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CHEMISTRY

4-ARYLBUTAN-2-ONES: STARTING MATERIALS IN THE SYNTHESIS OF NOVEL HEME OXYGENASE INHIBITORS

GHEORGHE ROMAN[1,2] and WALTER A. SZAREK[1]

[1] Queen's University, Department of Chemistry, Kingston, Ontario, K7L 3N6, Canada
[2] "Petru Poni" Institute of Macromolecular Chemistry, Department of Inorganic Polymers, Iaşi, 700487, Romania
gheorghe.roman@icmpp.ro

Synthetic organic chemistry and medicinal chemistry are the most significant fields of research in chemistry, where 4-arylbutan-2-ones find applications by allowing access to chemical entities otherwise difficult to synthesize, or in the *de novo* development of drug candidates. Structure-aided design based on previous results from our group has led to advances in shaping the structure of a series of novel imidazole-based heme oxygenase inhibitors. The practical generation of these inhibitors requires the synthesis of a set of 4-arylbutan-2-ones to be employed as starting materials in a reaction sequence that would afford in the end the desired imidazole-containing inhibitor target compounds. The present report illustrates the use of an one-step alkylation–cleavage synthetic approach toward such 4-arylbutan-2-ones featuring, in most cases, a hydrophobic *para*-substituent in the aromatic ring, starting from low-cost, commercially available organic reagents (pentane-2,4-dione and the suitably substituted benzyl bromides). The work described in this study represents an extension of a synthetic entry to this type of organic compounds, previously exploited in our group for the preparation of several structural analogs. The identity of the obtained 4-arylbutan-2-ones was established using nuclear magnetic resonance spectroscopy and high resolution mass spectrometry.

Keywords: organic synthesis, chemical intermediates, ketones, alkylation–cleavage, structural investigation

1. INTRODUCTION

4-Arylbutan-2-ones are both significant building blocks in organic chemistry and starting materials for pharmacologically important compounds. In addition to common chemical modifications of the reactive carbonyl function (such as reduction to secondary alcohol [1,2], addition of organometallic reagents [3–5], conversion to carbonyl functional derivatives [6–9], etc.) or to substitution reactions at carbon α to the carbonyl function [10–14], 4-arylbutan-2-ones have

been shown to participate as substrates in the Wittig reaction [15], Horner-Wadsworth-Emmons olefinations [16], Strecker-type aminocyanations [17], synthesis of *gem*-difluoroalkenes [18] or β,β-diaryl α,β-unsaturated ketones [19]. The presence of the 3-arylpropyl motif in the structure of 4-arylbutan-2-ones renders these compounds effective starting materials in the synthesis of benzofused heterocyclic and carbocyclic ring systems (such as quinolines [20], 1,2,3,4-tetrahydroquinolines [21], indanes [22] or 1,2,3,4-tetrahydronaphthalenes [23]), but also for various other heterocycles [24, 25]. In the realm of medicinal chemistry, 4-arylbutan-2-ones have proven to be crucial starting materials that allow access to photoactivatable propofol analogs [26], agents that strongly reduce the formation of *Pseudomonas aeruginosa* biofilms [27], compounds with inhibitory activity of tyrosinase [28], anti-inflammatory diarylheptanoids that deter the production of lipopolysaccharide-induced tumor necrosis factor-α [29], candidates with excellent binding affinity and subtype selectivity for σ_2 receptors, whose ^{11}C-labeled analogs are useful as radiotracers in brain positron emission tomography [30], structurally diverse agonists of β_2 adrenoreceptor potentially useful as bronchodilator agents in the treatment of asthma [31,32], or inhibitors of heme oxygenase for the therapy of hormone-refractory prostate cancer [33].

