Monatsh Chem (2015) 146:1557–1570
DOI 10.1007/s00706-015-1427-6

ORIGINAL PAPER

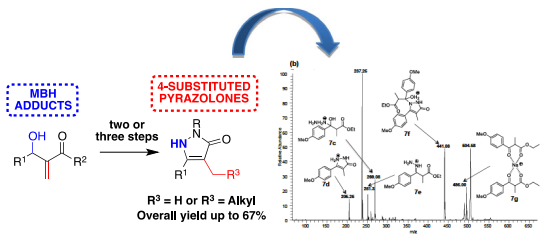
Morita–Baylis–Hillman adducts as building blocks of heterocycles: a simple approach to 4-substituted pyrazolones, and mechanism investigation via ESI–MS(/MS)

Rosimeire C. Barcelos · Lucas A. Zeoly · Manoel T. Rodrigues Jr. · Bruno R. V. Ferreira · Marcos N. Eberlin · Fernando Coelho

Received: 29 December 2014 / Accepted: 15 January 2015 / Published online: 10 February 2015

Abstract We describe herein an efficient approach for the preparation of 4-substituted 2,3-dihydro-1*H*-pyrazol-3-ones starting from Morita–Baylis–Hillman adducts. These heterocycles were obtained in two or three steps as single isomers with moderate to good overall yields. One efficient and alternative methodology for the synthesis of α-methyl-*β*-ketoesters is also reported (up to 91 % yield). Additionally, the mechanism of formation of pyrazolones was investigated employing ESI–MS/MS reaction monitoring.

Graphical abstract



Keywords Morita–Baylis–Hillman · Pyrazolones · *β*-Ketoesters · Heterocycles

Electronic supplementary material The online version of this article (doi:10.1007/s00706-015-1427-6) contains supplementary material, which is available to authorized users.

R. C. Barcelos · L. A. Zeoly · M. T. Rodrigues Jr. · F. Coelho (✉)
Laboratory of Synthesis of Natural Products and Drugs, University of Campinas, PO Box 6154, Campinas, SP 13083-970, Brazil
e-mail: coelho@iqm.unicamp.br

B. R. V. Ferreira · M. N. Eberlin
Laboratory ThoMSon of Mass Spectrometry, University of Campinas, PO Box 6154, Campinas, SP 13083-970, Brazil

Introduction

Heterocycles are one of the most important classes of compounds in nature and are present in almost all biologically active molecules [1]. Among them, the pyrazolone core has been gaining increasing attention due to its applications, representing a versatile template for combinatorial and medicinal chemistry [2–7].

A wide variety of patents featuring different syntheses of pyrazolones and applications for it have also appeared, which demonstrates the strong economical potential of this nucleus [8–10]. Their anticancer [11–14] and antimicrobial [15–17] properties have also been studied. Pyrazolones have traditionally been used due to their analgesic, antipyretic, and anti-inflammatory activities [18–22]. For example, dipyrone, phenazone, propyphenazone, and ampyrone, drugs in current use, show some or all of these properties (Fig. 1). Recently, Simon et al. [23] have reported a new class of pyrazolones and isoxazol-5-ones that inhibit Sirtuin, which can potentially be used in the treatment of lymphomas (Fig. 2).

Classically, 4-substituted pyrazolones have been synthesized from 1,3-dicarbonyl compounds, where *β*-ketoesters are combined with hydrazines to obtain simple rings, which are then functionalized. One of the ways by which this functionalization can be achieved is using Mannich or Michael chemistry to introduce the required substituent at position 4 (Scheme 1), but this strategy adds an additional step to the synthesis. Furthermore, dialkylated products can be obtained when Michael addition is used [24–26].

An alternative to eliminate these drawbacks would be to obtain the pyrazolones starting from substituted *β*-ketoesters. 1,3-Ketoesters substituted in the α position can be prepared by different approaches. One of them would be

via the alkylation of ketoesters, which can be done using a base and an alkylating agent. Dialkylation and the need of protecting groups for free amines and alcohols, however, are serious disadvantages. A Knoevenagel reaction could be used to overcome the problem of poly-alkylation, but it would also introduce an additional reduction step. Another approach would be to rely on Claisen chemistry, providing that one of the esters is nonenolizable, but this would require the use of a strong base and sometimes the presence of a Lewis acid, both making the reaction moisture and, in some cases, air sensitive. The Reformatsky reaction would be another alternative to obtain β-ketoesters; however, one more step would be necessary, consisting in the oxidation of the hydroxyl group primarily obtained. Another modern synthesis of 1,3-ketoesters employs alkyl diazoacetates, but it has a limited scope in varying substituents in the α position (Scheme 2) [27–37].

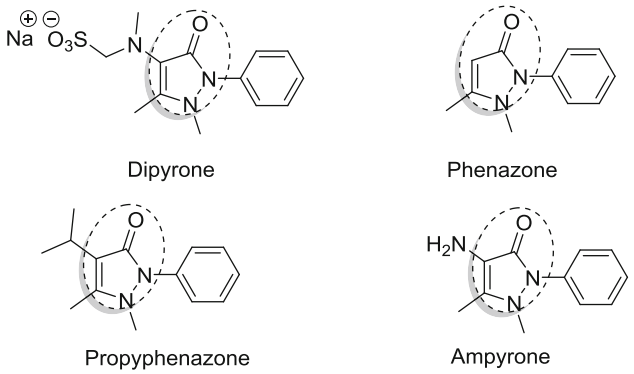


Fig. 1 Some biologically active pyrazolones

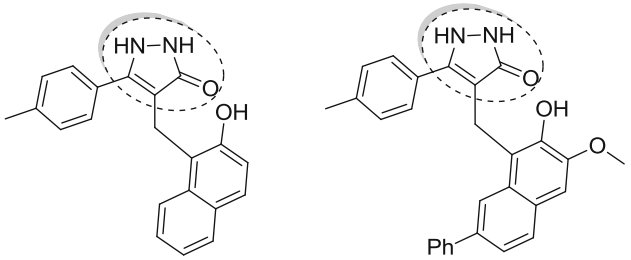


Fig. 2 Two pyrazolones with pronounced anti-lymphoma activity

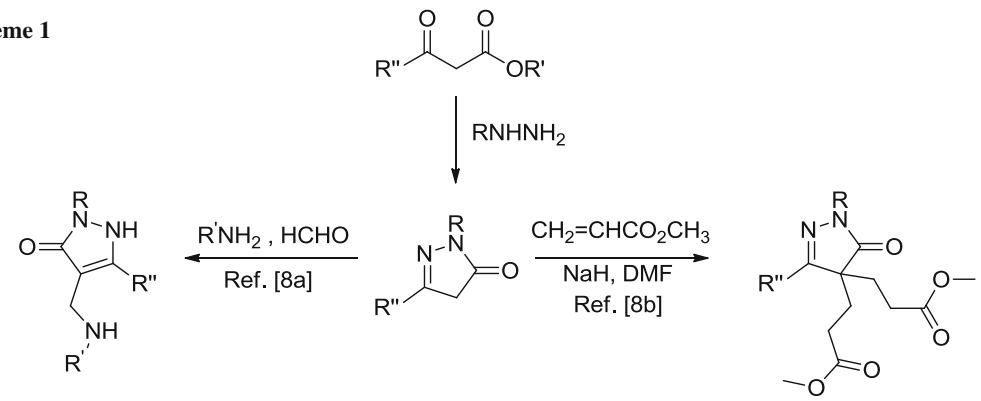
Based on the importance of this nucleus, and to overcome the drawbacks described above, we describe herein an efficient and alternative methodology to prepare β-ketoesters, which employ transformations on the allylic portion of the Morita–Baylis–Hillman (MBH) adducts to furnish pyrazolones in 1–2 steps, in good to excellent yields (70–96 %). These transformations employ either oxidation with IBX followed by a novel chemoselective reduction using the borane dimethyl sulfide complex of the double bond to give the α-methyl-substituted β-ketoesters in two steps, or a Heck reaction, which in a single step furnishes different substituted ketoesters. Using these two protocols, substituted 2,3-dihydro-1*H*-pyrazol-3-ones were synthesized in good overall yields (up to 70 %), in two or three steps starting from the MBH adducts (Scheme 3).

