U.P.B. Sci. Bull., Series B, Vol. 79, Iss. 2, 2017 ISSN 1454-2331

MULTISTEP SYNTHESIS OF PYRAZOLES FROM THIOPHENE-CONTAINING CHALCONE ANALOGUES

Gheorghe ROMAN[1]

Three thiophene-substituted NH-pyrazoles with potential biological activities have been obtained from the corresponding chalcone analogues in three synthetic steps. The reaction sequence comprised addition of bromine, conversion of chalcone dibromides into β-diketones, and ring closure. The enol-ketone tautomerism in the case of β-diketones, and the annular tautomerism for NH-pyrazoles were investigated in solution using NMR. The unusual replacement of the bromine atom β to the carbonyl with ethoxy in two chalcone dibromides having a para-methoxyphenyl moiety has also been reported.

Keywords: chalcones, 1,3-diketones, pyrazoles, ring closure, thiophenes

1. Introduction

One of the heteroaromatic ring systems that find many important practical applications and a particularly extensive use in medicinal chemistry is pyrazole [1]. As an example, over 200 biologically active pyrazoles have been reported in a general review that covers the 2002–2012 decade [2], while the progress in the development of novel pyrazoles with anti-inflammatory, antimicrobial and/or anticancer activities has been recently reviewed [3–5]. In addition, monoamine oxidase inhibitory activity of pyrazoles (as well as that of their partially and fully reduced analogues) has been surveyed in correlation with these compounds' usefulness as antidepressant and anticonvulsant agents [6], whereas a recent overview of pyrazole as the core scaffold in the generation of antimycobacterials is also available [7]. In particular, 3,5-diarylpyrazoles have been found to inhibit arylamine *N*-acetyltransferase, an enzyme that has been implicated as a potential anti-tubercular target [8], or to inhibit the growth of several carcinoma cell lines [9]. 3,5-Diarylpyrazoles also exhibited neuroprotective properties against excitotoxicity induced by *N*-methyl-ᴅ-aspartate, presumably through the inhibition of voltage-gated sodium channels [10], and their tautomers were shown to undergo a significant equilibrium perturbation that is induced during the specific recognition by monoamine oxidases A and B isoforms [11]. As for the thienyl-substituted pyrazoles, a close inspection of the literature revealed the paucity of information regarding their biological activities [12, 13], which could

---

[1] Senior Researcher, Department of Inorganic Polymers, *Petru Poni* Institute of Macromolecular Chemistry, Iaşi, Romania, e-mail: gheorghe.roman@icmpp.ro

be a consequence of the small number (less than 20) of pyrazoles featuring as substituent a thiophene ring that have been described both in journal articles or patents. Therefore, the present study aims at establishing a reliable multistep synthetic pathway for the preparation of thienyl-substituted pyrazoles for subsequent biological evaluation, and reports the synthesis and the structural characterization of both the target compounds and the required intermediates.

2. Experimental

All chemical reagents and solvents were purchased from commercial suppliers (Sigma–Aldrich, Alfa Aesar and Merck), and were used without further purification. Melting points were taken on a Mel-Temp II apparatus and are uncorrected. ^{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 $CDCl_3$ (δ = 77.16 ppm) or d_6-DMSO (δ = 39.52 ppm) [14].

3-(4-Methoxyphenyl)-1-(thiophen-2-yl)prop-2-en-1-one (**5**). A solution of 2-acetylthiophene **1** (2.52 g, 20 mmol) and 4-methoxybenzaldehyde **2** (2.72 g, 20 mmol) in ethanol (10 mL) was treated with 10% NaOH (10 drops), and then it was stirred at room temperature overnight. The resulting solid was filtered, sequentially washed with 2-propanol (5 mL) and petroleum ether (10 mL), air-dried, and recrystallized from ethanol to afford yellow crystals (3.07 g, 63%), mp 81–82 ºC (lit. mp 81–82 ºC [15]; lit. mp 80–82 ºC [16]); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.86 (s, 3H), 6.94 (d, J = 8.4 Hz, 2H), 7.18 (dd, J = 4.0 and 4.8 Hz, 1H), 7.31 (d, J = 15.6 Hz, 1H), 7.60 (d, J = 8.4 Hz, 2H), 7.66 (dd, J = 0.8 and 4.8 Hz, 1H), 7.83 (d, J = 15.6 Hz, 1H), 7.85 (dd, J = 0.8 and 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 55.5, 114.6, 119.4, 127.6, 128.3, 130.4, 131.6, 133.6, 144.0, 145.9, 161.9, 182.2.

3-(2,4-Dichlorophenyl)-1-(thiophen-2-yl)prop-2-en-1-one (**6**). To a solution of 2-acetylthiophene **1** (2.52 g, 20 mmol) and 2,4-dichlorobenzaldehyde **3** (3.50 g, 20 mmol) in ethanol (20 mL), 10% NaOH (10 drops) was added, and then the mixture was stirred at room temperature overnight. The solid was filtered, washed with ethanol (10 mL), air-dried, and recrystallized from ethanol to give yellowish crystals (4.58 g, 81%), mp 120–121 ºC (lit. mp 119–120 ºC [17]); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.19 (dd, J = 4.0 and 4.8 Hz, 1H), 7.30 (dd, J = 2.0 and 8.4 Hz, 1H), 7.36 (d, J = 16.0 Hz, 1H), 7.46 (d, J = 2.0 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.70 (dd, J = 1.2 and 4.8 Hz, 1H), 7.86 (dd, J = 1.2 and 4.0 Hz, 1H), 8.14 (d, J = 16.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 124.8, 127.7, 128.5, 128.7, 130.3, 131.8, 132.3, 134.5, 136.3, 136.7, 138.7, 145.2, 181.7.

3-(3,4-Dimethoxyphenyl)-1-(thiophen-2-yl)prop-2-en-1-one (**7**). A mixture of 2-acetylthiophene **1** (2.52 g, 20 mmol) and 3,4-dimethoxybenzaldehyde **4** (3.22 g, 20 mmol) in abs. ethanol (10 mL) was dropwise treated with $SOCl_2$ (1 mL). The mixture was stirred at room temperature for 1 h, and then it was kept at room temperature overnight. The reaction mixture was carefully diluted with water (50 mL), and stirred at room temperature for 2 h. The resulting solid was filtered, washed thoroughly with water, air-dried, and recrystallized from ethanol to give yellow crystals (3.81 g, 63%), mp 104–105 ºC (lit. mp 106 ºC [18]); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.93 (s, 3H), 3.95 (s, 3H), 6.90 (d, J = 8.4 Hz, 1H), 7.15 (d, J = 2.0 Hz, 1H), 7.18 (dd, J = 4.0 and 4.8 Hz, 1H), 7.24 (dd, J = 2.0 and 8.4 Hz, 1H), 7.29 (d, J = 15.6 Hz, 1H), 7.66 (dd, J = 0.8 and 4.8 Hz, 1H), 7.81 (d, J = 15.6 Hz, 1H), 7.86 (d, J = 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 56.1 (2 C atoms), 110.3, 111.3, 119.6, 123.3, 127.8, 128.3, 131.6, 133.7, 144.3, 145.8, 149.3, 151.6, 182.1.