Some time ago, we have designed and synthesized a collection of imidazole-containing inhibitors of heme oxygenase as simplified versions of azalanstat **1** (Fig. 1), which retained the basic scaffold of the parent compound, while various oxygen-based substituents were installed onto its central region, with a view to render any potentially active, structurally related molecules accessible through facile synthetic approaches that featured a small number of stages [14]. Structure–activity relationship in this library of inhibitors suggested that the nature of the *para* substituent of the phenyl ring in these heme oxygenase (HO) inhibitors could be essential to their activity (which was excellent especially in the case of the bromine- and iodine-substituted compounds), owing to its ability to undergo polar–polar interactions with some unidentified amino acid residues at the far end of substrate's binding loops. This hypothesis was subsequently confirmed through the analysis of the X-ray crystal structure of the ternary complex of rat HO-1 with inhibitor **2** (Fig. 1) and heme [34], which showed that the inhibitor is stabilized inside the active site of the enzyme through contacts between its chlorine substituent of the phenyl ring and Phe33 and Phe37 of the rat HO-1–heme complex. Further investigations of other X-ray crystal structures of ternary complexes of rat HO-1 with heme and various excellent inhibitors of HO-1 **3**, **4** and **5** (Fig. 1) also substantiate the significance of the binding of the western region of these inhibitors through hydrophobic interactions involving residues lining the distal hydrophobic pocket (*i.e.* Phe33, Met34, Phe37, Val50, Leu54, Leu147, Phe167 and Phe214) of truncated human HO-1 on the stabilization of the inhibitor-containing complex [35–38]. Relying on the conclusion drawn from these studies, structure-aided design of a next generation of inhibitors that feature hydrophobic substituents in

the phenyl ring of their western region has been undertaken. The present study deals with the synthesis of several 4-arylbutan-2-ones, which are required as starting materials in the reaction sequence leading to these novel inhibitors.

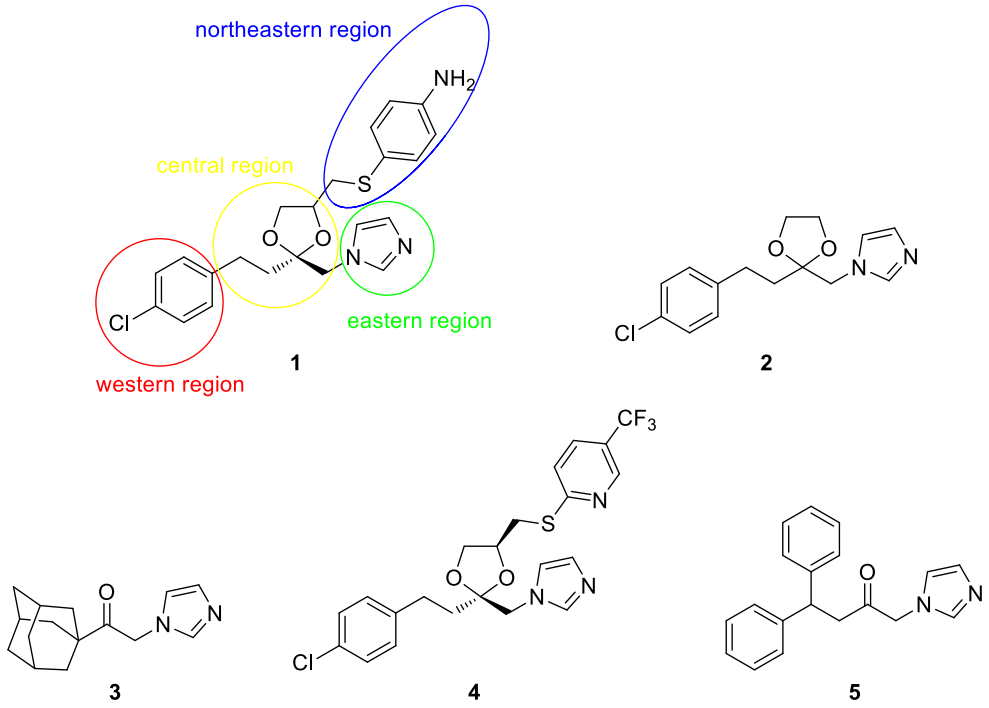

Fig. 1. Topological analysis of azalanstat **1**, and structures of various selective imidazole-based HO inhibitors **2**–**5** that have been co-crystallized with HO-1 isozyme and heme.