Results and discussion

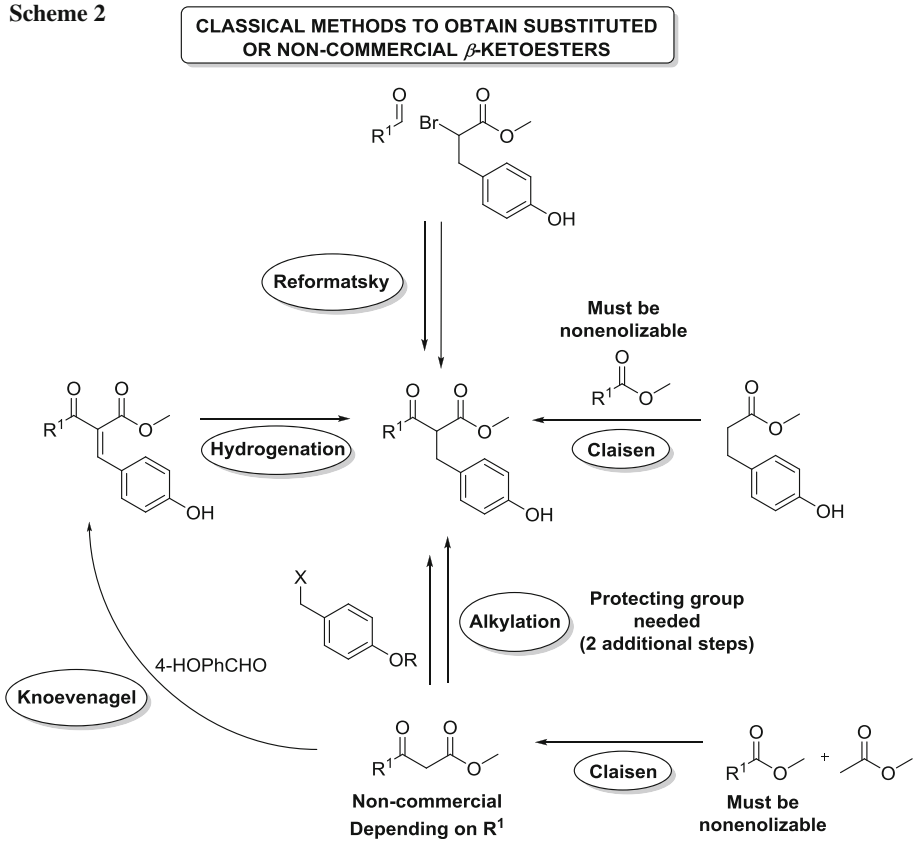
The synthesis of the pyrazolone derivatives was accomplished in three or four steps starting from the commercial aldehydes, depending on the strategy employed to prepare β-ketoesters. The first step of both approaches consisted of an MBH reaction [38–45]. A series of MBH adducts (**2a**–**2j**) was prepared in good yields (70–96 %) from different aldehydes (**1a**–**1j**), containing aromatic, heterocyclic, or aliphatic substituents (Scheme 4; Table 1).

Next, we attempted the synthesis of 2-methylated β-ketoesters from MBH adducts in two steps. The hydroxyl groups in **2a**–**2g** and **2j** were oxidized using IBX [46], and then the conjugated double bond was reduced using the borane dimethyl sulfide complex (Scheme 5; Table 2).

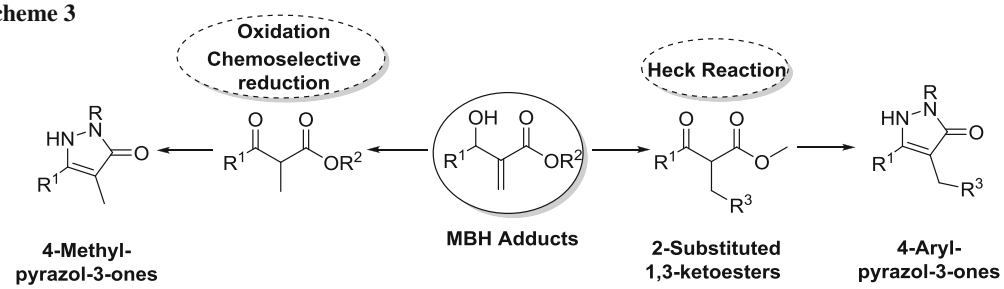
Scheme 1



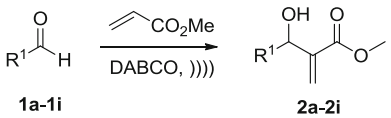
Scheme 2



Scheme 3



Scheme 4



Boranes have already been used in combination with silanes as reducing agents for some particular type of double bonds [47–51]; however, the only example where the borane dimethyl sulfide complex was used to reduce electronically poor double bonds was reported some years ago for cyclic vinylphosphine oxides or dihydrophosphole oxides [52–54]. Thus, the usage of the borane dimethyl sulfide complex to reduce the double bonds of oxidized MBH adducts represents a new and chemoselective methodology to reduce this type of system.

The yields for the two-step synthesis of β-ketoesters **3a**–**3g** and **3j** varied from 70 to 91 %. The α-methylene-β-ketoesters that are produced as intermediates do not need to be purified. Simple filtration for IBA (2-iodosobenzoic acid) removal, followed by solvent removal, furnishes the intermediates with enough purity to proceed with the reduction.

The main limitation reported for the synthesis of β-ketoesters occurs for the preparation of α-substituted

Table 1 Preparation of MBH adducts **2a–2j**

Entry	Substrates	Yields **2**/%[a,b,c]
1	**1a**, R^1 = 3,4,5-$MeOC_6H_2$; R^2 = Me	**2a** (75)
2	**1b**, R^1 = 4-$MeOC_6H_4$; R^2 = Me	**2b** (70)
3	**1c**, R^1 = Piperonyl; R^2 = Me	**2c** (85)
4	**1d**, R^1 = 4-BrC_6H_4; R^2 = Me	**2d** (85)
5	**1e**, R^1 = 4-$O_2NC_6H_4$; R^2 = Me	**2e** (96)
6	**1f**, R^1 = C_6H_5; R^2 = Me	**2f** (74)
7	**1g**, R^1 = 2-Thienyl; R^2 = Me	**2g** (90)
8	**1h**, R^1 = Ethyl; R^2 = Me	**2h** (85)
9	**1i**, R^1 = 4-ClC_6H_4; R^2 = Me	**2i** (85)
10	**1j**, R^1 = 4-$MeOC_6H_4$; R^2 = Et	**2j** (81)

[a] Yields refer to isolated and purified compounds

[b] Spectroscopic data are compatible for the proposed structures

[c] Spectroscopic data of all MBH adducts are described in our previous work [38, 39, 46]

Scheme 5

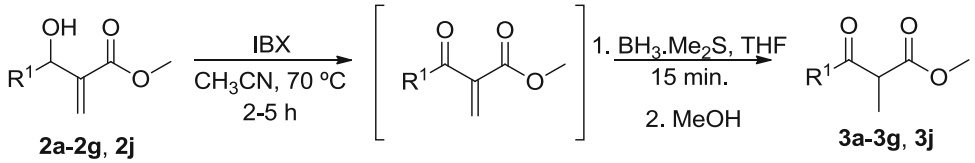


Table 2 Preparation of *β*-ketoesters **3a–3g** and **3j**

Entry	Substrates	Yields **3**/%[a,b]
1	**2a**, R^1 = 3,4,5-$CH_3OC_6H_2$; R^2 = Me	**3a** (71)
2	**2b**, R^1 = 4-$CH_3OC_6H_4$; R^2 = Me	**3b** (91)
3	**2c**, R^1 = Piperonyl; R^2 = Me	**3c** (70)
4	**2d**, R^1 = 4-BrC_6H_4; R^2 = Me	**3d** (91)
5	**2e**, R^1 = 4-$NO_2C_6H_4$; R^2 = Me	**3e** (65)
6	**2f**, R^1 = C_6H_5; R^2 = Me	**3f** (80)
7	**2g**, R^1 = 2-Thienyl; R^2 = Me	**3g** (83)
8	**2j**, R^1 = 4-$CH_3OC_6H_4$; R^2 = Et	**3j** (90)

[a] Yields refer to isolated and purified compounds

[b] All spectroscopic data are compatible with the proposed structures

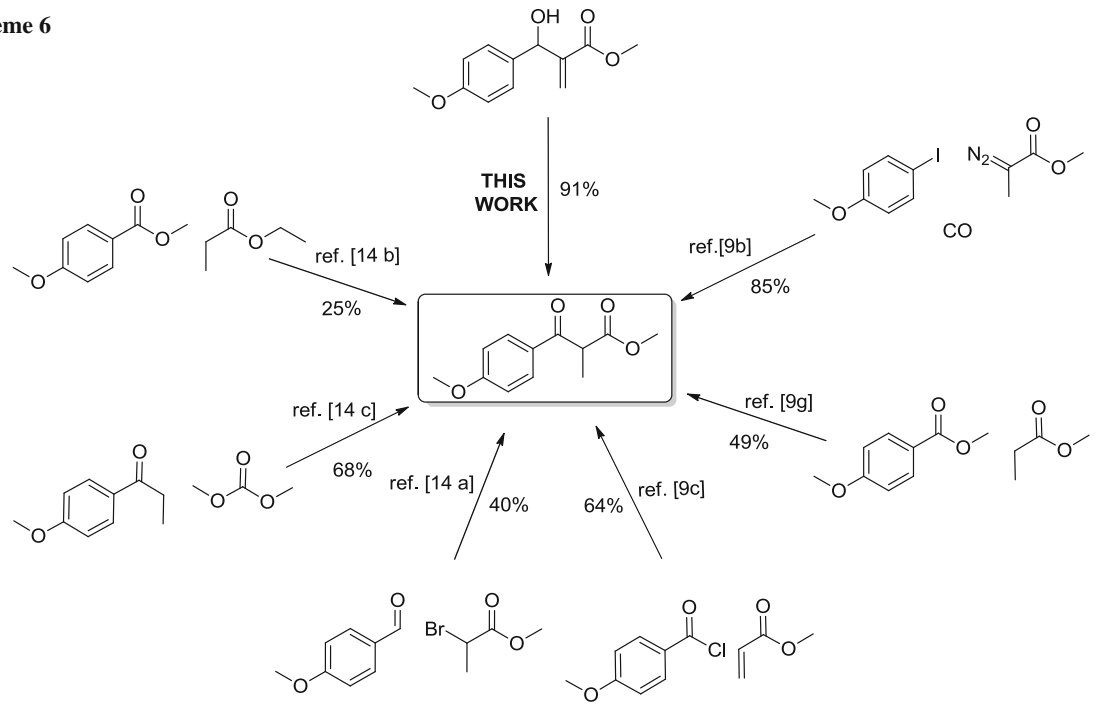
substrates. Here, we prepared the 2-methylated *β*-ketoesters observing no issues regarding dialkylation. Our protocol avoids the use of strong bases and acylating reagents and leads to both, yields and scope, comparable or even better than those reported in literature [27, 29, 32, 33, 55–60]. This was clearly shown for compound **3b**, where different methodologies and their respective yields are presented (Scheme 6) [27, 29, 33, 55–57].