2,3-Dibromo-3-(4-methoxyphenyl)-1-(thiophen-2-yl)propan-1-one (**8**). To a solution of 3-(4-methoxyphenyl)-1-(thiophen-2-yl)prop-2-en-1-one **5** (2.44 g, 10 mmol) in chloroform (6 mL) a solution of bromine (1.6 g, 10 mmol) in chloroform (6 mL) was dropwise added, and the mixture was stirred at room temperature for 2 h. The solid that resulted after dilution with hexanes (40 mL) and refrigeration for 3 h was filtered, washed with hexanes and air-dried to give off-white crystals (3.715 g, 92%), mp 153–154 ºC (dec.) (lit. mp 148–149 ºC [19]); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.84 (s, 3H), 5.61 (d, J = 11.2 Hz, 1H), 5.66 (d, J = 11.2 Hz, 1H), 6.94 (d, J = 8.8 Hz, 2H), 7.23 (dd, J = 4.0 and 4.8 Hz, 1H), 7.44 (d, J = 8.8 Hz, 2H), 7.80 (dd, J = 0.8 and 4.8 Hz, 1H), 7.94 (dd, J = 0.8 and 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 48.7, 50.2, 55.5, 114.4, 128.7, 129.7, 130.3, 133.5, 136.0, 141.2, 160.3, 184.4.

2,3-Dibromo-3-(2,4-dichlorophenyl)-1-(thiophen-2-yl)propan-1-one (**9**). This compound was prepared from 3-(2,4-dichlorophenyl)-1-(thiophen-2-yl)prop-2-en-1-one **6** (2.83 g, 10 mmol) and bromine (1.6 g, 10 mmol) in chloroform (12 mL) in a manner similar to that described for dibromide **8**. Recrystallization from ethanol afforded off-white crystals (3.145 g, 71%), mp 138–139 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.62 (br s, 1H), 6.15 (br s, 1H), 7.23 (dd, J = 4.0 and 4.8 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 1.2 Hz, 1H), 7.57 (br s, 1H), 7.81 (d, J = 4.8 Hz, 1H), 7.94 (d, J = 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 43.6, 47.1, 128.1, 128.8, 130.1 (br, 2 C atoms), 133.6, 134.6, 134.9, 135.7, 136.2, 140.9, 183.6.

2,3-Dibromo-3-(3,4-dimethoxyphenyl)-1-(thiophen-2-yl)propan-1-one (**10**). This compound was prepared from 3-(3,4-dimethoxyphenyl)-1-(thiophen-2-yl)prop-2-en-1-one **7** (2.74 g, 10 mmol) and bromine (1.6 g, 10 mmol) in chloroform (12 mL) in a manner similar to that described for dibromide **8**. Off-white crystals (3.73 g, 86%), mp 134–135 ºC (lit. mp 133–134 ºC [19]); ^{1}H NMR

($CDCl_3$, 400 MHz): δ 3.92 (s, 3H), 3.95 (s, 3H), 5.59 (d, J = 11.6 Hz, 1H), 5.64 (d, J = 11.6 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 6.99 (d, J = 2.0 Hz, 1H), 7.09 (dd, J = 2.0 and 8.4 Hz, 1H) 7.23 (dd, J = 4.0 and 4.8 Hz, 1H), 7.80 (dd, J = 0.4 and 4.8 Hz, 1H), 7.95 (dd, J = 0.4 and 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 48.6, 50.6, 56.1, 56.2, 111.1, 111.3, 121.3, 128.7, 130.6, 133.5, 136.0, 141.2, 149.3, 150.0, 184.3.

2-Bromo-3-ethoxy-3-(4-methoxyphenyl)-1-(thiophen-2-yl)propan-1-one (**11**). 2,3-Dibromo-3-(4-methoxyphenyl)-1-(thiophen-2-yl)propan-1-one **8** (404 mg, 1 mmol) was dissolved under efficient stirring in boiling abs. ethanol (6 mL), and then the solution was allowed to slowly cool to room temperature. Addition of hexanes (6 mL) and refrigeration at -10 ºC overnight afforded colorless crystals (284 mg, 77%), mp 96–97 ºC; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 0.87 (t, J = 7.2 Hz, 3H, -CH_3), 3.25 (q, J = 7.2 Hz, 2H, -OCH_2-), 3.78 (s, 3H, -OCH_3), 4.78 (d, J = 10.0 Hz, 1H, >CHOEt), 5.59 (d, J = 10.0 Hz, 1H, >CHBr), 6.97 (d, J = 8.4 Hz, 2H, aromatic protons *ortho* to –OCH_3), 7.32 (dd, J = 4.0 and 4.8 Hz, 1H, aromatic proton at C-4 in thiophene), 7.47 (d, J = 8.4 Hz, 2H, aromatic protons *meta* to –OCH_3), 8.15 (dd, J = 0.8 and 4.8 Hz, 1H, aromatic proton at C-5 in thiophene), 8.36 (dd, J = 0.8 and 4.0 Hz, 1H, aromatic proton at C-3 in thiophene); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 14.9 (-CH_3), 48.3 (>CHBr), 55.1 (-OCH_3), 64.3 (-OCH_2-), 80.7 (>CHOEt), 113.5 (tertiary C atom *ortho* to ≡C-OCH_3), 129.1 (C-4 in thiophene), 129.8 (tertiary C atom *meta* to ≡C-OCH_3), 130.0 (quaternary C atom *para* to ≡C-OCH_3), 135.2 (C-3 in thiophene), 137.0 (C-5 in thiophene), 141.8 (quaternary C-2 in thiophene), 159.4 (≡C-OCH_3), 186.5 (>C=O).