2. EXPERIMENTAL

2.1. REAGENTS, MATERIALS AND INSTRUMENTATION

All chemical reagents and solvents were obtained from Sigma-Aldrich (Oakville, ON, Canada). Column chromatography was performed on Silicycle (Quebec City, QC, Canada) silica gel (230–400 mesh, 60 Å). Analytical thin-layer chromatography was performed on glass-backed Silicycle precoated silica gel 60 F254 plates, and the compounds were visualized by UV illumination (254 nm). Melting points were taken on a Mel-Temp II apparatus (Laboratory Devices, Inc., Holliston, MA, USA) and are uncorrected. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 400 MHz spectrometer (Bruker

BioSpin Ltd., Milton, ON, Canada). The signal owing to residual protons in deuterated chloroform (δ = 7.26 ppm) was used as internal standard for the ^{1}H NMR spectra. The chemical shifts for the carbon atoms are given relative to $CDCl_3$ (δ = 77.16 ppm). High-resolution mass spectra (HRMS) were obtained on an Applied Biosystems/MDS Sciex QSTAR XL spectrometer (Applied Biosystems, Inc., Foster City, CA, USA) equipped with an Agilent HP1100 Cap-LC system, in electron ionization (EI) mode.

2.2. SYNTHESIS

General procedure for the synthesis of 4-arylbutan-2-ones

A mixture of pentane-2,4-dione **11** (500 mg, 5 mmol), a 4-substituted benzyl bromide **6**–**10** (5 mmol), and anh. K_2CO_3 (690 mg, 5 mmol) in methanol (25 mL) was heated at reflux temperature overnight (at least 16 h). The mixture was then cooled to room temperature, the solvent was removed under reduced pressure, and the resulting residue was partitioned between ethyl acetate (20 mL) and water (20 mL). The organic layer was separated, and the aqueous layer was further extracted with ethyl acetate (2 × 10 mL). The combined organic phase was washed with water (15 mL), dried over anh. Na_2SO_4, and then the solvent was removed under reduced pressure. The resulting oil was chromatographed on a silica gel column using hexanes–ethyl acetate as the mobile phase to give the title compounds.

4-(4-Methylphenyl)butan-2-one ***12***. This compound was obtained from 4-methylbenzyl bromide **6** (925 mg, 5 mmol) according to the general procedure, as a clear oil (495 mg, 61%), R_f = 0.14 (hexanes–ethyl acetate 15:1, *v*/*v*). ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 2.14 (s, 3H), 2.32 (s, 3H), 2.74 (t, J = 7.4 Hz, 2H), 2.87 (t, J = 7.4 Hz, 2H), 7.05–7.12 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 21.1, 29.4, 30.2, 45.4, 128.3, 129.3, 135.7, 138.0, 208.2. HRMS (EI), *m/z*: calcd. for $C_{11}H_{14}O$: 162.1045 (M^+). Found 162.1049. NMR data is in agreement with the literature [39].

4-[4-(Isopropyl)phenyl]butan-2-one ***13***. This compound was obtained from 4-(isopropyl)benzyl bromide **7** (1065 mg, 5 mmol) according to the general procedure, as a clear oil (620 mg, 65%), R_f = 0.31 (hexanes–ethyl acetate 9:1, *v*/*v*). ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 1.24 (d, J = 6.8 Hz, 6H), 2.15 (s, 3H), 2.76 (t, J = 7.6 Hz, 2H), 2.83–2.94 (m, 3H), 7.14 (dd, J = 8.0 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 24.1, 29.5, 30.1, 33.8, 45.4, 126.7, 128.3, 138.4, 146.8, 208.0. HRMS (EI), *m/z*: calcd. for $C_{13}H_{18}O$: 190.1358 (M^+). Found 190.1352.

4-[4-(tert-Butyl)phenyl]butan-2-one ***14***. This compound was obtained from 4-(*t*-butyl)benzyl bromide **8** (1135 mg, 5 mmol) according to the general procedure, as a clear oil (735 mg, 72%), R_f = 0.26 (hexanes–ethyl acetate 9:1, *v*/*v*). ^{1}H NMR (400 MHz, CDCl3), δ (ppm): 1.32 (s, 9H), 2.15 (s, 3H), 2.76 (t, J = 7.2 Hz, 2H), 2.88 (t, J = 7.6 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H). ^{13}C

NMR (100 MHz, $CDCl_3$), δ (ppm): 29.3, 30.1, 31.5, 34.5, 45.3, 125.5, 128.1, 138.0, 149.1, 208.2. HRMS (EI), *m/z*: calcd. for $C_{14}H_{20}O$: 204.1514 (M^+). Found 204.1510. ^{1}H NMR data is in agreement with the literature [40].