Note that we used boranes for what seems to be an unusual task: as a selective reducing agent for (activated) double bonds. Boranes are normally used for hydroboration–oxidation of double bonds or reduction of carbonyls [61, 62]. But we have noted that, rather than reducing the carbonyl group of oxidized MBH adducts, the borane dimethyl sulfide complex reduces the double bond in a fully selective fashion. Our mechanistic proposal for this chemoselective reduction (Scheme 7) invokes an intermediate boron enolate [63] which, after work-up with methanol, furnishes the desired α-methyl-*β*-ketoester.

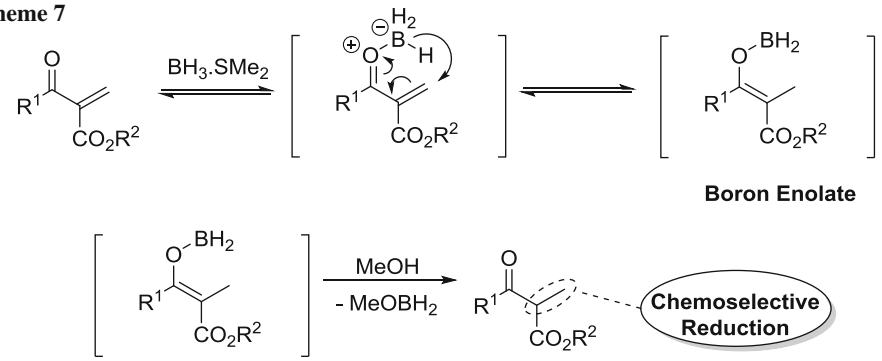
The last step in the synthesis of 4-methylpyrazolones was the cyclization of the *β*-ketoesters **3a–3g** and **3j** with hydrazine hydrate, a classical procedure that furnished 4-methyl-2,3-dihydro-1*H*-pyrazol-3-ones **4a–4h** with yields ranging from 50 to 95 % (Scheme 8; Table 3). Note that even substituted hydrazines can be used (Table 3, entry 6) to give higher substituted pyrazolones.

To increase the structural diversity of the pyrazolones, we have employed MBH adducts in an intermolecular Heck reaction with different aryl iodides to obtain *β*-ketoesters with substituents other than methyl in the α-position. Adducts **2b**, **2c**, and **2e–2i** were used as substrates for this reaction (Scheme 9; Table 4) [39, 64], and this approach allowed the synthesis of *β*-ketoesters **5a–5h** in a single step with very good yields (70–96 %, Table 4),

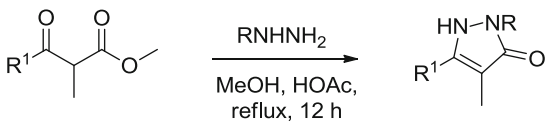
Scheme 6



Scheme 7



Scheme 8



enabling structural diversification. Our yields were similar or even better than those reported in literature [28, 65–75]. The synthesis of α-functionalized *β*-ketoesters by other methodologies, such as alkylation or via Knoevenagel, would require protection group chemistry for the free amines and phenols or the use of large quantities of base, adding at least two additional steps to the synthesis (protection/deprotection).

To confirm that our approach was a useful alternative to the preparation of *β*-ketoesters, we show different methodologies to synthesize compound **5e** (Scheme 10). We can observe that our yield was similar or even better than those reported in literature [27, 65, 66, 68–74].

Finally, substrates **5a**–**5h** were submitted to the same conditions of cyclization employing hydrazine hydrate, leading to the synthesis of 4-(4-hydroxybenzyl)-2,3-dihydro-1*H*-pyrazol-3-ones **6a**–**6h** with good yields (60–92 %, Table 4).

Mechanistic study employing mass spectrometry

In 1987, Katrizky and co-workers [76] reported a ^{13}C NMR mechanistical study of the pyrazolone ring formation by the reaction of *β*-ketoesters with hydrazines. Analyzing the

Table 3 Synthesis of 4-methylpyrazolones **4a–4h**

Entry	Substrates	Yields **4**/%[a,b]
1	**3a**, R^1 = 3,4,5-$CH_3OC_6H_2$; R^2 = Me; R = H	**4a** (65)
2	**3b**, R^1 = 4-$CH_3OC_6H_4$; R^2 = Me; R = H	**4b** (74)
3	**3c**, R^1 = Piperonyl; R^2 = Me; R = H	**4c** (65)
4	**3d**, R^1 = 4-BrC_6H_4; R^2 = Me; R = H	**4d** (70)
5	**3e**, R^1 = 4-$NO_2C_6H_4$; R^2 = Me; R = H	**4e** (95)
6	**3e**, R^1 = 4-$NO_2C_6H_4$; R^2 = Me; R = Ph	**4f** (50)
7	**3f**, R^1 = C_6H_5; R^2 = Me; R = H	**4 g** (78)
8	**3g**, R^1 = 2-Thienyl; R^2 = Me; R = H	**4 h** (64)
9	**3j**, R^1 = 4-$CH_3OC_6H_4$; R^2 = Et; R = H	**4b** (76)

[a] Yields refer to isolated and purified compounds

[b] All spectroscopic data are compatible with the proposed structures

Scheme 9

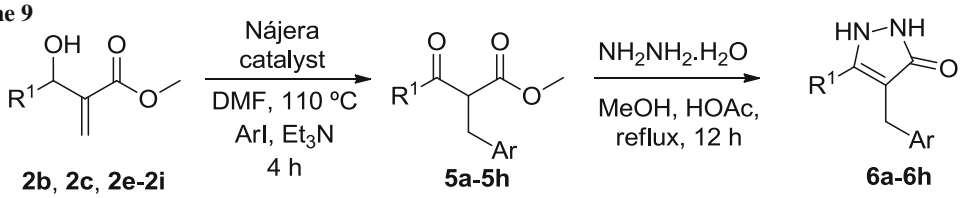


Table 4 Synthesis of 4-arylated β-ketoesters **5a–5h** and 4-arylated pyrazolones **6a–6h**

Entry	Substrates	Ar	Yields/%[a]	
			5	**6**
1	**2b**, R = 4-$MeOC_6H_4$	C_6H_5	**5a** (86)	**6a** (69)
2	**2c**, R = Piperonyl	C_8H_7N	**5b** (77)	**6b** (80)
3	**2e**, R = 4-$NO_2C_6H_4$	4-HOC_6H_4	**5c** (96)	**6c** (73)
4	**2e**, R = 4-$NO_2C_6H_4$	C_6H_5	**5d** (76)	**6d** (75)
5	**2f**, R = C_6H_5	C_6H_5	**5e** (78)	**6e** (76)
6	**2g**, R = 2-Thienyl	4-HOC_6H_4	**5f** (80)	**6f** (60)
7	**2h**, R = C_2H_5	4-HOC_6H_4	**5g** (70)	**6g** (92)
8	**2i**, R = 4-ClC_6H_4	C_6H_5	**5h** (75)	**6h** (70)

[a] Yields refer to isolated and purified products

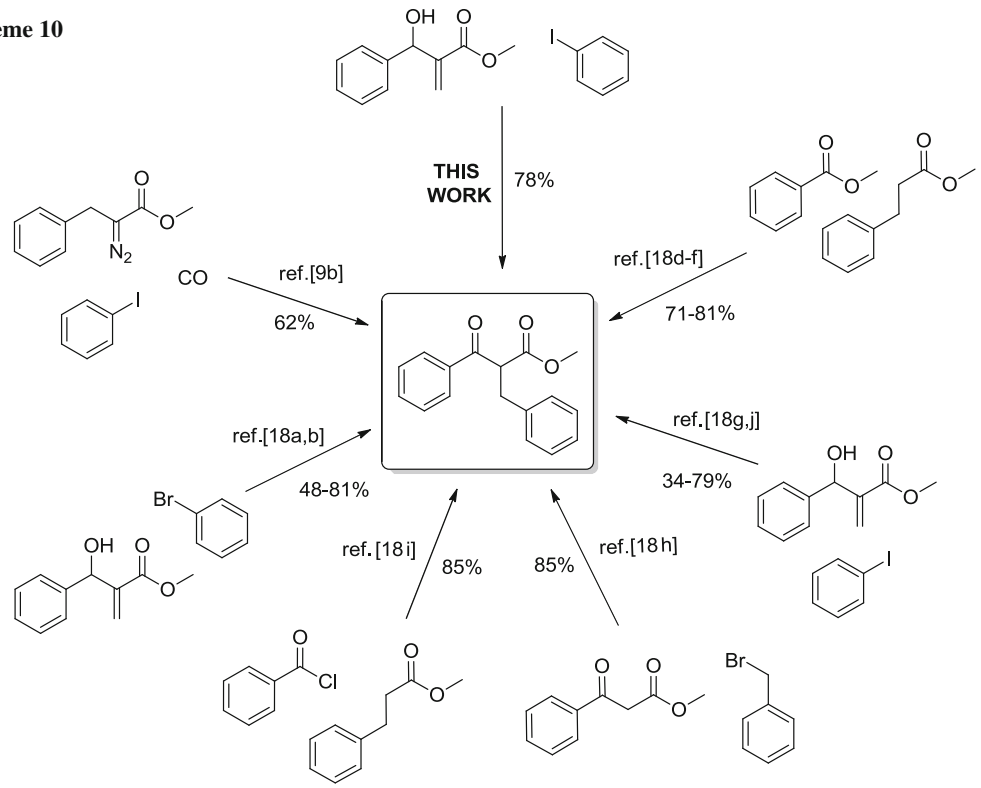
spectra, peaks were assigned to the starting materials, intermediates, and products, but correct assignment of intermediates was not possible when substituted β-ketoesters were employed. Based on these ^{13}C NMR, a reaction mechanism via a hydrazide rather than a hydrazone intermediate was proposed (Scheme 11).

