; *Anal*. Calcd. for $C_{21}H_{18}O_3S$: C, 71.98; H, 5.18. Found: C, 71.77; H, 4.94.

(E)-1-(Thiophen-2-yl)-3-(3,4,5-trimethoxyphenyl)-2-propen-1-one (**15**)

This compound was obtained from 2-acetylthiophene **1** and 3,4,5-trimethoxybenzaldehyde **8** as light yellow crystals (1370 mg, 90%), mp 149–150 °C (ethanol) (lit.[25] mp 147–148 °C); ^{1}H NMR ($CDCl_3$): δ 3.90 (s, 3H), 3.92 (s, 6H), 6.86 (s, 2H), 7.18 (dd, *J* = 4.0 and 5.2 Hz, 1H), 7.31 (d, *J* = 16.0 Hz, 1H), 7.68 (dd, J = 1.2 and 5.2 Hz, 1H), 7.77 (d, *J* = 16.0 Hz, 1H), 7.88 (dd, *J* = 1.2 and 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 56.3, 61.0, 105.8, 120.9, 128.2, 130.2, 131.8, 133.9, 140.5, 144.2, 145.6, 153.5, 182.0; *Anal*. Calcd. for $C_{16}H_{16}O_4S$: C, 63.14; H, 5.30. Found: C, 63.43; H, 5.02.

Weitz-Scheffer epoxidation of thiophene-containing chalcone analogues – General procedure

A solution of the thiophene-containing chalcone analogue (2 mmol) in the solvent (a mixture of methanol and acetone) was sequentially treated with 30% hydrogen peroxide (2 mL) and 2N NaOH (0.5 mL). The mixture was stirred at room temperature for 1 h, and then it was gradually diluted with water (50 mL) and kept in refrigerator overnight. The solid that separated was filtered, air-dried and recrystallized from the appropriate solvent.

trans-(3-(2,6-Difluorophenyl)oxiran-2-yl)(thiophen-2-yl)methanone (**16**)

This compound was obtained from 3-(2,6-difluorophenyl)-1-(thiophen-2-yl)-2-propen-1-one **9** in methanol–acetone (14 mL, 1:1, v/v) as off-white crystals (270 mg, 51%), mp 62–63 °C (methanol); ^{1}H NMR ($CDCl_3$): δ 4.33 (d, *J* = 2.0 Hz, 1H), 4.65 (d, *J* = 2.4 Hz, 1H), 6.89–6.98 (m, 2H), 7.21 (dd, *J* = 4.0 and 5.2 Hz, 1H), 7.29–7.38 (m, 1H), 7.77 (dd, *J* = 1.2 and 4.8 Hz, 1H), 8.07 (dd, *J* = 1.2 and 4.0, Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 51.6, 57.6, 111.4 (t, *J* = 15.0 Hz), 112.1, (dd, *J* = 5.9 and 19.0 Hz), 128.7, 131.1 (t, *J* = 10.5 Hz), 133.8, 135.5, 141.3, 162.2 (dd, *J* = 7.0 and 250.5 Hz), 186.8; *Anal*. Calcd. for $C_{13}H_8F_2O_2S$: C, 58.64; H, 3.03. Found: C, 58.48; H, 3.15.

trans-(Thiophen-2-yl)(3-(3,4,5-trifluorophenyl)oxiran-2-yl)methanone (**17**)

This compound was obtained from 1-(thiophen-2-yl)-3-(3,4,5-trifluorophenyl)-2-propen-1-one **10** in methanol–acetone (15 mL, 1:2, v/v) as colorless crystals (350 mg, 62%), mp 116–117 °C (methanol); ^{1}H NMR ($CDCl_3$): δ 3.96 (d, *J* = 1.6 Hz, 1H), 4.12 (d, *J* = 1.6 Hz, 1H), 6.94–7.04 (m, 2H), 7.20 (dd, 1H, *J* = 4.0 and 5.2 Hz), 7.77 (dd, *J* = 1.2 and 5.2 Hz, 1H), 7.99 (dd, *J* = 1.2 and 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 57.8, 61.8, 110.2 (dd, *J* = 6.4 and 16.2 Hz), 128.7, 131.8–132.2 (m), 133.9, 135.8, 140.3 (dt, J = 15.0 and 252.3 Hz), 140.9, 151.8 (ddd, J = 4.2, 10.1 and 251 Hz), 185.4. *Anal*. Calcd. for $C_{20}H_{15}ClO_3S_2$: C, 59.62; H, 3.75. Found: C, 59.89; H, 3.64.