4-[4-(Trifluoromethyl)phenyl]butan-2-one ***15***. This compound was obtained from 4-(trifluoromethyl)benzyl bromide **9** (1195 mg, 5 mmol) according to the general procedure, as a pale yellow oil (250 mg, 23%), R_f = 0.32 (hexanes–ethyl acetate 6:1, *v*/*v*). ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 2.15 (s, 3H), 2.78 (t, J = 7.6 Hz, 2H), 2.95 (t, J = 7.6 Hz, 2H) 7.30 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 29.5, 30.1, 44.6, 124.4 (q, $J^1_{C,F}$ = 270 Hz), 125.6 (q, $J^3_{C,F}$ = 3 Hz), 128.7 (q, $J^2_{C,F}$ = 32 Hz), 128.8, 145.3, 207.2. ^{19}F NMR (376 MHz, $CDCl_3$), δ (ppm): -63.4. HRMS (EI), *m/z*: calcd. for $C_{11}H_{11}F_3O$: 216.0762 (M^+). Found 216.0763. NMR data is in agreement with the literature [41].

4-(4-Nitrophenyl)butan-2-one ***16***. This compound was obtained from 4-nitrobenzyl bromide **10** (1080 mg, 5 mmol) according to the general procedure, as an amber solid (485 mg, 50%), mp 37–38 ºC (lit. mp 37–40 ºC [42]), R_f = 0.36 (hexanes–ethyl acetate 3:1, *v*/*v*). ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 2.15 (s, 3H), 2.81 (t, J = 7.4 Hz, 2H), 2.99 (t, J = 7.4 Hz, 2H), 7.34 (d, J = 8.8 Hz, 2H), 8.12 (d, J = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 29.5, 30.2, 44.3, 123.9, 129.4, 146.7, 149.1, 206.8. HRMS (EI), *m/z*: calcd. for $C_{10}H_{11}NO_3$: 193.0739 (M^+). Found 193.0734. NMR data is in agreement with the literature [42].

3. RESULTS AND DISCUSSION

Access to 4-arylbutan-2-ones can be achieved through numerous synthetic strategies and, while some of these approaches have a limited use, others are of a broader scope. Among the latter, two-stage synthetic pathways are well represented by a sequence comprising the generation of an arylideneacetone (either through the base-catalyzed Claisen–Schmidt condensation of a suitably substituted aromatic aldehyde with acetone or through a Horner-Wadsworth-Emmons reaction between a conveniently substituted aromatic aldehyde and triphenylphosphoranylidenepropan-2-one) in the first step, followed by chemoselective conjugate reduction of the double carbon–carbon bond in the resulting enone (route *i* in Fig. 2) [21,32], or by the procedure involving the base-catalyzed alkylation of an acetoacetic ester with a benzyl halide, followed by cleavage of the ester moiety in the alkylated β-keto ester, either in the presence of an acid or base [43], or by the Krapcho dealkoxycarbonylation (route *ii* in Fig. 2) [44]. The advent of palladium-catalyzed cross-coupling reaction in the past decades has provided more opportunities for access to 4-arylbutan-2-ones through the one-stage reaction between an aromatic halide and 3-buten-2-ol in the general framework of the Heck–Mizoroki reaction (route *iii* in Fig. 2) [45, 46]. Route *iv* in Figure 2 illustrates the one-step preparative entry to 4-arylbutan-2-ones that comprises the reaction between a benzyl halide-

type of alkylating agent and pentane-2,4-dione through an one-pot alkylation–cleavage approach that was employed in this study. This latter procedure appears more convenient than the two-stage methodologies in routes *i* and *ii*, because it does not require the isolation and purification of the intermediate enone and alkylated β-keto ester, respectively, and it seems also more advantageous than the type of reactions depicted in route *iii*, which require the use of more expensive, oxygen-sensitive palladium-based catalysts.