Due to the cationic nature of the intermediates proposed for pyrazolone formation from MBH adducts, which should favor ESI(+) "fishing", this reaction seems ideal to ESI(+)-MS(/MS) monitoring [77–81]. This technique has offered an exceptional tool for mechanistic studies, providing proper and continuous [82] snapshots of the ionic composition of reaction solutions. The method is also able to gently transfer reaction intermediates to the gas phase with great speed and sensitivity for proper MS and MS/MS characterization. Organic reactions or metal catalysis has been extensively investigated via ESI–MS, and efficient "fishing" of multiple intermediates and products directly from the reaction solution have been attained [83–88].

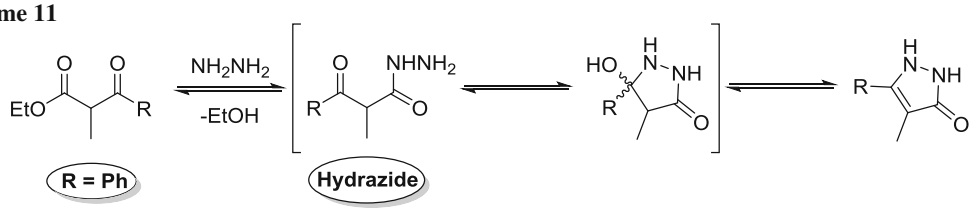
ESI(+)-MS(/MS) monitoring was therefore performed, first for a reaction solution containing **3j** (0.42 mmol), hydrazine hydrate (1.3 equiv.), AcOH (10 mol %), and 5.0 cm^3 methanol as the solvent under reflux. Aliquots (0.5 mm^3) were diluted in methanol with a trace amount of formic acid, and directly subjected to ESI(+) in 1-h intervals up to 24 h. Figure 3 shows typical ESI(+)-MS of the reaction solution (t = 0 min and t = 3 h) as well as ESI–MS/MS of a key intercepted intermediate.

At t = 0 min (Fig. 3a), ESI(+)-MS detected **7a** of m/z = 237, a ion that corresponds to the protonated MBH adduct $[\mathbf{3j} + H]^+$, as well as **7b** of m/z = 269 and **7c** of m/z = 504, corresponding to $[\mathbf{3j}$ + hydrazine + $H]^+$ and $[\mathbf{3j} + \mathbf{3j}$ + hydrazine + $H]^+$.

Scheme 10



Scheme 11



At $t = 3$ h, the reaction has progressed far enough that other key reaction intermediates could then be properly detected and characterized (Fig. 3b), such as **7d** ($m/z = 205$), **7e** ($m/z = 251$), **7f** ($m/z = 441$), and **7g** ($m/z = 495$). Note that **7d** corresponds in fact to the protonated final product $[\mathbf{4b} + H]^+$. Note also that **7e** results from dehydration of **7b**. ESI–MS/MS data firmly corroborate the proposed structures, as illustrated that for **7e** in Fig. 3c. The reaction mechanism we propose (Scheme 12) is therefore corroborated by the species intercepted and characterized via ESI (+)-MS(/MS) monitoring.

In conclusion, the two methodologies presented herein for β-ketoester preparation are both simple, fast, and could be successfully applied to a large diversity of MBH adducts. The reduction of the double bond employing borane proved to be very chemoselective, and provided an alternative method to reduce highly activated double bonds. The β-ketoesters synthesized were also proved to be useful in the direct preparation of 4-substituted pyrazolones. Since both methods are applicable to different esters, their use in the synthesis of pharmaceutically important pyrazolones can be anticipated. Compounds similar to those described as sirtuin inhibitors (Fig. 1) could also be prepared using our protocols. Studies of the biological potential of the novel pyrazolones described herein are underway. By ESI–MS monitoring experiments new insights into the mechanism of formation of pyrazolones from β-ketoesters were also provided.

Experimental

Aldehydes used as substrates for the reactions are commercial and were purchased. The other chemicals were

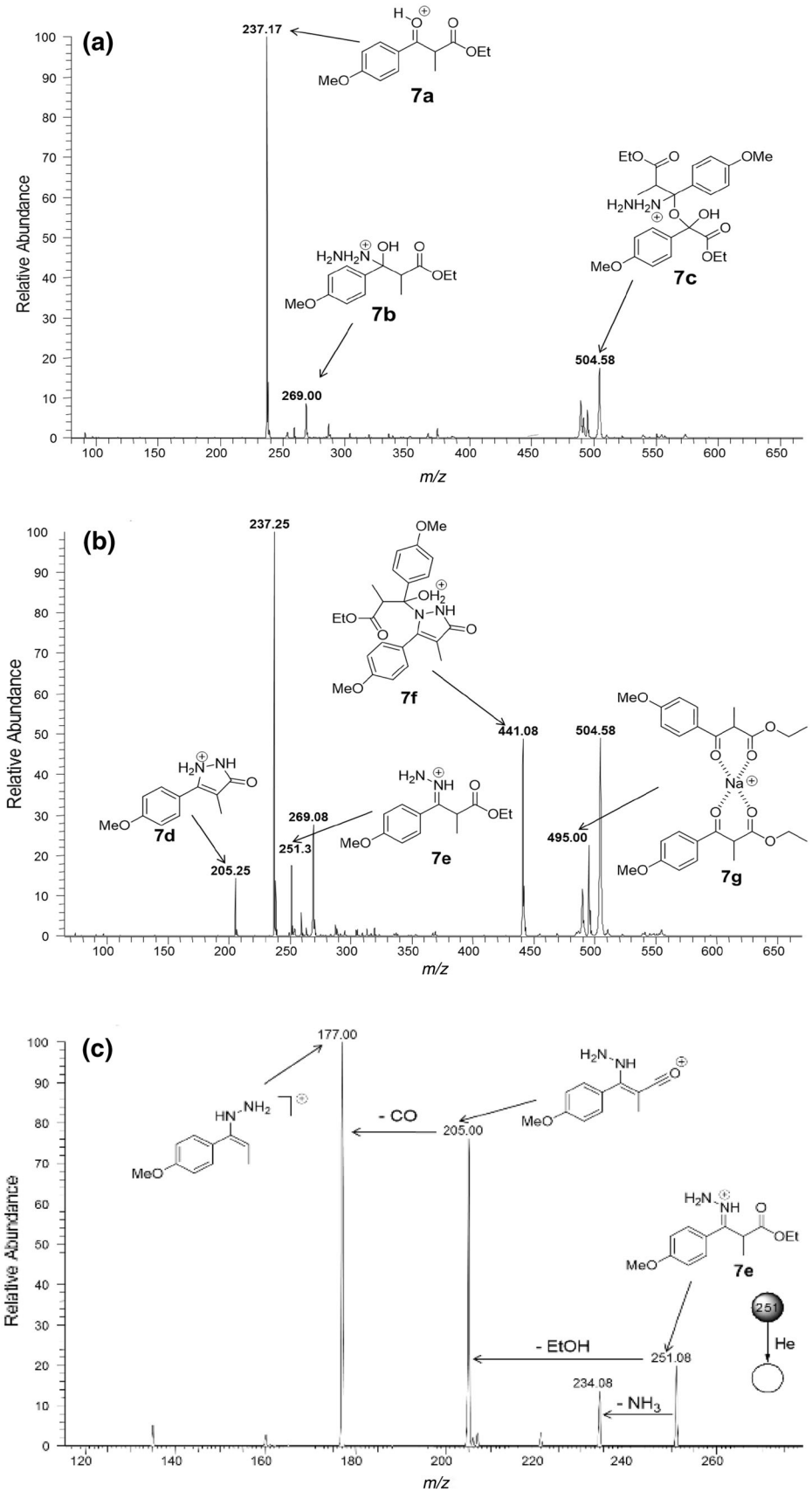
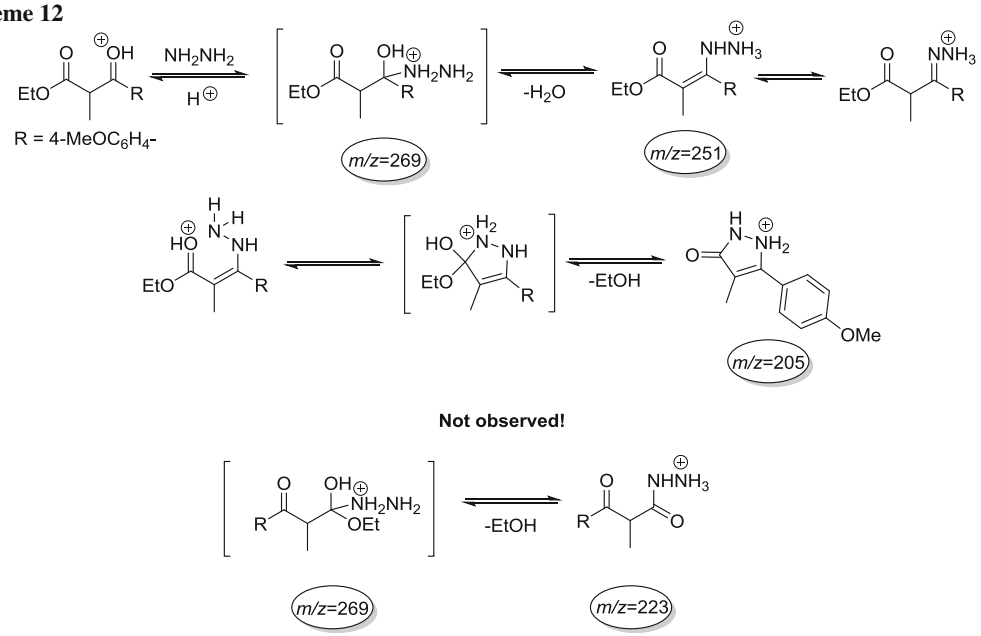