trans-(3-(3-Bromo-4-methoxyphenyl)oxiran-2-yl)(thiophen-2-yl)methanone (**18**)

This compound was obtained from 3-(3-bromo-4-methoxyphenyl)-1-(thiophen-2-yl)-2-propen-1-one **11** in methanol–acetone (12 mL, 1:2, v/v) as colorless crystals (500 mg, 74%), mp 166–167 °C (acetone); ^{1}H NMR ($CDCl_3$): δ 3.91 (s, 3H), 4.04 (d, *J* = 1.6 Hz, 1H), 4.09 (d, *J* = 1.6 Hz,

1H), 6.90 (d, *J* = 8.4 Hz, 1H), 7.17 (dd, *J* = 4.0 and 5.2 Hz, 1H), 7.26 (dd, *J* = 2.0 and 8.4 Hz, 1H), 7.51 (d, *J* = 2.0 Hz, 1H), 7.75 (dd, *J* = 0.8 and 4.8 Hz, 1H), 7.99 (dd, *J* = 0.8 and 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 56.5, 58.7, 61.9, 112.0, 112.3, 126.5, 128.6, 128.8, 130.7, 133.8, 135.5, 141.0, 156.6, 186.3; *Anal*. Calcd. for $C_{14}H_{11}BrO_3S$: C, 49.57; H, 3.27. Found: C, 49.69; H, 3.34.

trans-(3-(5-Bromo-2-methoxyphenyl)oxiran-2-yl)(thiophen-2-yl)methanone (**19**)

This compound was obtained from 3-(5-bromo-2-methoxyphenyl)-1-(thiophen-2-yl)-2-propen-1-one **12** in methanol–acetone (12 mL, 1:2, v/v) as colorless crystals (525 mg, 78%), mp 141–142 °C (acetone); ^{1}H NMR ($CDCl_3$): δ 3.77 (s, 3H), 3.92 (s, 1H), 4.41 (s, 1H), 6.74 (d, *J* = 8.8 Hz, 1H), 7.16 (dd, *J* = 4.0 and 5.2 Hz, 1H), 7.30 (d, *J* = 2.0 Hz, 1H), 7.37 (dd, *J* = 1.2 and 8.0 Hz, 1H), 7.72 (d, *J* = 4.8 Hz, 1H), 7.98 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 54.8, 55.6, 62.1, 112.1, 113.0, 126.1, 128.0, 128.4, 132.2, 133.6, 135.1, 140.9, 157.2, 186.3; *Anal.* Calcd. for $C_{14}H_{11}BrO_3S$: C, 49.57; H, 3.27. Found: C, 49.37; H, 3.21.

trans-(3-(4-(Benzyloxy)phenyl)oxiran-2-yl)(thiophen-2-yl)methanone (**20**)

This compound was obtained from 3-(4-benzyloxyphenyl)-1-(thiophen-2-yl)-2-propen-1-one **13** in methanol–acetone (12 mL, 1:2, v/v) as colorless crystals (550 mg, 82%), mp 140–141 °C (acetone); ^{1}H NMR ($CDCl_3$): δ 4.04 (d, *J* = 2.0 Hz, 1H), 4.09 (d, *J* = 2.0 Hz, 1H), 5.06 (s, 2H), 6.97 (d, *J* = 7.6 Hz, 2H), 7.16 (dd, *J* = 4.0 and 5.2 Hz, 1H), 7.24 (d, *J* = 6.6 Hz, 2H), 7.28–7.47 (m, 5H), 7.71 (d, *J* = 5.2 Hz, 1H), 7.98 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 59.4, 62.0, 70.1, 115.1, 127.2, 127.4, 128.1, 128.4, 128.6, 133.5, 135.1, 136.6, 141.0, 159.5, 186.6; *Anal*. Calcd. for $C_{20}H_{16}O_3S$: C, 71.41; H, 4.79. Found: C, 71.29; H, 4.84.

trans-(3-(4-(Benzyloxy)-3-methoxyphenyl)oxiran-2-yl(thiophen-2-yl)methanone (**21**)