2-Bromo-3-ethoxy-3-(3,4-dimethoxyphenyl)-1-(thiophen-2-yl)propan-1-one (**12**). 2,3-Dibromo-3-(3,4-dimethoxyphenyl)-1-(thiophen-2-yl)propan-1-one **10** (434 mg, 1 mmol) and abs. ethanol (5 mL) were stirred efficiently at reflux temperature until the solid dissolved. Upon slow cooling to room temperature, the solution deposited colorless crystals (315 mg, 79%), mp 133–134 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.00 (t, J = 7.2 Hz, 3H), 3.39 (q, J = 7.2 Hz, 2H), 3.90 (s, 3H), 3.93 (s, 3H), 4.85 (d, J = 10.0 Hz, 1H), 4.94 (d, J = 10.0 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 6.98 (d, J = 1.6 Hz, 1H), 7.02 (dd, J = 1.6 and 8.0 Hz, 1H), 7.17 (dd, J = 4.0 and 4.8 Hz, 1H), 7.73 (dd, J = 0.8 and 4.8 Hz, 1H), 7.86 (dd, J = 0.8 and 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 15.2, 49.5, 56.0, 56.1, 65.7, 81.5, 110.6, 110.7, 121.0, 128.4, 131.0, 133.2, 135.2, 142.2, 149.1, 149.4, 186.3.

3-Hydroxy-1-(4-methoxyphenyl)-3-(thiophen-2-yl)prop-2-en-1-one (or *3-hydroxy-3-(4-methoxyphenyl)-1-(thiophen-2-yl)prop-2-en-1-one*) (**13**). A solution of sodium methoxide, previously obtained from sodium (230 mg, 10 g-atom) and abs. methanol (10 mL), was gradually added to a suspension of 2,3-dibromo-3-(4-methoxyphenyl)-1-(thiophen-2-yl)propan-1-one **10** (1616 mg, 4 mmol) in abs. methanol (10 mL) at room temperature. The mixture was heated at reflux temperature for 1 h, then it was cooled in a water bath to approximately 40 ºC.

Concentrated HCl (36.5%, 4 mL) was carefully added to the reaction mixture, which was subsequently heated at reflux temperature for 5 min. Gradual addition of water (80 mL) gave a solid material, which was filtered, washed with water, air-dried, and recrystallized to afford yellow crystals (820 mg, 79%), mp 124–125 ºC (2-propanol); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.88 (s, 3H), 6.62 (s, 1H), 6.97 (d, J = 8.8 Hz, 2H), 7.16 (dd, J = 4.0 and 4.8 Hz, 1H), 7.61 (dd, J = 0.8 and 4.8 Hz, 1H), 7.78 (dd, J = 0.8 and 4.0 Hz, 1H), 7.92 (d, J = 8.8 Hz, 2H), 16.53 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 55.6, 92.2, 114.2, 127.1, 128.4, 129.1, 130.0, 132.2, 142.3, 163.2, 181.6, 181.8.

1-(2,4-Dichlorophenyl)-3-hydroxy-3-(thiophen-2-yl)prop-2-en-1-one (or *3-(2,4-dichlorophenyl)-3-hydroxy-1-(thiophen-2-yl)prop-2-en-1-one*) (**14**). This compound was prepared from 2,3-dibromo-3-(2,4-dichlorophenyl)-1-(thiophen-2-yl)propan-1-one **9** (1772 mg, 4 mmol) in a manner identical to that described for keto-enol **13**. Recrystallization afforded yellow crystals (775 mg, 65%), mp 95–96 ºC (ethanol); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.61 (s, 1H), 7.17 (dd, J = 4.0 and 4.8 Hz, 1H), 7.35 (dd, J = 2.0 and 8.8 Hz, 1H), 7.50 (d, J = 2.0 Hz, 1H), 7.62–7.69 (m, 2H), 7.77 (dd, J = 1.2 and 4.0 Hz, 1H), 15.92 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 98.7, 127.6, 128.6, 130.8, 131.1, 131.3, 133.0, 133.3, 133.5, 137.3, 141.7, 179.5, 182.6.

3-Hydroxy-1-(3,4-dimethoxyphenyl)-3-(thiophen-2-yl)prop-2-en-1-one (or *3-hydroxy-3-(3,4-dimethoxyphenyl)-1-(thiophen-2-yl)prop-2-en-1-one*) and *1-(3,4-dimethoxyphenyl)-3-(thiophen-2-yl)propan-1,3-dione* (**15**). This compound was prepared from 2,3-dibromo-3-(3,4-dimethoxyphenyl)-1-(thiophen-2-yl)propan-1-one **10** (1736 mg, 4 mmol) in a manner identical to that described for keto-enol **13**. Addition of water to the reaction mixture led to the separation of a heavy reddish oil, which did not solidify after having been stirred at room temperature for 1 h. The supernatant was then removed as thoroughly as possible, and the oil was dissolved in hot ethanol (8 mL). Slow cooling of the solution to room temperature and subsequent refrigeration afforded yellow crystals (755 mg, 65%), mp 78–79 ºC; for the keto-enol form: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.95 (s, 3H), 3.96 (s, 3H), 6.62 (s, 1H), 6.92 (d, J = 8.4 Hz, 1H), 7.15 (dd, J = 4.0 and 4.8 Hz, 1H), 7.49 (d, J = 2.0 Hz, 1H), 7.56 (dd, J = 2.0 and 8.4 Hz, 1H), 7.60 (dd, J = 0.8 and 4.8 Hz, 1H), 7.78 (dd, J = 0.8 and 4.0 Hz, 1H), 16.58 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 56.2, 92.3, 109.6, 110.7, 121.1, 127.6, 128.4, 130.0, 130.2, 142.0, 149.2, 152.9, 181.1, 182.3; for the β-diketone form: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.91 (s, 3H), 3.93 (s, 3H), 4.50 (s, 2H), 6.89 (d, J = 8.4 Hz, 1H), 7.11–7.16 (m, 1H), 7.54–7.59 (m, 1H), 7.65–7.73 (m, 2H), 7.87 (dd, J = 0.8 and 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 51.6, 56.1, 56.2, 110.3, 110.8, 124.5. 128.5, 129.6, 130.0, 134.2, 135.1, 149.2, 186.6, 191.8.