Fig. 3 ESI(+)-MS of the reaction solution containing **3j** and hydrazine **a** at $t = 0$ min, **b** at $t = 3$ h, **c** ESI(+)-MS/MS of **7e** of $m/z = 251$

Scheme 12



used as purchased unless otherwise noticed. Acetonitrile was distilled from calcium hydride immediately prior to use. IBX was prepared according to Martin's procedure [89]. Reaction progress was monitored by thin-layer chromatography on silica gel (aluminum foils) and spotted under UV light (254 nm), followed by staining with ethanolic 25 % phosphomolybdic solution, aqueous $KMnO_4$ or sulfuric vanillin. Purification by column chromatography was carried out with silica gel (70–230 or 230–400 Mesh). ^{1}H NMR spectra were measured at 250 MHz and the ^{13}C NMR spectra at 62.5 MHz, in $CDCl_3$, MeOD, TFA-*d* or DMSO-d_6 at room temperature. Chemical shifts (δ) were reported in ppm and the coupling constants (*J*) in Hertz (Hz). Signal multiplicity was assigned as singlet (s), doublet (d), double doublet (dd), triplet (t), quartet (q), multiplet (m), and broad (br). The IR spectra were obtained by means of the FT-IR spectrophotometer NicoletTM iSTM5 with the frequencies expressed in cm^{-1}. The ESI–MS(/MS) data were acquired using a high-resolution QT of mass spectrometer (Manchester, UK) with a resolution of 5,000 and less than 50.0 ppm accuracy in TOF mass analyzer. The mechanistic study was performed on an LTQ FT Ultra equipment (Thermo Scientific). Melting points were obtained using an Electrothermal equipment model 9100 and the values are corrected.

General procedure for the preparation of Morita–Baylis–Hillman adducts ***2a–2i***

A mixture of the aliphatic or aromatic aldehydes (18–20 mmol), methyl or ethyl acrylate (2.5 equiv.), and DABCO (0.65 equiv.) was sonicated using an ultrasonic cleaner UNIQUE model GA 1000 (1,000 W, 25 kHz) for 16–120 h at room temperature. The reaction mixture was then diluted with 50 cm^3 dichloromethane. The organic solution was washed with 2 × 10 cm^3 water and 10 cm^3 brine, concentrated under reduced pressure, and dried over $MgSO_4$. After filtration and solvent removal, the residue was purified by column chromatography (gradient elution acetate:*n*-hexane 10:90 to 40:60 v/v). All data obtained for the adducts prepared are in agreement with literature [38].

General procedure for the preparation of the α-methyl-β-ketoesters ***3a–3g*** *and* ***3j***

To a stirred solution of a MBH adduct (1.0 mmol) in acetonitrile (final concentration: 0.14 mol/dm^3), 420 mg *o*-iodoxybenzoic acid (IBX, 1.5 equivalents) was added. The resulting mixture was then stirred at 70 °C and the progression of the reaction was monitored by TLC. At the end, the mixture was cooled to room temperature, filtered, and the solvent was removed under reduced pressure. After that, under a nitrogen atmosphere, the oxidized MBH adduct was dissolved in 10 cm^3 THF, borane in dimethyl sulfide (2 mol/dm^3 in THF, 1.0 equivalent) was added to the mixture, and the resulting solution was stirred. The reaction was monitored by TLC. After reaction completion, 2 cm^3 methanol was added, the inert atmosphere was removed, and the solvent evaporated under reduced pressure. The crude product was purified by silica gel flash column chromatography (gradient elution acetate:*n*-hexane 5:95 to 30:70 v/v) to give the corresponding β-ketoesters **3a–3g**

and **3j**. The yields were calculated for the two-step procedure.

Methyl 2-methyl-3-oxo-3-(3,4,5-trimethoxyphenyl)-propanoate (**3a**, $C_{14}H_{18}O_6$)
Yield: 71 %; white solid; m.p.: 61–63 °C; IR (ATR): $\bar{\nu}$ = 3,058, 2,943, 2,840, 1,739, 1,680, 1,583, 1,128 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 1.47 (d, J = 7.1 Hz, 3H), 3.67 (s, 3H), 3.88 (s, 6H), 3.89 (s, 3H), 4.33 (q, J = 7.1 Hz, 1H), 7.22 (s, 2H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 14.1, 48.3, 52.7, 56.5 (2 OCH_3), 61.1, 106.4 (2C), 131.0, 143.2, 153.4 (2C), 171.6, 194.5 ppm; HRMS (ESI^+): *m/z* calcd. for $C_{14}H_{19}O_6$ 283.1182 ($[M+H]^+$), found 283.1133.

Methyl 3-(4-methoxyphenyl)-2-methyl-3-oxopropanoate (**3b**, $C_{12}H_{14}O_4$)
Yield: 91 %; colorless oil; IR (ATR): $\bar{\nu}$ = 3,057, 2,954, 2,843, 1,741, 1,677, 1,601, 1,264, 1,171, 1,029, 844 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 1.37 (d, J = 7.0 Hz, 3H), 3.57 (s, 3H), 3.75 (s, 3H), 4.29 (q, J = 7.0 Hz, 1H), 6.84 (d, J = 8.9 Hz, 2H), 7.86 (d, J = 8.9 Hz, 2H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 13.9, 47.6, 52.3, 55.4, 113.9 (2C), 128.6, 130.9 (2C), 163.9, 171.4, 194.3 ppm.

Methyl 3-(2H-1,3-benzodioxol-5-yl)-2-methyl-3-oxopropanoate (**3c**, $C_{12}H_{12}O_5$)
Yield: 70 %; yellow oil; IR (ATR): $\bar{\nu}$ = 2,992, 2,953, 2,905, 1,739, 1,676, 1,441, 1,248, 1,037, 736 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 1.36 (d, J = 7.1 Hz, 3H), 3.58 (s, 3H), 4.24 (q, J = 7.1 Hz, 1H), 5.94 (s, 2H), 6.75 (d, J = 8.2 Hz, 1H), 7.33 (d, J = 1.6 Hz, 1H), 7.48 (dd, J = 8.2, 1.6 Hz, 1H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 14.0, 47.7, 52.4, 102.0, 107.9, 108.2, 125.0, 130.5, 148.4, 152.2, 171.3, 193.9 ppm.

Methyl 3-(4-bromophenyl)-2-methyl-3-oxopropanoate (**3d**, $C_{11}H_{11}BrO_3$)
Yield: 91 %; pale-yellow oil; IR (ATR): $\bar{\nu}$ = 2,993, 2,952, 1,742, 1,687, 1,585, 1,397, 1,217, 1,198, 1,071, 940 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 1.43 (d, J = 7.1 Hz, 3H), 3.63 (s, 3H), 4.30 (q, J = 7.1 Hz, 1H), 7.56 (d, J = 8.6 Hz, 2H), 7.78 (d, J = 8.6 Hz, 2H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 13.8, 48.2, 52.7, 128.9, 130.2 (2C), 132.2 (2C), 134.7, 171.1, 194.9 ppm.

Methyl 2-methyl-3-(4-nitrophenyl)-3-oxopropanoate (**3e**, $C_{11}H_{11}NO_5$)
Yield: 65 %; yellow solid; m.p.: 66–68 °C; IR (ATR): $\bar{\nu}$ = 2,994, 2,956, 1,744, 1,698, 1,528, 1,347, 1,223, 856, 704 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 1.47 (d, J = 7.0 Hz, 3H), 3.64 (s, 3H), 4.38 (q, J = 7.0 Hz, 1H), 8.08 (d, J = 8.8 Hz, 2H), 8.26 (d, J = 8.8 Hz, 2H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 13.5, 48.5, 52.7, 124.0 (2C), 129.6 (2C), 140.4, 150.5, 170.6, 194.5 ppm.