This compound was obtained from 3-(4-benzyloxy-3-methoxyphenyl)-1-(thiophen-2-yl)-2-propen-1-one **14** in methanol–acetone (12 mL, 1:2, v/v) as colorless crystals (490 mg, 67%), mp 105–106 °C (methanol); ^{1}H NMR ($CDCl_3$): δ 3.89 (s, 3H), 4.08 (d, *J* = 2.0 Hz, 1H), 4.10 (d, *J* = 2.0 Hz, 1H), 5.16 (s, 2H), 6.81–6.88 (m, 3H), 7.16 (dd, *J* = 4.0 and 5.2 Hz, 1H), 7.26–7.46 (m, 5H), 7.73 (dd, *J* = 1.2 and 5.2 Hz, 1H), 7.99 (dd, *J* = 1.2 and 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 56.1, 59.6, 62.1, 71.0, 108.6, 113.9, 118.7, 127.2, 128.0, 128.2, 128.4, 128.6, 133.6, 135.2, 136.8, 140.9, 148.9, 150.1, 186.5; *Anal*. Calcd. for $C_{21}H_{18}O_4S$: C, 68.83; H, 4.95. Found: C, 69.19; H, 5.04.

trans-(Thiophen-2-yl)(3-(3,4,5-trimethoxyphenyl)oxiran-2-yl)methanone (**22**)

This compound was obtained from 1-(thiophen-2-yl)-3-(3,4,5-trimethoxyphenyl)-2-propen-1-one **15** in methanol–acetone (10 mL, 1:1, v/v) as colorless crystals (395 mg, 62%), mp 118–119 °C (acetone); ^{1}H NMR ($CDCl_3$): δ 3.85 (s, 3H), 3.87 (s, 6H), 4.03 (d, *J* = 2.0 Hz, 1H), 4.12 (d, *J* = 2.0 Hz, 1H), 6.57 (s, 2H), 7.18 (dd, *J* = 4.0 and 5.2 Hz, 1H), 7.75 (dd, *J* = 1.2 and 5.2 Hz, 1H), 8.00 (dd, *J* = 1.2 and 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 56.2, 59.6, 60.9, 61.9, 102.5, 128.5, 130.9, 133.7, 135.3, 138.6, 141.0, 153.7, 186.3; *Anal*. Calcd. for $C_{16}H_{16}O_5S$: C, 59.99; H, 5.03. Found: C, 59.89; H, 5.08.

Reaction of thiophene-containing chalcone epoxides with hydrazine – General procedure

Hydrazine hydrate (75 mg, 1.5 mmol) was added to a suspension of the chalcone epoxide (1 mmol) in absolute ethanol (15 mL), and the mixture was heated at reflux temperature for 6 h. The solvent was removed under reduced pressure, and the residue was dissolved in the minimum volume of boiling 96% ethanol. The crystals that separated upon refrigeration overnight were filtered, washed with little cold 96% ethanol, and air-dried.

5-(4-(Benzyloxy)phenyl)-3-(thiophen-2-yl)-4,5-dihydro-1H-pyrazol-4-ol (**23**)

This compound was obtained from (3-(4-(benzyloxy)phenyl)oxiran-2-yl)(thiophen-2-yl)methanone **20** as yellowish crystals (213 mg, 61%), mp 138–139 °C; ^{1}H NMR (d_6-DMSO): δ 4.46 (dd, *J* = 3.6 and 8.0 Hz, 1H), 4.89 (dd, *J* = 8.0 and 8.4 Hz, 1H), 5.10 (s, 2H), 6.07 (d, *J* = 7.6 Hz, 1H), 7.00 (d, *J* = 8.8 Hz, 2H), 7.05 (dd, *J* = 3.6 and 5.2 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.29–7.49 (m, 7H), 7.59 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (d_6-DMSO): δ 69.1, 71.7, 82.6, 114.8, 125.5, 125.7, 127.4, 127.6, 127.7, 127.8, 128.4, 133.2, 136.1, 137.1, 146.5, 157.6; *Anal*. Calcd. for $C_{20}H_{18}N_2O_2S$: C, 68.55; H, 5.18; N, 7.99. Found: C, 68.73; H, 5.04; N, 8.11.