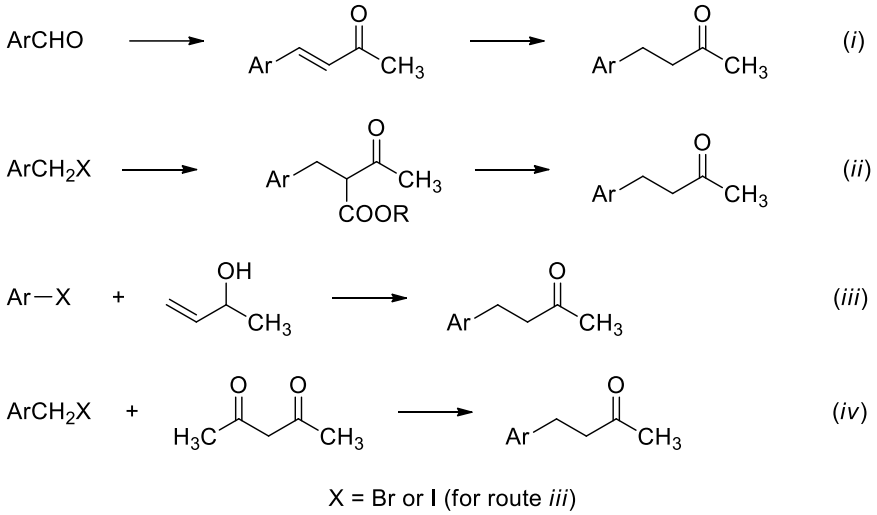

Fig. 2. Overview of the most representative synthetic routes for 4-arylbutan-2-ones

The alkylation–cleavage approach to form 4-arylbutan-2-ones in a single procedure can be successfully conducted in anhydrous low molecular weight alcohols, while anhydrous K_2CO_3 plays the role of the required base, being suitable in both processes (alkylation of pentane-2,4-dione, and cleavage of the acetyl residue from the alkylated β-diketone) of this approach [14]. The reaction is performed at the reflux temperature of the solvent for long periods of time (usually overnight), with a view to ensure the complete conversion of the alkylating agent. Despite having a lower boiling point than ethanol, methanol has been the solvent of choice in the employed method because commercial methanol (having usually a water content lower than 0.05%) is cheaper than anhydrous ethanol. The crude material that resulted at the end of work-up of the reaction mixture was subjected to column chromatography, and the pure compound was obtained by pooling only those fractions that contained a single spot on the thin layer chromatography plates, which spot was associated with the target 4-arylbutan-2-one. According to the data provided in the Experimental part and also to our previous experience in very similar cases [14], this approach normally produces the desired compounds in

satisfactory yields. However, butanone **15** represents a notable exception to this canon, with a low yield of 23%. Being outside the scope of this study, this unexpected behavior of benzyl bromide **9** in this reaction has not been investigated any further with respect to the nature of the by-products resulted from side reactions occurring in this process. To the best of our knowledge, this particular synthetic strategy has been already employed so far only for the preparation of compound **12** in 62% yield [47] and for compound **16** in 66% yield [48], while butanones **13**, **14** and **15** have been obtained using other synthetic methods (such as those illustrated by routes *i* to *iii* in Fig. 2).