Methyl 2-methyl-3-oxo-3-phenylpropanoate (**3f**, $C_{11}H_{12}O_3$)
Yield: 80 %; pale-yellow oil; IR (ATR): $\bar{\nu}$ = 3,065, 2,993, 2,953, 1,741, 1,686, 1,597, 1,449, 1,220, 1,199, 949, 735 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 1.35 (d, J = 7.1 Hz, 3H), 3.52 (s, 3H), 4.31 (q, J = 7.1 Hz, 1H), 7.27–7.38 (m, 2H), 7.39–7.48 (m, 1H), 7.80–7.90 (m, 2H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 13.7, 47.8, 52.2, 128.4 (2C), 128.6 (2C), 133.4, 135.6, 171.1, 195.7 ppm.

Methyl 2-methyl-3-oxo-3-(thiophen-2-yl)propanoate (**3g**, $C_9H_{10}O_3S$)
Yield: 83 %; yellow oil; IR (ATR): $\bar{\nu}$ = 1,740, 1,663, 1,413, 1,240, 1,266, 1,059, 861 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 1.38 (d, J = 7.0 Hz, 3H), 3.57 (s, 3H), 4.18 (q, J = 7.0 Hz, 1H), 7.04–7.11 (m, 1H), 7.59 (d, J = 4.7 Hz, 1H), 7.69 (d, J = 3.7 Hz, 1H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 13.9, 49.1, 52.4, 128.4, 133.0, 134.9, 142.9, 170.7, 188.5 ppm.

Ethyl 3-(4-methoxyphenyl)-2-methyl-3-oxopropanoate (**3j**, $C_{13}H_{16}O_4$)
Yield: 90 %; colorless oil; IR (ATR): $\bar{\nu}$ = 3,050, 2,952, 2,840, 1,741, 1,675, 1,598, 1,260, 1,174, 1,032, 840 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 1.17 (t, J = 7.2 Hz, 3H), 1.46 (d, J = 7.2 Hz, 3H), 3.86 (s, 3H), 4.13 (q, J = 7.2 Hz, 1H), 4.32 (q, J = 7.2 Hz, 1H), 6.93 (d, J = 8.9 Hz, 2H), 7.96 (d, J = 8.9 Hz, 2H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 13.8, 13.9, 48.1, 55.5, 61.3, 114.1 (2C), 128.9, 130.9 (2C), 164.0, 171.2, 194.5 ppm.

*General procedure for the preparation of the Heck adducts **5a–5h***

In a 10-cm^3 round-bottom flask, aryl iodide (1.1 mmol), Morita–Baylis–Hillman adduct (1 mmol), 0.32 cm^3 triethylamine (2.3 mmol), palladacycle A (0.5 mol %), and 2–3 cm^3 DMF were mixed. The mixture was stirred at 110 °C in air and the reaction progress was analyzed by TLC. The crude reaction mixture was extracted with 15 cm^3 water and 3 × 15 cm^3 ethyl acetate. The organic phase was dried over Na_2SO_4 and evaporated to yield the crude product of the corresponding α-benzyl-β-ketoesters **5a–5h**.

Methyl 2-benzyl-3-(4-methoxyphenyl)-3-oxopropanoate (**5a**, $C_{18}H_{18}O_4$)
Yield: 86 %; yellow oil; IR (ATR): $\bar{\nu}$ = 3,058, 3,022, 2,949, 1,740, 1,679, 1,612, 1,227 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 3.31 (dd, J = 7.2, 4.1 Hz, 2H), 3.61 (s, 3H), 3.81 (s, 3H), 4.62 (t, J = 7.2 Hz, 1H), 6.86 (d, J = 8.9 Hz, 2H), 7.14–7.23 (m, 5H), 7.93 (d, J = 8.9 Hz, 2H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 35.0, 52.5, 55.5, 55.6, 114.0 (2C), 126.7, 128.6 (2C), 128.9 (2C), 129.1, 131.1 (2C), 138.6, 164.0, 170.0, 192.8 ppm.

Methyl 3-(2H-1,3-benzodioxol-5-yl)-2-(1H-indol-5-ylmethyl)-3-oxopropanoate (**5b**, $C_{20}H_{17}NO_5$)
Yield: 77 %; brown oil; IR (ATR): $\bar{\nu}$ = 3,400, 2,953, 2,911, 1,734, 1,670, 1,604, 1,506, 1,442, 1,251, 1,037 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 3.42 (dd, J = 7.4, 4.7 Hz, 2H), 3.64 (s, 3H), 4.64 (t, J = 7.4 Hz, 1H), 6.00 (s, 2H), 6.47 (s, 1H), 6.79 (d, J = 8.2 Hz, 1H), 7.06 (d, J = 7.8 Hz, 1H), 7.13–7.16 (m, 1H), 7.24–7.28 (m, 1H), 7.43–7.51 (m, 2H), 7.57 (dd, J = 8.2, 1.5 Hz, 1H), 8.2 (br s, 1H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 35.4, 52.6, 56.7, 102.4, 102.5, 108.1, 108.5, 111.3, 120.8, 123.2, 124.7, 125.4, 128.3, 129.8, 131.2, 134.9, 148.5, 152.4, 170.3, 193.1 ppm; HRMS (ESI^+): *m/z* calcd. for $C_{20}H_{18}NO_5$ 352.1185 ($[M+H]^+$), found 352.1217.

Methyl 2-[(4-hydroxyphenyl)methyl]-3-(4-nitrophenyl)-3-oxopropanoate (**5c**, $C_{17}H_{15}NO_6$)
Yield: 96 %; orange oil; IR (ATR): $\bar{\nu}$ = 3,443, 1,737, 1,693, 1,605, 1,527, 1,527, 1,438, 1,347, 1,320, 1,231, 736 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 3.26 (d, J = 7.3 Hz, 2H), 3.64 (s, 3H), 4.57 (t, J = 7.3 Hz, 1H), 4.98 (s, 1H), 6.69 (d, J = 8.4 Hz, 2H), 7.04 (d, J = 8.4 Hz, 2H), 8.02 (d, J = 8.8 Hz, 2H), 8.25 (d, J = 8.8 Hz, 2H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 34.1, 53.1, 56.9, 115.8 (2C), 124.1 (2C), 129.8 (2C), 129.9, 130.3 (2C), 140.9, 150.7, 154.7, 169.3, 193.7 ppm.

Methyl 2-benzyl-3-(4-nitrophenyl)-3-oxopropanoate (**5d**, $C_{17}H_{15}NO_5$)
Yield: 76 %; yellow oil; IR (ATR): $\bar{\nu}$ = 1,741, 1,694, 1,256, 1,346, 1,229, 863, 852 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 3.35 (d, J = 7.4 Hz, 2H), 3.67 (s, 3H), 4.64 (t, J = 7.4 Hz, 1H), 7.16–7.29 (m, 5H), 8.04 (d, J = 8.7 Hz, 2H), 8.26 (d, J = 8.7 Hz, 2H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 34.7, 52.7, 56.2, 123.8 (2C), 126.8, 128.6 (2C), 128.8 (2C), 129.6 (2C), 137.7, 140.6, 150.3, 169.0, 193.5 ppm.

Methyl 2-benzyl-3-oxo-3-phenylpropanoate (**5e**, $C_{17}H_{16}O_3$)
Yield: 78 %; yellow oil; IR (ATR): $\bar{\nu}$ = 3,062, 3,029, 2,953, 1,739, 1,686, 1,597, 1,448, 1,267, 948 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 3.32 (dd, J = 7.4, 2.5 Hz, 2H), 3.58 (s, 3H), 4.67 (t, J = 7.4 Hz, 1H), 7.10–7.22 (m, 5H), 7.35–7.43 (m, 2H), 7.48–7.55 (m, 1H), 7.89–7.98 (m, 2H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 34.9, 52.5, 55.9, 126.7, 128.6 (2C), 128.7 (2C), 128.8 (2C), 128.9 (2C), 133.6, 136.1, 138.4, 169.7, 194.5 ppm.

Methyl 2-[(4-hydroxyphenyl)methyl]-3-oxo-3-(thien-2-yl)-propanoate (**5f**, $C_{15}H_{14}O_4S$)
Yield: 80 %; yellow oil; IR (ATR): $\bar{\nu}$ = 3,410, 1,736, 1,657, 1,519, 1,412, 1,242, 733 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 3.23 (dd, J = 7.2, 2.1 Hz, 2H), 3.63 (s, 3H), 4.42 (t, J = 7.2 Hz, 1H), 5.99 (br s, 1H), 6.68 (d, J = 8.2 Hz, 2H), 6.98–7.12 (m, 3H), 7.64 (d, J = 4.8 Hz, 1H), 7.71 (d, J = 3.8 Hz, 1H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 34.3, 52.9, 57.7, 115.7 (2C), 128.6, 129.9, 130.2 (2C), 133.6, 135.5, 143.4, 154.9, 169.9, 187.6 ppm.