5-(4-(Benzyloxy)-3-methoxyphenyl)-3-(thiophen-2-yl)-4,5-dihydro-1H-pyrazol-4-ol (**24**)

This compound was obtained from ((3-(4-(benzyloxy)-3-methoxyphenyl)oxiran-2-yl(thiophen-2-yl)methanone **21** as yellowish crystals (277 mg, 73%), mp 153–154 °C; ^{1}H NMR (d_6-DMSO): δ 3.77 (s, 3H), 4.46 (dd, *J* = 3.6 and 8.4 Hz, 1H), 4.93 (t, *J* = 8.0 Hz, 1H), 5.07 (s, 2H), 6.08 (d, *J* = 8.0 Hz, 1H), 6.83 (dd, *J* = 2.0 and 8.4 Hz, 1H), 6.96–7.03 (m, 2H), 7.05 (dd, *J* = 3.6 and 8.4 Hz, 1H), 7.29–7.48 (m, 7H), 7.56 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (d_6-DMSO): δ 55.5, 70.0, 72.1, 82.6, 110.6, 113.7, 118.7, 125.5, 125.7, 127.4, 127.7, 127.8, 128.4, 133.9, 136.1, 137.2, 146.6, 147.1, 149.2; *Anal*. Calcd. for $C_{21}H_{20}N_2O_3S$: C, 66.29; H, 5.30; N, 7.36. Found: C, 66.10; H, 5.13; N, 7.52.

3-(Thiophen-2-yl)-5-(3,4,5-trimethoxyphenyl)-4,5-dihydro-1H-pyrazol-4-ol (**25**)

This compound was obtained from (thiophen-2-yl)(3-(3,4,5-trimethoxyphenyl)oxiran-2-yl)methanone **22** as yellowish crystals (227 mg, 68%), mp 150–151 °C; ^{1}H NMR (d_6-DMSO): δ 3.65 (s, 3H), 3.77 (s, 6H), 4.47 (dd, *J* = 4.0 and 8.4 Hz, 1H), 4.97 (t, *J* = 8.0 Hz, 1H), 6.13 (d, *J* = 8.0 Hz, 1H), 6.67 (s, 2H), 7.06 (dd, *J* = 3.6 and 5.2 Hz, 1H), 7.35 (dd, *J* = 0.8 and 3.6 Hz, 1H), 7.46 (dd, *J* = 1.2 and 5.2 Hz, 1H), 7.58 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (d_6-DMSO): δ 55.8, 59.9, 72.4, 82.7, 103.8, 125.5, 125.7, 127.4, 136.0, 136.7, 136.8, 146.6, 152.9; *Anal*. Calcd. for $C_{16}H_{18}N_2O_4S$: C, 57.47; H, 5.43; N, 8.38. Found: C, 57.69; H, 5.24; N, 8.57.

Synthesis of 2-hydroxypropanoic acids from thiophene-containing chalcone epoxides – General procedure

The thiophene-containing chalcone epoxide (2.5 mmol) was heated at reflux temperature with NaOH (0.5 g, 12.5 mmol) in a mixture of ethanol (10 mL) and water (3 mL) for 4 h. The solution was cooled at room temperature and filtered. The filtrate was diluted with water (40 mL) and gradually treated with 10% HCl until pH 1. The crude solid α-hydroxy acids were filtered, air-dried and recrystallized. In the case of compound **28**, which separated as a sticky solid after the addition of 10% HCl, the supernatant was pipetted off, and then the residue was crystallized from the appropriate solvent.

3-(4-(Benzyloxy)phenyl)-2-hydroxy-2-(thiophen-2-yl)propanoic acid (**26**)

This compound was obtained from (3-(4-(benzyloxy)phenyl)oxiran-2-yl)(thiophen-2-yl)methanone **20** as off-white crystals (515 mg, 58%), mp 149–150 ºC (ethanol–water); ^{1}H NMR (d_6-DMSO): δ 3.09 (d, *J* = 13.6 Hz, 1H), 3.34 (d, *J* = 13.6 Hz, 1H), 5.04 (s, 2H), 6.85 (d, *J* = 8.8 Hz, 2H),

6.97 (dd, *J* = 3.6 and 5.2 Hz, 1H), 7.08–7.15 (m, 3H), 7.28–7.42 (m, 6H); ^{13}C NMR (d_6-DMSO): δ 45.8, 69.1, 77.2, 113.9, 124.0, 124.9, 126.7, 127.7, 127.8, 128.4, 131.5, 137.2, 148.1, 157.1, 174.2; *Anal*. Calcd. for $C_{20}H_{18}O_4S$: C, 67.78; H, 5.12. Found: C, 67.53; H, 5.33.