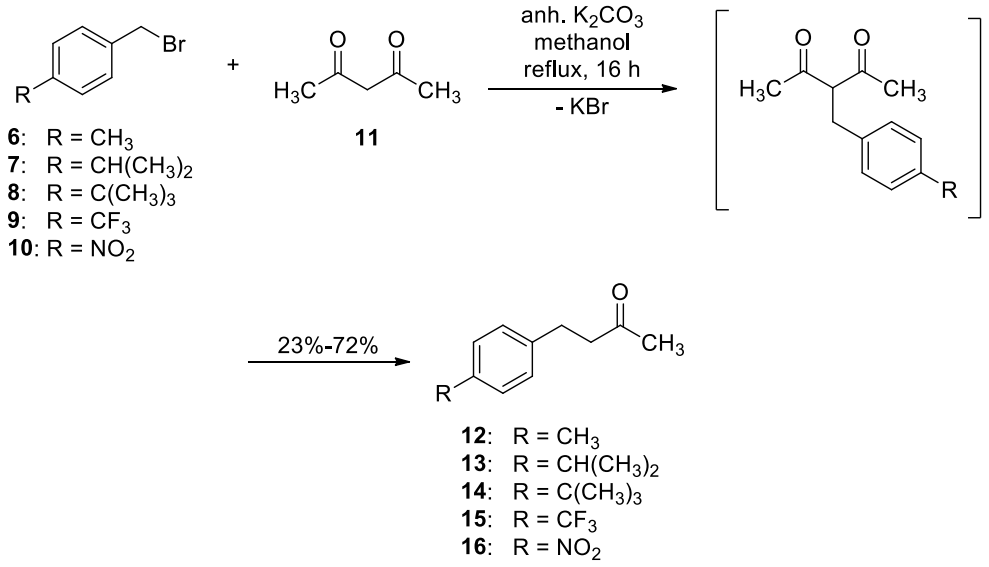

Fig. 3. Synthesis of 4-arylbutan-2-ones through an alkylation–cleavage strategy

The structure of the synthesized 4-arylbutan-2-ones **12**–**16** has been investigated using NMR and HRMS spectroscopy. The signals that should be considered a hallmark for these compounds in terms of structure ascertainment by proton NMR are the two well-defined triplets (integrating each for two protons and corresponding to the protons in the methylene groups) and a singlet at approximately 2.15 ppm (integrating for three protons and assigned to the protons in the methyl group), these signals having been identified for each of these compounds in the aliphatic region of their proton NMR spectra. The chemical shift values for the triplets associated with protons in the methylene groups are usually close to 2.75 ppm (for the protons in the methylene adjacent to the carbonyl group) and close to 2.88 ppm for the protons in the methylene adjacent to the aromatic ring in compounds **12**–**14** that have an alkyl substituent in the aromatic ring. On the other hand, the electron withdrawing influence of the CF_3 substituent in compound

15 and of the NO_2 substituent in compound **16** has a deshielding effect on the protons in the methylene adjacent to the aromatic ring in these compounds, which manifests itself in their chemical shift values higher (2.95 ppm for **15** and 2.99 ppm for **16**) than those recorded for their analogs **12**–**14**. In the case of compound **13**, the signal of the methine proton from the isopropyl substituent of the phenyl ring is superimposed over the triplet of the protons in the methylene adjacent to the aromatic ring, making the peaks associated with these three protons to appear as a multiplet. In addition, the correct number of aromatic protons whose signals display the splitting that is common for the AA′BB′ spin systems of *para*-disubstituted benzene rings with non-identical substituents has been found in the aromatic region of the proton NMR spectra of the target butanones. In the carbon NMR spectra of 4-arylbutan-2-ones **12**–**16**, the peak corresponding to the carbon atom in the terminal methyl group has been found at chemical shift values slightly above 30 ppm. The chemical shift value for the carbon atom in the methylene group neighboring the aromatic ring has been found at or close to 29.5 ppm, while the carbon atom in the methylene group adjacent to the carbonyl function usually gives a peak at approximately 45 ppm. The carbon atom in the carbonyl group has been assigned to the peak at approximately 208 ppm, which is typical for aliphatic ketones that normally present a peak in their ^{13}C NMR spectra for this carbon atom at chemical shifts above 200 ppm. All of the aromatic carbon atoms in the structure of 4-arylbutanon-2-ones **12**–**16** have been accounted for, while the effect of the fluorine in the trifluoromethyl group on the splitting of the peaks of the aromatic carbon atoms in the structure of compound **15** has been detailed in the description of this compound's spectra in Experimental. Also, the peak identified at -63.4 ppm in the ^{19}F NMR spectra of compound **15** is typical for a simple trifluoromethyl-substituted aromatic ring, as the magnetically identical flourine atoms in trifluorotoluene itself have a similar chemical shift value (-63.72 ppm). Finally, the monoisotopic mass values that have been determined experimentally for 4-arylbutan-2-ones **12**–**16** present deviations from the calculated *m/z* lower than 5 ppm and well within the accepted margin of error for this type of experimental data.

4. CONCLUSIONS

The one-step synthetic approach comprising the alkylation of pentane-2,4-dione with alkyl bromides and subsequent cleavage of an acetyl fragment from the alkylated β-diketone has provided facile access to the desired 4-arylbutan-ones, usually with satisfactory yields. Structural analysis of the target compounds has confirmed beyond any doubt their structure. These intermediates have been subsequently showed to act as starting materials in a reaction sequence leading to imidazoles useful as inhibitors of heme oxygenase, whose synthesis and biological activity will be reported elsewhere.

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Authors' **contributions. Gheorghe Roman**: methodology, investigation, formal analysis, data curation, writing – original draft, writing – review & editing; **Walter A. Szarek**: conceptualization, formal analysis, supervision, writing – review & editing.

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