Methyl 2-[(4-hydroxyphenyl)methyl]-3-oxopentanoate (**5g**, $C_{13}H_{16}O$)
Yield: 70 %; colorless oil; IR (ATR): $\bar{\nu}$ = 3,413, 1,728, 1,709, 1,516, 1,438, 1,266, 1,217, 1,171, 838 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 0.97 (t, J = 7.0 Hz, 3H), 2.21–2.62 (m, 2H), 3.07 (d, J = 7.6 Hz, 2H), 3.66 (s, 3H), 3.74 (t, J = 7.6 Hz, 1H), 5.00 (br s, 1H), 6.70 (d, J = 8.2 Hz, 2H), 7.00 (d, J = 8.2 Hz, 2H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 7.7, 33.7, 36.5, 52.7, 60.6, 115.7 (2C), 130.2 (2C), 130.3, 154.6, 170.0, 205.9 ppm.

Methyl 2-benzyl-3-(4-chlorophenyl)-3-oxopropanoate (**5h**, $C_{17}H_{15}ClO_3$)
Yield: 75 %; colorless viscous oil; IR (ATR): $\bar{\nu}$ = 1,738, 1,681, 1,589, 1,274, 1,233, 1,091, 831 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 3.31 (dd, J = 7.4, 1.7 Hz, 2H), 3.63 (s, 3H), 4.59 (t, J = 7.4 Hz, 1H), 7.16–7.24 (m, 5H), 7.38 (d, J = 6.8 Hz, 2H), 7.86 (d, J = 6.8 Hz, 2H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 34.9, 52.8, 56.0, 126.9, 128.7 (2C), 129.0 (2C), 129.2 (2C), 130.2 (2C), 134.6, 138.3, 140.3, 169.6, 193.4 ppm.

*General procedure for the preparation of the pyrazolones **4a–4h** and **6a–6h***

To a stirred solution of the β-ketoester (1.0 mmol) in 3 cm^3 methanol, a catalytic amount of acetic acid (0.1 mmol) was added. The mixture was allowed to stir for 10 min, and hydrazine hydrate (5.0 mmol) or phenyl hydrazine hydrochloride was added, and the reaction was heated to reflux and kept stirring for 12 h. After that, the solvent was evaporated and the crude material was purified using flash column chromatography (CH_2Cl_2:MeOH—90:10 v/v) to yield the corresponding 2,3-dihydro-1*H*-pyrazol-3-ones **4a–4h** and **6a–6h**.

4-Methyl-5-(3,4,5-trimethoxyphenyl)-2,3-dihydro-1H-pyrazol-3-one (**4a**, $C_{13}H_{16}N_2O_4$)
Yield: 65 %; white solid; m.p.: 110–112 °C; IR (ATR): $\bar{\nu}$ = 3,054, 2,926, 2,853, 1,590, 1,508, 1,415, 1,265, 1,127 cm^{-1}; ^1H NMR (250 MHz, MeOH-d_4): δ = 2.07 (s, 3H), 3.80 (s, 3H), 3.88 (s, 6H), 6.82 (s, 2H) ppm; ^{13}C NMR (62.5 MHz, MeOH-d_4): δ = 7.8, 56.9 (2C), 61.3, 98.7, 105.9 (2C), 128.2, 139.5, 144.4, 154.9 (2C), 163.1 ppm; HRMS (ESI^+): *m/z* calcd. for $C_{13}H_{17}N_2O_4$ 265.1188 ($[M+H]^+$), found 265.1177.

5-(4-Methoxyphenyl)-4-methyl-2,3-dihydro-1H-pyrazol-3-one (**4b**, $C_{11}H_{12}N_2O_2$)
Yield: 74 %; yellow solid; m.p.: 178–180 °C; IR (ATR): $\bar{\nu}$ = 3,251, 3,054, 2,964, 2,841, 1,682, 1,610, 1,517, 1,265,

838 cm^{-1}; ^1H NMR (250 MHz, TFA-*d*): $\delta = 2.00$ (s, 3H), 3.84 (s, 3H), 7.02 (d, $J = 8.8$ Hz, 2H), 7.41 (d, $J = 8.8$ Hz, 2H) ppm; ^{13}C NMR (62.5 MHz, TFA-*d*): $\delta = 7.2$, 57.7, 102.3, 117.6 (2C), 122.0, 131.9 (2C), 150.5, 158.4, 163.4 ppm; HRMS (ESI^+): *m/z* calcd. for $C_{11}H_{13}N_2O_2$ 205.0977 ($[M+H]^+$), found 205.1021.

5-(2H-1,3-Benzodioxol-5-yl)-4-methyl-2,3-dihydro-1H-pyrazol-3-one (**4c**, $C_{11}H_{10}N_2O_3$)
Yield: 65 %; white solid; m.p.: 126–128 °C; IR (ATR): $\bar{\nu} = 3{,}224$, 2,981, 2,905, 1,712, 1,610, 1,505, 1,457, 1,236, 1,195, 1,038, 816 cm^{-1}; ^1H NMR (250 MHz, TFA-*d*): $\delta = 2.18$ (s, 3H), 6.07 (s, 2H), 6.90–7.23 (m, 3H) ppm; ^{13}C NMR (62.5 MHz, TFA-*d*): $\delta = 6.7$, 101.9, 103.9, 109.8, 111.3, 121.7, 125.0, 150.1, 150.6, 152.3, 158.0 ppm; HRMS (ESI^+): *m/z* calcd. for $C_{11}H_{11}N_2O_3$ 219.0770 ($[M+H]^+$), found 219.0746.

5-(4-Bromophenyl)-4-methyl-2,3-dihydro-1H-pyrazol-3-one (**4d**, $C_{10}H_{19}BrN_2O$)
Yield: 70 %; white solid; m.p.: 127–129 °C; IR (ATR): $\bar{\nu} = 2{,}926$, 2,711, 1,667, 1,610, 1,443, 1,209, 1,187, 1,187, 1,137, 1,008, 830 cm^{-1}; ^1H NMR (250 MHz, TFA-*d*): $\delta = 2.07$ (s, 3H), 7.35 (d, $J = 7.9$ Hz, 2H), 7.62 (d, $J = 7.9$ Hz, 2H) ppm; ^{13}C NMR (62.5 MHz, TFA-*d*): $\delta = 6.8$, 102.7, 126.8, 128.5, 131.1 (2C), 134.9 (2C), 149.4, 158.2 ppm; HRMS (ESI^+): *m/z* calcd. for $C_{10}H_{10}BrN_2O$ 252.9977 ($[M+H]^+$), found 252.9948.

4-Methyl-5-(4-nitrophenyl)-2,3-dihydro-1H-pyrazol-3-one (**4e**, $C_{10}H_9N_3O_3$)
Yield: 95 %; yellow solid; m.p.: >255.4 °C (dec.); IR (ATR): $\bar{\nu} = 3{,}364$, 1,599, 1,507, 1,350, 1,335, 1,145, 852 cm^{-1}; ^1H NMR (250 MHz, TFA-*d*): $\delta = 2.12$ (s, 3H), 7.76 (d, $J = 8.5$ Hz, 2H), 8.39 (d, $J = 8.5$ Hz, 2H) ppm; ^{13}C NMR (62.5 MHz, TFA-*d*): $\delta = 6.9$, 104.3, 126.8 (2C), 131.6 (2C), 135.1, 147.4, 151.3, 158.5 ppm; HRMS (ESI^+): *m/z* calcd. for $C_{10}H_{10}N_3O_3$ 220.0722 ($[M+H]^+$), found 220.0737.

4-Methyl-5-(4-nitrophenyl)-2-phenyl-2,3-dihydro-1H-pyrazol-3-one (**4f**, $C_{16}H_{13}N_3O_3$)
Yield: 50 %; yellow solid; m.p.: 167–169 °C; IR (ATR): $\bar{\nu} = 3{,}014$, 1,621, 1,558, 1,512, 1,457, 1,340, 1,275, 1,105, 859 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6): $\delta = 2.17$ (s, 3H), 7.25–7.37 (m, 1H), 7.49 (t, $J = 8.0$ Hz, 2H), 7.81 (d, $J = 8.0$ Hz, 2H), 7.99 (d, $J = 8.8$ Hz, 2H), 8.27 (d, $J = 8.8$ Hz, 2H), 10.99 (br s, 1H) ppm; ^{13}C NMR (62.5 MHz, DMSO-d_6): $\delta = 5.4$, 93.5, 118.6, 120.8 (2C), 123.2, 124.4, 125.9 (2C), 135.6, 137.8, 143.3, 143.4, 147.8 ppm; HRMS (ESI^+): *m/z* calcd. for $C_{16}H_{14}N_3O_3$ 296.1035 ($[M+H]^+$), found 296.1059.

4-Methyl-5-phenyl-2,3-dihydro-1H-pyrazol-3-one (**4g**, $C_{10}H_{10}N_2O$)
Yield: 78 %; white solid; m.p.: 203–205 °C; IR (ATR): $\bar{\nu} = 3{,}270$, 2,923, 2,854, 1,730, 1,598, 1,507, 1,159, 766 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6): $\delta = 1.99$ (s, 3H), 3.35 (br s, 1H), 7.28–7.38 (m, 1H), 7.40–7.49 (m, 2H), 7.50–7.58 (m, 2H) ppm; ^{13}C NMR (62.5 MHz, DMSO-d_6): $\delta = 7.6$, 95.9, 126.3 (2C), 127.4, 128.7 (2C), 131.1, 139.5, 160.2 ppm; HRMS (ESI^+): *m/z* calcd. for $C_{10}H_{11}N_2O$ 175.0871 ($[M+H]^+$), found 175.0822.