3-(4-(Benzyloxy)-3-methoxyphenyl)-2-hydroxy-2-(thiophen-2-yl)propanoic acid (**27**)

This compound was obtained from (3-(4-(benzyloxy)-3-methoxyphenyl)oxiran-2-yl(thiophen-2-yl)methanone **21** as off-white crystals (770 mg, 80%), 145–146 ºC (dec.) (ethanol–water); ^{1}H NMR (d_6-DMSO): δ 3.08 (d, *J* = 13.6 Hz, 1H), 3.33 (d, *J* = 13.6 Hz, 1H), 3.68 (s, 3H), 5.01 (s, 2H), 5.88 (s, 1H, exchangeable with deuterium), 6.71 (d, *J* = 8.0 Hz, 1H), 6.80 (s, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 6.98 (dd, *J* = 3.6 and 4.8 Hz, 1H), 7.11–7.16 (m, 1H), 7.28–7.48 (m, 6H), 13.13 (br s, 1H, exchangeable with deuterium); ^{13}C NMR (d_6-DMSO): δ 46.4, 55.3, 69.9, 77.3, 113.0, 114.7, 122.6, 124.1, 125.0, 126.7, 127.8, 128.4, 129.0, 137.3, 146.5, 148.1, 148.2, 174.2; *Anal*. Calcd. for $C_{21}H_{20}O_5S$: C, 65.61; H, 5.24. Found: C, 65.78; H, 5.08.

2-Hydroxy-2-(thiophen-2-yl)-3-(3,4,5-trimethoxyphenyl)propanoic acid (**28**)

This compound was obtained from (thiophen-2-yl)(3-(3,4,5-trimethoxyphenyl)oxiran-2-yl)methanone **22** as off-white crystals (405 mg, 48%), 86–87 ºC (ethanol–water); ^{1}H NMR (d_6-DMSO): δ 3.08 (d, *J* = 13.6 Hz, 1H), 3.34 (d, *J* = 13.6 Hz, 1H), 3.61 (s, 3H), 3.69 (s, 6H), 5.93 (s, 1H, exchangeable with deuterium), 6.49 (s, 2H), 7.00 (dd, *J* = 3.6 and 5.2 Hz, 1H), 7.15 (dd, *J* = 1.2 and 3.6 Hz, 1H), 7.40 (dd, *J* = 1.2 and 5.2 Hz, 1H), 13.17 (br s, 1H, exchangeable with deuterium); ^{13}C NMR (d_6-DMSO): δ 47.2, 55.7, 59.9, 77.3, 107.9, 124.2, 125.0, 126.8, 131.7, 136.2, 148.1, 152.0, 174.2; *Anal*. Calcd. for $C_{16}H_{18}O_6S$: C, 56.79; H, 5.36. Found: C, 57.02; H, 5.04.

Attempted rearrangement of thiophene-containing chalcone epoxide 20 to 1-((4-benzyloxy)phenyl)-3-(thiophen-2-yl)propane-1,2-dione

(3-(4-(Benzyloxy)phenyl)oxiran-2-yl)(thiophen-2-yl)methanone **20** (336 mg, 1 mmol) was dissolved in dichloromethane (10 mL), and then *n*-hexane (40 mL) was added to the solution, followed by silica gel (5 g). The slurry was stirred at room temperature for 24 h, then silica gel was removed by filtration and washed with dichloromethane (3× 10 mL). The solvents in the combined fractions were removed under reduced pressure (temperature of the water bath was 22 °C) to yield an orange residue (143 mg), which was analyzed by ^{1}H NMR. The solid consisted mainly of 4-(benzyloxy)benzaldehyde.

CONCLUSIONS

Four novel thiophene-substituted α,β-unsaturated ketones have been reported, whereas three previously known analogues have been thoroughly characterized from a structural point of view. From these chalcone analogues, seven corresponding *trans*-oxiranes have been obtained through the Weitz-Scheffer epoxidation. These intermediates, whose chemical reactivity has been well-documented in the recent literature, have been subsequently employed in the investigation of some reactions involving epoxide ring opening. Reaction of the thiophene-containing chalcone epoxides with hydrazine led to hydroxypyrazolines; full NMR analysis of one of these hydroxypyrazolines allowed the unequivocal and complete attribution of the NMR signals for the protons and carbon atoms in the pyrazole ring for the first time. Treatment of the same chalcone epoxides with NaOH afforded the hitherto unknown thiophene-containing 2-hydroxypropanoic acids. The attempted rearrangement of a chalcone epoxide to the corresponding 1,2-diketone over silica gel was unsuccessful.

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