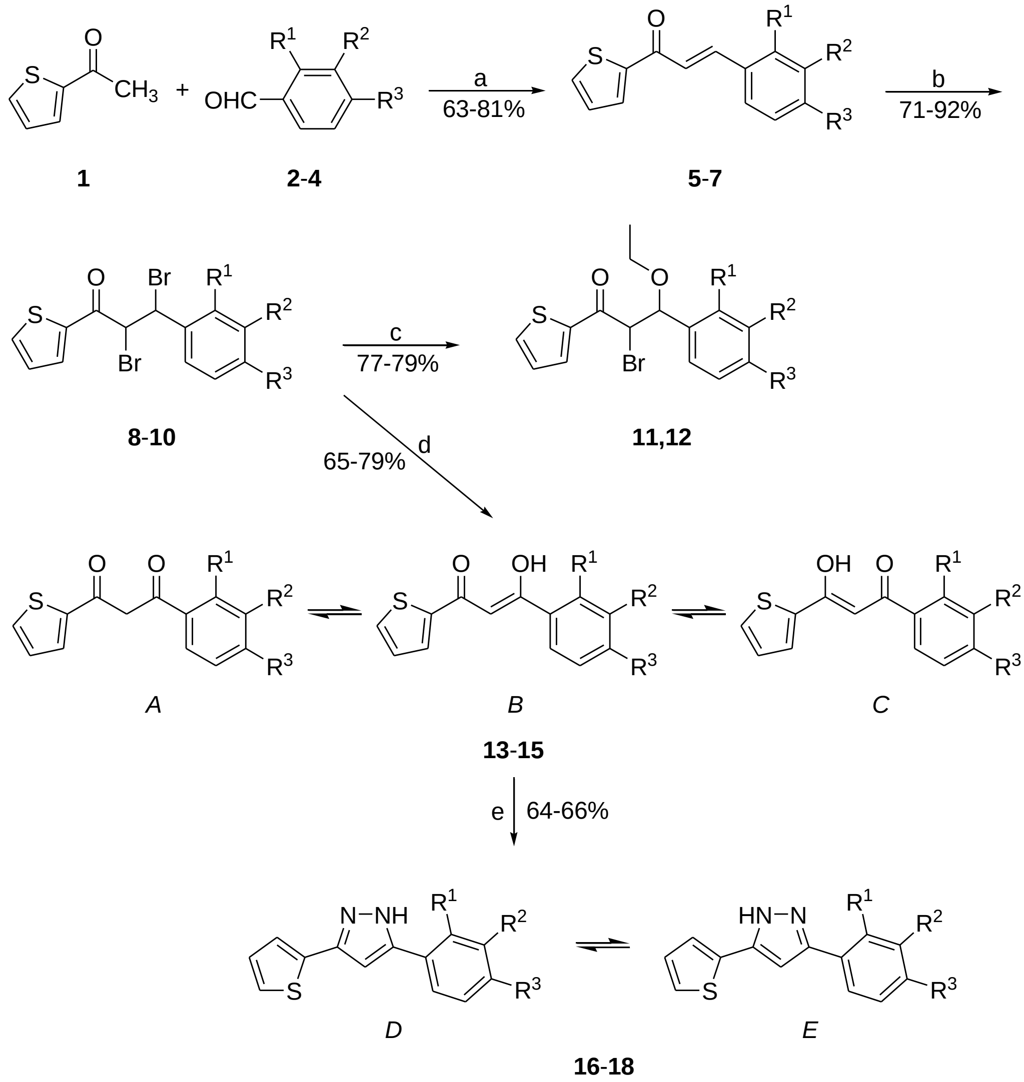
5(3)-(4-Methoxyphenyl)-3(5)-(thiophen-2-yl)-1H-pyrazole (**16**). A mixture of diketone **13** (520 mg, 2 mmol) and hydrazine hydrate (800 mg, 16 mmol) in ethanol (5 mL) was heated at reflux temperature for 2 h. The mixture was cooled to room temperature and gradually diluted with water (45 mL). The solid was filtered, thoroughly washed with water, air-dried, and recrystallized from 2-propanol to give colorless crystals (328 mg, 64%), mp 158–159 ºC (lit. mp 100 ºC [20]); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.78 (s, 3H), 6.54 (s, 1H), 6.79 (d, J = 8.4 Hz, 2H), 6.96 (dd, J = 4.0 and 4.8 Hz, 1H), 7.17 (d, J = 5.2 Hz, 1H), 7.21 (d, J = 4.4 Hz, 1H), 7.54 (d, J = 8.4 Hz, 2H), 10.17 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 55.4, 99.3, 114.3, 122.8, 124.1, 124.6, 127.0, 127.6, 135.5, 145.7, 146.5, 159.8.

5(3)-(2,4-Dichlorophenyl)-3(5)-(thiophen-2-yl)-1H-pyrazole (**17**). This compound was prepared from diketone **14** (598 mg, 2 mmol) in a manner identical to that described for pyrazole **16**. Recrystallization afforded colorless crystals (389 mg, 66%), mp 187–188 ºC (2-propanol); ^{1}H NMR (DMSO-d_6, 400 MHz) for both tautomers: δ 6.94–7.04 ($1H_{major}$ + $1H_{minor}$), 7.10 (dd, J = 4.0 and 4.8 Hz, $1H_{major}$), 7.17 dd, J = 4.0 and 4.8 Hz, $1H_{minor}$), 7.42–7.54 ($2H_{major}$ + $2H_{minor}$), 7.54–7.65 ($1H_{major}$ + $1H_{minor}$), 7.65–7.73 ($1H_{major}$ + $1H_{minor}$), 7.79 (s, $1H_{major}$), 7.87 (d, J = 8.4 Hz, $1H_{minor}$); ^{13}C NMR (DMSO-d_6, 100 MHz) for both tautomers: δ 103.2, 123.9, 124.8, 126.2, 127.3, 127.5, 127.6, 127.7, 128.1, 129.6, 129.8, 130.9, 131.0, 131.5, 131.8, 132.0, 132.8, 133.8, 136.5, 137.3, 139.1, 146.4, 147.8.

5(3)-(3,4-Dimethoxyphenyl)-3(5)-(thiophen-2-yl)-1H-pyrazole (**18**). This compound was prepared from diketone **15** (580 mg, 2 mmol) in a manner identical to that described for pyrazole **16**. Recrystallization afforded colorless crystals (378 mg, 66%), mp 163–164 ºC (2-propanol); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.60 (s, 3H), 3.83 (s, 3H), 6.46 (s, 1H), 6.67 (d, J = 8.0 Hz, 1H), 6.86 (dd, J = 4.0 ad 4.8 Hz, 1H), 7.04–7.22 (m, 4H), 11.66 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 55.7, 55.9, 98.8, 108.6, 111.2, 118.2, 122.8, 124.0, 124.4, 127.5, 135.1, 145.4, 146.6, 149.1 (2 C atoms).

3. Results and discussion

The reaction of 1,3-diarylpropane-1,3-diones with hydrazine or hydrazine derivatives is by far the broadest and most efficient method for the preparation of 3,5-diarylpyrazoles [21], making 1,3-diketones the most widely used intermediates in the synthesis of these heterocycles. Although 1,3-diaryl-substituted β-diketones are typically obtained through the mixed Claisen condensation of an acetophenone with an aromatic ester in the presence of a strong base [22], we decided to explore a different, less employed route using chalcone analogues as starting materials. This approach, which requires a couple of additional but undemanding steps compared to the aforementioned direct one-step Claisen condensation, leads to the desired β-diketones through a sequence



2, **5**, **8**, **11**, **13**, **16** $R^3 = OCH_3$; $R^1 = R^2 = H$
3, **6**, **9**, **14**, **17** $R^1 = R^3 = Cl$; $R^2 = H$
4, **7**, **10**, **12**, **15**, **18** $R^2 = R^3 = OCH_3$; $R^1 = H$

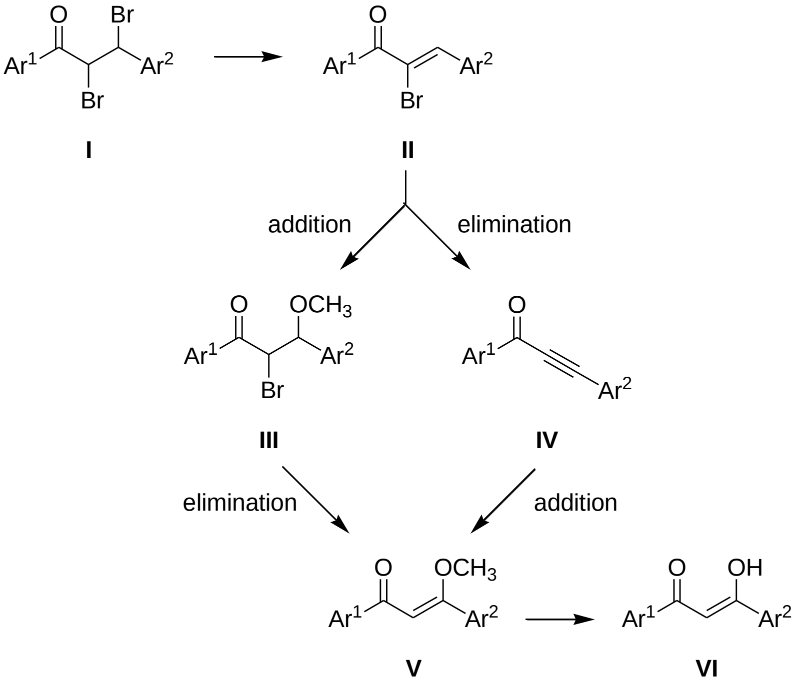
Scheme 1. Multistep synthesis of 3(5)-aryl-5(3)-(thiophen-2-yl)pyrazoles from chalcone analogues: a) ethanol, NaOH, rt, overnight (or ethanol, $SOCl_2$, rt, overnight); b) bromine, chloroform, rt, 2 h; c) ethanol, reflux, 1 min; d) sodium methoxide, methanol, reflux, 1 h, then 36% HCl, reflux, 5 min; e) hydrazine hydrate, ethanol, reflux, 2 h.

that comprises a Claisen–Schmidt condensation giving the desired chalcone analogues, followed by addition of bromine to afford the corresponding chalcone dibromides, which were subsequently converted in the key step of this sequence into propane-1,3-diones, as previously reported for similar compounds [23]. Finally, ring closure of these propane-1,3-diones to the target thienyl-substituted pyrazoles was accomplished using excess hydrazine hydrate (Scheme 1).

The thienyl-containing chalcone analogues **5** and **6** required as starting materials in this study were synthesized with very good yields through the NaOH-catalyzed Claisen condensation of 2-acetylthiophene **1** with the appropriate commercially available benzaldehydes **2** and **3** (Scheme 1). Alternatively, chalcone analogue **6** has been synthesized using a recently described protocol [24] which uses catalyst HCl generated *in situ* from thionyl chloride and ethanol as catalyst, and has proved very useful for the preparation of phenolic chalcone analogues. All of the chalcone analogues **5**–**7** are known compounds, and their identity has been confirmed by comparing the melting point recorded for each of the compounds synthesized with the literature data (see Experimental). Furthermore, the ^{1}H and ^{13}C NMR spectra of chalcone analogues **5**–**7** are identical with the ones reported in the literature [25, 26]. The ^{1}H NMR spectra of these chalcone analogues present the two characteristic doublets, one at approximately 7.30 ppm for one olefinic proton, and another at 7.80 ppm (in the case of methoxy-substituted chalcone analogues **5** and **7**) or 8.14 ppm (for chalcone analogue **6**) for the second olefinic proton. The *E* geometry of these chalcone analogues is supported by the value of the coupling constant (16 Hz) of these two doublets.

Compounds **5**–**7** were then transformed into the corresponding thienyl-containing chalcone dibromides **8**–**10** by treatment with bromine at room temperature (Scheme 1) [19]. The value of the coupling constant (approximately 11 ppm) between the protons at the chiral carbon atoms indicates that dibromides **8**–**10** exist in *erythro* form in solution [27]. Addition of hexanes to the reaction mixture provided 2,3-dibromopropan-1-ones **8**–**10** in good yields and excellent purity, and they were used as such in the subsequent step. The attempt to recrystallize compound **8** from ethanol led to the recovery of derivative **11** in whose structure an ethoxy group had replaced the bromine atom β to the carbonyl group (Scheme 1). Chalcone dibromide **10** behaved analogously to afford compound **12**, whereas 2,3-dibromopropan-1-one **9** did not undergo any transformation upon recrystallization. Similar replacements of the extremely labile bromine atom adjacent to a phenyl ring *para*-substituted with an electron-donating group with alkoxy or hydroxy groups have been previously documented [28–30]. In order to unequivocally establish the position of the ethoxy group in compound **11**, a complete NMR analysis (including 2D correlation spectra) was performed. The data allowed the accurate assignment of the signals in both ^{1}H and ^{13}C NMR spectra (see Experimental), and showed that *erythro* is the preferred diastereomer of compound **11** in solution ($J_{H,H}$ = 10 Hz). More importantly, through the strong correlation between the signal at 80.7 ppm (aliphatic carbon in the ethoxy group directly linked to oxygen) and the signal at 7.47 ppm (aromatic protons *meta* to the methoxy group), the HMBC spectrum recorded for compound **11** confirmed beyond any doubt that the substitution of bromine with ethoxy had occurred at the carbon atom β to carbonyl.

The key intermediate compounds **13**–**15** were obtained in good yield by the reaction of chalcone dibromides **8**–**10**, respectively, with sodium methoxide in methanol and subsequent hydrolysis in the presence of HCl. Based on a study [31] which describes the stepwise transformation of 2,3-dibromopropan-1-ones into enol-ketones, the most likely intermediates in this reaction appear to be the corresponding 2-bromoprop-2-en-1-ones and 2-bromo-3-methoxypropan-1-ones, although prop-2-yn-1-ones should also be considered as potential intermediates [32]. It is very likely that the first step in the mechanism of methoxide-catalyzed formation of enol–ketones from chalcone dibromide **I** is its dehydrobromination to give α-bromoenone **II**. Recent data [33] suggests that intermediate **II** could subsequently either undergo addition of methanol to yield 2-bromo-3-methoxydihydrochalcone **III** or a second dehydrobromination to afford ynone **IV** (Scheme 2). Both intermediates **III** and **IV** lead through elimination of HBr and addition of methanol, respectively, to methoxyenone **V**, which is hydrolyzed in the last step to enol-ketone **VI** in the presence of a mineral acid (Scheme 2). Despite the experimental evidence which supports the above mentioned



Scheme 2. Proposed mechanism for the transformation of chalcone dibromides into enol-ketones

mechanism, one should not exclude the possibility that enol-ketone **VI** is formed directly from α-bromoenone **II** through nucleophilic *cine*-substitution [34].

Compounds **13**–**15** are known to exist as two fast interchanging enolic tautomers (***B*** and ***C***) which are also involved in a slower keto-enol tautomerism with β-diketone ***A*** (Scheme 1). Because *cis*-enolic forms ***B*** and ***C*** are so more stable than the corresponding *trans*-enolic forms (not shown) owing to the presence of an intramolecular hydrogen bond, the *trans*-enolic forms have no real contribution to the tautomeric mixture. In addition, enolic forms ***B*** and ***C*** are usually more stable than the diketone form ***A***, although the preference for either the enolic or the keto form depends on the nature of substituents, temperature, or the polarity of the solvent. Amongst the spectroscopic methods, NMR provides the most suitable techniques for the study of enol-ketone tautomerism in solution and also in solid state [35]. The energy barrier that separates the keto tautomer form the enol tautomers allows the observation of distinct signals in the NMR spectrum for these tautomers at room temperature, but the low energy for the enol ***B***/enol ***C*** interconversion is so small that the NMR spectrum of the *cis*-enolic tautomers are a weighted average of the two forms. Consequently, the non-symmetric *cis*-enolic forms ***B*** and ***C*** of compounds **13**–**15** give a single resonance for each type of nuclei, and the tautomeric equilibrium is not apparent. Structural investigation of compounds **13**–**15** in $CDCl_3$ solution at room temperature using NMR has shown that **13** and **14** exist solely as the enolic form. On the other hand, the NMR spectra recorded for **15** suggest that this compound is a mixture of tautomers in which the enolic form is the major constituent. Thus, the enolic proton can be associated with a broad signal at approximately 16 ppm in the ^{1}H NMR spectra of compounds **13**–**15**, and the vinylic proton gives a sharp singlet at 6.6 ppm. The presence of a peak in the vicinity of 95 ppm in the ^{13}C NMR spectra of compounds **13**–**15**, which is associated with the vinylic carbon atom, is also indicative for the presence of the enol form in solution. The existence of the keto tautomer for compound **15** has been inferred from the presence of a small intensity singlet at 4.5 ppm in its proton spectrum corroborated with the presence of a peak at 51.6 ppm in its carbon spectrum, which have been assigned to the corresponding type of atoms in the methylene group of tautomer ***A***.

Reaction of compounds **13**–**15** with excess hydrazine in refluxing ethanol afforded good yields of NH-unsubstituted pyrazoles **16**–**18**. These compounds present annular tautomerism owing to the potential existence of forms ***D*** and ***E*** for a given NH-pyrazole. Although the similarity between NH-pyrazole tautomers ***D*** and ***E*** and enol-ketone tautomers ***B*** and ***C***, respectively, is striking, the analogy with enol-ketones stops here, as the existence of a NH-pyrazole tautomer analogous to diketone tautomer ***A*** is highly unlikely due to its obvious lack of aromaticity. Interconversion of tautomers occurs through an intermolecular transfer of proton from N-1 in a molecule to N-2 in another molecule of an NH-pyrazole, and it has a low energy barrier which results in NMR spectra usually presenting average signals arising from both forms ***D*** and ***E***. However, under certain conditions, mixtures of both tautomers can be evidenced in solution by NMR. For example, Elguero *et al.* have shown that NH-pyrazoles derived from curcumin exhibit tautomerism in DMSO-d_6 [36], and Dzvinchuk *et al.* have proven that a few 3,5-diaryl-1*H*-pyrazoles having an imidazole-2-yl [37] or a benzimidazol-2-yl moiety [38] at position 4 also display tautomerism in DMSO-d_6. In the case of our compounds, the NMR spectra of NH-pyrazoles **16** and **18** were recorded in $CDCl_3$, and only one set of signals representing the average signals of both tautomers is noticeable. The NMR analysis of NH-pyrazole **17** has been performed in DMSO-d_6, and in this case two sets of signals from both tautomers can be observed. It is, however, worth mentioning that no tautomerism was observed for compound **16** when his NMR structural investigation was conducted in DMSO-d_6 [39]. In the ^{1}H NMR spectrum of **17**, the proton at C-4 in the pyrazole ring has been assigned the singlets at 6.97 and 7.00 ppm for the two tautomers, while the singlets in the off-set (13.31 and 13.68 ppm) correspond to the NH proton in the individual tautomers. The ratio between the major and the minor tautomer of NH-prazole **17** is approximately 1.5 to 1. Not all of the carbon atoms in the two sets of signals of the distinct tautomers are noticeable in the ^{13}C NMR spectrum of pyrazole **17**, presumably due to superimposition in the crowded aromatic region of the spectrum. The tentative assignment of signals for C-3, C-4 and C-5 in both tautomers of compound **17** was accomplished through 2D NMR spectroscopy. Only one signal can be observed for the C-4 of both pyrazole tautomers (103.2 ppm), which correlates in HMQC with both signals for the protons at C-4 in the distinct tautomers. In the HMQC spectrum, the singlet for the NH proton (13.31 ppm) and the singlet for the proton at C-4 (7.00 ppm) in the major tautomer strongly correlate with the peaks at 146.4 ppm and 139.1 ppm, which have been tentatively assigned the C-3 and C-5, respectively. On the other hand, the signals for the NH proton (13.68 ppm) and for the proton at C-4 (6.97 ppm) in the minor tautomer show a correlation with the peaks at 147.8 ppm and 137.3 ppm, which most likely correspond to C-3 and C-5, respectively. No definite structural assignment (*D* or *E*) for the major and minor tautomers of NH-pyrazole **17** could be inferred from the NMR analysis in solution alone, and no supplementary experiments (such as solid-state NMR Cross-Polarization Magic Angle Spinning (CPMAS), or X-ray crystallography structure determination) have been performed at this stage with a view to establish their identity.

4. Conclusions

A three-step approach has been described for the synthesis of pharmacologically relevant 3(5)-(substituted aryl)-5(3)-(thiophen-2-yl)-1*H*-pyrazoles starting from thiophene-containing chalcone analogues. The key intermediate β-diketones have been obtained through bromine addition to the chalcone analogues and subsequent conversion of the resulting chalcone dibromides in the presence of sodium methoxide. These key intermediates underwent ring closure with hydrazine to afford the target NH-pyrazoles with satisfactory total yields (46%, 30% and 37%) after three steps. Attempts to recrystallize two chalcone bromides having a *para*-methoxyphenyl moiety from ethanol led to the substitution of the labile bromine atom adjacent to the aforementioned ring with ethoxy. According to the NMR analysis, only the enol form could be detected in $CDCl_3$ for two of the prepared β-diketones, whereas the third β-diketones was present as a mixture of both tautomers, the enol being the major component in this case as well. Two of the target NH-pyrazole did not present annular tautomerism in $CDCl_3$, while both possible tautomers (ratio 1.5 to 1) were evidenced for the third NH-pyrazole in DMSO-d_6.

REFERENCES

[1]. *J. Elguero,* Comprehensive Heterocyclic Chemistry, vol. 5, Pergamon, Oxford, 1996.

[2]. *R. Pérez-Fernández, P. Goya and J. Elguero*, “A review of recent progress (2002–2012) on the biological activities of pyrazoles”, in Arkivoc, no. 2, 2014, pp. 233–293.

[3]. *J.-J. Liu, M.-Y. Zhao, X. Zhang, X. Zhao and H.-L. Zhu,* “Pyrazole derivatives as antitumor, anti-inflammatory and antibacterial agents”, in Mini-Rev. Med. Chem., **vol. 13**, no. 13, 2013, pp. 1957–1966.

[4]. *A. A. Bekhit, A. Hymete, A. El-Din A. Bekhit, A. Damtew and H. Y. Aboul-Enein*, “Pyrazoles as promising scaffold for the synthesis of anti-inflammatory and/or antimicrobial agent: A review”, in Mini-Rev. Med. Chem., **vol. 10**, no 11, 2010, pp. 1014–1033.

[5]. *H. Kumar, D. Saini, S. Jain and N. Jain*, “Pyrazole scaffold: a remarkable tool in the development of anticancer agents”, in Eur. J. Med. Chem., **vol. 70**, 2013, pp. 248–258.

[6]. *D. Secci, A. Bolasco, P. Chimenti and S. Carradori*, “The state of the art of pyrazole derivatives as monoamine oxidase inhibitors and antidepressant/anticonvulsant agents”, in Curr. Med. Chem., **vol. 18**, no. 33, 2011, pp. 5114–5144.

[7]. *R. S. Keri, K. Chand, T. Ramakrishnapp and, B. M. Nagaraja*, “Recent progress on pyrazole scaffold-based antimycobacterial agents”, in Arch. Pharm. (Weinheim), **vol. 348**, no. 5, 2015, pp. 299–314.

[8]. *E. Fullam, J. Talbot, A. Abuhammed, I. Westwood, S. G. Davies, A. J. Russell, E. Sim*, “Design, synthesis and structure–activity relationships of 3,5-diaryl-1*H*-pyrazoles as inhibitors of arylamine *N*-acetyltransferase”, in Bioorg. Med. Chem. Lett., **vol. 23**, no. 9, 2013, pp. 2759–2764.

[9]. *A. Y. Shaw, H.-H. Liau, P.-J. Lu, C.-N. Yang, C.-H. Lee, J.-Y. Chen, Z. Xu and G. Flynn*, “3,5-Diaryl-1*H*-pyrazole as a molecular scaffold for the synthesis of apoptosis-inducing agents”, in Bioorg. Med. Chem., **vol. 18**, no. 9, 2010, pp. 3270–3278.

[10]. *G. Cocconcelli, E. Diodato, A. Caricasole, G. Gaviraghi, E. Genesio, C. Ghiron, L. Magnoni, E. Pecchioli, P. V. Plazzi and G. C. Terstappen*, “Aryl azoles with neuroprotective activity-Parallel synthesis and attempts at target identification”, in Bioorg. Med. Chem., **vol. 16**, no. 4, 2008, pp. 2043–2052.

[11]. *F. Chimenti, R. Fioravanti, A. Bolasco, F. Manna, P. Chimenti, D. Secci, O. Befani, P. Turini, F. Ortuso and S. Alcaro*, “Monoamine oxidase isoform-dependent tautomeric influence in the recognition of 3,5-diaryl pyrazole inhibitors”, in J. Med. Chem., **vol. 50**, no. 3, 2007, pp. 425–428.

[12]. *D. Catarzi, V. Colotta, F. Varano, D. Poli, L. Squarcialupi, G. Filacchioni, K. Varani, F. Vincenzi, P. A. Borea, D. Dal Ben, C. Lambertucci and G. Cristalli*, “Pyrazolo[1,5-*c*]quinazoline derivatives and their simplified analogues as adenosine receptor antagonists: Synthesis, structure–affinity relationships and molecular modeling studies”, in Bioorg. Med. Chem., **vol. 21**, no. 1, 2013, pp. 283–294.

[13]. *F. F. Vangoor, S. S. Hadida Ruah, A. K. Singh, E. R. Olson, L. R. Makings, J. E. Gonzalez, III, J. A. Rader, F. Chambers, III, M. T. Miller, P. Grootenhuis and Y. Liu (Vertex Pharmaceuticals Inc.)*, “Pirazole modulators of ATP-binding cassette transporters”, WO2004/80972, 2004.

[14]. *H. E. Gottlieb, V. Kotlyar and A. Nudelman*, “NMR chemical shifts of common laboratory solvents as trace impurities”, in J. Org. Chem., **vol. 62**, no. 21, 1997, pp. 7512–7515.

[15]. *A. Thangamani*, “Regiospecific synthesis and biological evaluation of spirooxindolo-pyrrolizidines via [3+2] cycloaddition of azomethine ylide”, in Eur. J. Med. Chem, **vol. 45**, no. 12, 2010, pp. 6120–6126.

[16]. *S. A. F. Rostom, H. M. Faidallah and M. S. Al-Saadi*, “A facile synthesis of some 3-cyano-1,4,6-trisubstituted-2(1*H*)-pyridinones and their biological evaluation as anticancer agents”, in Med. Chem. Res, **vol. 20**, no. 8, 2011, pp. 1260–1272.

[17]. *H. H. Szmant and A. J. Basso*, “The ultraviolet absorption spectra of 2-thienyl ketones”, in J. Am. Chem. Soc, **vol. 73**, no. 10, 1951, pp. 4521–4523.

[18]. *L. Greiner-Bechert and H.-H. Otto*, “1,4-Pentandien-3-ones, XXXII: Reaction of 2-acetylthiophene and 2-acetylfuran with malononitrile and aldehydes, and synthesis and properties of phenylene-bis[(thienyl/furyl)nicotinonitrile] derivative”, in Arch. Pharm. (Weinheim), **vol. 324**, no. 9, 1991, pp. 563–572.

[19]. *F. G. Weber*, “Reaktion substituierter Thiophenanaloga des Chalkons mit Brom und Jodmonochlorid”, in Z. Chem., **vol. 10**, no. 4, 1970, pp. 143–144.

[20]. *A V. Ingle, A. G. Doshi, A. W. Raut and N. S. Kadu*, “Synthesis of 3,5-disubstituted pyrazoles and their derivatives”, in Orient. J. Chem., **vol. 27**, no. 4, 2011, pp. 1691–1698.

[21]. *A. Schmidt and A. Dreger*, “Recent advances in the chemistry of pyrazoles. Properties, biological activities, and syntheses”, in Curr. Org. Chem., **vol. 15**, no. 9, 2011, pp. 1423–1463.

[22]. *A. V. Kel'in*, “Recent advances in the synthesis of 1,3-diketones”, in Curr. Org. Chem., **vol. 7**, no. 16, 2003, pp. 1691–1711.

[23]. *G. E. Southard and G. M. Murray*, “Synthesis of vinyl-substituted β-diketones for polymerizable metal complexes”, in J. Org. Chem., **vol. 70**, no. 22, 2005, pp. 9036–9039.

[24]. *O. Petrov, Y. Ivanova and M. Gerova*, “$SOCl_2$/EtOH: Catalytic system for synthesis of chalcones”, in Catal. Commun., **vol. 9**, no. 2, 2008, pp. 315–316.

[25]. *M. Kinger, Y. D. Park, J. H. Park, M. G. Hur, H. J. Jeong, S.-J. Park, W. S. Lee, S. W. Kim and S. D. Yang*, “Design, synthesis, and anti-influenza viral activities of 1,3-diarylprop-2-en-1-ones: a novel class of neuraminidase inhibitors”, in Arch. Pharm. Res., **vol. 35**, no. 4, 2012, pp. 633–638.

[26]. *K.-J. Hwang, H.-S. Kim, I.-C. Han and B.-T. Kim*, “Synthesis of heterocyclic chalcone derivatives and their radical scavenging ability toward 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radicals”, in Bull. Korean Chem. Soc., **vol. 33**, no. 8, 2012, pp. 2585–2591.

[27]. *F. G. Weber*, “^{1}H-NMR- und IR-spektren von 2,3-dibrom-1-aryl-3-[thienyl-(2)]- und 2,3-dibrom-1-[thienyl-(2)]-3-arylpropanonen-(1)”, in Tetrahedron, vol. 26, no. 10, 1970, pp. 2507–2517.

[28]. *J. A. Donnelly and D. F. Farrell*, “Chalcone derivatives as precursors of 1,2,3,4-tetrahydro-4-quinolones”, in Tetrahedron, vol. 46, no. 3, 1990, pp. 885–894.

[29]. *F. Fischer and W. Arlt*, “Konfigurative Zuordnung über sterisch definierte Epoxydringe V. Die intramolekulare Spaltung von substituierten (±)-*trans*-2′-Acetoxy-chalkonepoxyden zu Dihydroflavonolen”, in Chem. Ber, **vol. 97**, no. 7, 1964, pp. 1910–1914.

[30]. *W. B. Black and R. E. Lutz*, “Ultraviolet absorption spectra of chalcones. Identification of chromophores”, in J. Am. Chem. Soc., **vol. 77**, no. 19, 1955, pp. 5134–5140.

[31]. *C. Weygand*, “Beiträge zum Konstitutionsproblem der Keto-enole aus 1,3-Diketonen”, in Justus Liebigs Ann. Chem., **vol. 459**, 1927, pp. 99–122.

[32]. *C. Weygand, E. Bauer and H. Hennig*, “Über Beziehungen zwischen Polymorphismus und Äthylen-Stereomerie, zugleich VI. Mitteilung über die Isomerie-Verhältnisse in der Chalkon-Reihe”, in Ber. Dtsch. Chem. Ges., **vol. 62**, no. 3, 1929, pp. 562–573.

[33]. *A. V. Mareev, I. A. Ushakov and A. Yu. Rulev*, “Nucleophilic substitution of α-haloenones with phenols”, in Tetrahedron, **vol. 71**, no. 13, 2015, pp. 1971–1974.

[34]. *J. Suwiński and K. Świerczek*, “*cine*- and *tele*-Substitution reactions”, in Tetrahedron, **vol. 57**, no. 9, 2001, pp. 1639–1662.

[35]. *R. M. Claramunt, C. López, M. D. Santa Maria, D. Sanz and J. Elguero*, “The use of NMR spectroscopy to study tautomerism”, in Prog. Nucl. Magn. Reson. Spectrosc., **vol. 49**, no. 3–4, 2006, pp. 169–206.

[36]. *P. Cornago, P. Cabildo, R. M. Claramunt, L. Bouissane, E. Pinilla, M. Rosario Torres and J. Elguero*, “The annular tautomerism of the curcuminoid NH-pyrazoles”, in New J. Chem., **vol. 33**, no. 1, 2009, pp. 125–135.

[37]. *I. B. Dzvinchuk, A. M. Nesterenko and M. O. Lozinskii*, “Synthesis of 3,5-diaryl-4-(1H-imidazol-2-yl)-1H-pyrazoles from 2-phenacyl-1H-imidazole”, in Chem. Heterocycl. Compd. (N. Y.), **vol. 46**, no. 1, 2010, pp. 66–71.

[38]. *I. B. Dzvinchuk and M. O. Lozinskii*, “Synthesis and tautomerism of 2-(3,5-diaryl-1H-pyrazol-4-yl)-1-methyl-1H-benzimidazoles”, in Chem. Heterocycl. Compd. (N. Y.), **vol. 46**, no. 12, 2011, pp. 1454–1458.

[39]. *S. T. Heller and S. R. Natarajan*, “1,3-Diketones from acid chlorides: a rapid and general one-pot synthesis of pyrazoles”, in Org. Lett., **vol. 8**, no. 13, 2006, pp. 2675–2678.