4-Methyl-5-(thien-2-yl)-2,3-dihydro-1H-pyrazol-3-one (**4h**, $C_8H_8N_2OS$)
Yield: 64 %; brown solid; m.p.: >172.5 °C (dec.); IR (ATR): $\bar{\nu} = 3{,}162$, 1,665, 1,513, 1,413, 1,258, 1,132 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6): $\delta = 2.00$ (s, 3H), 7.08–7.17 (m, 1H), 7.28–7.35 (m, 1H), 7.48–7.57 (m, 1H), 10.82 (br s, 1H) ppm; ^{13}C NMR (62.5 MHz, DMSO-d_6): $\delta = 7.6$, 95.8, 124.0, 125.4, 127.7, 133.2, 135.5, 159.3 ppm; HRMS (ESI^+): *m/z* calcd. for $C_8H_9N_2OS$ 181.0436 ($[M+H]^+$), found 181.0438.

4-Benzyl-5-(4-methoxyphenyl)-2,3-dihydro-1H-pyrazol-3-one (**6a**, $C_{17}H_{16}N_2O_2$)
Yield: 69 %; white solid; m.p.: 202–204 °C; IR (ATR): $\bar{\nu} = 3{,}435$, 1,663, 1,618, 1,513, 1,453, 1,293, 1,251, 1,111 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6): $\delta = 3.73$ (s, 3H), 3.81 (s, 2H), 6.96 (d, $J = 8.6$ Hz, 2H), 7.07–7.29 (m, 5H), 7.40 (d, $J = 8.6$ Hz, 2H), 10.94 (br s, 1H) ppm; ^{13}C NMR (62.5 MHz, DMSO-d_6): $\delta = 27.6$, 55.2, 99.0, 114.3 (2C), 123.3, 125.7, 127.9 (2C), 127.9 (2C), 128.3 (2C), 140.2, 141.6, 159.0, 160.8 ppm; HRMS (ESI^+): *m/z* calcd. for $C_{17}H_{17}N_2O_2$ 281.1290 ($[M+H]^+$), found 281.1282.

5-(2H-1,3-Benzodioxol-5-yl)-4-(1H-indol-5-ylmethyl)-2,3-dihydro-1H-pyrazol-3-one (**6b**, $C_{19}H_{15}N_3O_3$)
Yield: 80 %; brown oil; IR (ATR): $\bar{\nu} = 3{,}420$, 2,255, 2,128, 1,662, 1,506, 1,455, 1,293, 1,235, 1,152 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6): $\delta = 3.89$ (s, 2H), 5.89 (s, 2H), 6.33 (s, 1H), 6.91–7.02 (m, 4H), 7.26–7.33 (m, 3H) ppm; ^{13}C NMR (62.5 MHz, DMSO-d_6): $\delta = 27.6$, 100.1, 100.8, 101.2, 106.9, 108.6, 111.2, 118.6, 120.3, 121.7, 125.0, 125.3, 127.9, 131.7, 134.5, 140.1, 146.9, 147.6, 160.7 ppm; HRMS (ESI^+): *m/z* calcd. for $C_{19}H_{16}N_3O_3$ 334.1192 ($[M+H]^+$), found 334.1182.

4-[(4-Hydroxyphenyl)methyl]-5-(4-nitrophenyl)-2,3-dihydro-1H-pyrazol-3-one (**6c**, $C_{16}H_{13}N_3O_4$)
Yield: 73 %; yellow solid; m.p.: >285.4 °C (dec.); IR (ATR): $\bar{\nu} = 3{,}437$, 3,307, 1,599, 1,589, 1,541, 1,514, 1,505, 1,330, 1,209, 857 cm^{-1}; ^1H NMR (250 MHz, TFA-*d*): $\delta = 3.93$ (s, 2H), 6.87 (d, $J = 8.5$ Hz, 2H), 7.06

(d, $J = 8.5$ Hz, 2H), 7.70 (d, $J = 8.8$ Hz, 2H), 8.37 (d, $J = 8.8$ Hz, 2H) ppm; ^{13}C NMR (62.5 MHz, TFA-*d*): $\delta = 27.7$, 107.6, 118.0 (2C), 126.5 (2C), 131.3 (2C), 131.8 (2C), 133.5, 134.8, 147.9, 151.3, 154.6, 158.6 ppm; HRMS (ESI$^+$): *m/z* calcd. for $C_{16}H_{14}N_3O_4$ 312.0984 ([M+H]$^+$), found 312.0991.

4-Benzyl-5-(4-nitrophenyl)-2,3-dihydro-1H-pyrazol-3-one (**6d**, $C_{16}H_{13}N_3O_3$)
Yield: 75 %; yellow solid; m.p.: >199.4 °C (dec.); IR (ATR): $\bar{\nu} = 3{,}394$, 1,600, 1,513, 1,347, 1,210, 1,110, 855 cm^{-1}; ^{1}H NMR (250 MHz, TFA-*d*): $\delta = 3.86$ (s, 2H), 6.94–7.21 (m, 5H), 7.58 (d, $J = 7.7$ Hz, 2H), 8.23 (d, $J = 7.7$ Hz, 2H) ppm; ^{13}C NMR (62.5 MHz, TFA-*d*): $\delta = 28.6$, 107.6, 126.6 (2C), 129.3, 129.8 (2C), 131.1 (2C), 131.9 (2C), 134.8, 139.4, 148.0, 151.3, 158.7 ppm; HRMS (ESI$^+$): *m/z* calcd. for $C_{16}H_{14}N_3O_3$ 296.1035 ([M+H]$^+$), found 296.0969.

4-Benzyl-5-phenyl-2,3-dihydro-1H-pyrazol-3-one (**6e**, $C_{16}H_{14}N_2O$)
Yield: 76 %; white solid; m.p.: >183.5 °C (dec.); IR (ATR): $\bar{\nu} = 3{,}060$, 3,027, 2,924, 1,589, 1,513, 1,451, 1,211, 1,114, 808 cm^{-1}; ^{1}H NMR (250 MHz, TFA-*d*): $\delta = 3.81$ (s, 2H), 6.92–7.19 (m, 5H), 7.24–7.46 (m, 5H) ppm; ^{13}C NMR (62.5 MHz, DMSO-d_6): $\delta = 27.6$, 99.5, 125.6, 126.4 (2C), 127.8, 127.8 (2C), 128.2 (2C), 128.8 (2C), 130.8, 140.2, 141.4, 160.6 ppm; HRMS (ESI$^+$): *m/z* calcd. for $C_{16}H_{15}N_2O$ 251.1184 ([M+H]$^+$), found 251.1159.

4-[(4-Hydroxyphenyl)methyl]-5-(thien-2-yl)-2,3-dihydro-1H-pyrazol-3-one (**6f**, $C_{14}H_{12}N_2O_2S$)
Yield: 60 %; yellow solid; m.p.: >240.4 °C (dec.); IR (ATR): $\bar{\nu} = 3{,}100$, 2,915, 2,848, 1,616, 1,591, 1,511, 1,436, 1,240, 711 cm^{-1}; ^{1}H NMR (250 MHz, TFA-*d*): $\delta = 4.03$ (s, 2H), 6.90 (d, $J = 8.4$ Hz, 2H), 7.09–7.21 (m, 3H), 7.46 (d, $J = 4.0$ Hz, 1H), 7.61 (d, $J = 4.0$ Hz, 1H) ppm; ^{13}C NMR (62.5 MHz, TFA-*d*): $\delta = 28.0$, 105.5, 117.9 (2C), 127.5, 130.3, 131.4 (2C), 132.1, 132.4, 133.6, 145.1, 154.4, 158.5 ppm; HRMS (ESI$^+$): *m/z* calcd. for $C_{14}H_{13}N_2O_2S$ 273.0698 ([M+H]$^+$), found 273.0694.

5-Ethyl-4-[(4-hydroxyphenyl)methyl]-2,3-dihydro-1H-pyrazol-3-one (**6g**, $C_{12}H_{14}N_2O_2$)
Yield: 92 %; colorless viscous oil; IR (ATR): $\bar{\nu} = 1{,}700$, 1,587, 1,514, 1,431, 1,382, 1,250, 827 cm^{-1}; ^{1}H NMR (250 MHz, TFA-*d*): $\delta = 1.16$ (td, $J = 7.6$, 1.2 Hz, 3H), 2.64 (q, $J = 7.6$ Hz, 2H), 3.74 (s, 2H), 6.86 (d, $J = 7.8$ Hz, 2H), 7.07 (d, $J = 7.8$ Hz, 2H) ppm; ^{13}C NMR (62.5 MHz, TFA-*d*): $\delta = 12.7$, 20.6, 27.7, 105.8, 118.2 (2C), 131.7 (2C), 134.1, 154.6, 154.7, 157.8 ppm; HRMS (ESI$^+$): *m/z* calcd. for $C_{12}H_{15}N_2O_2$ 219.1134 ([M+H]$^+$), found 219.1163.

4-Benzyl-5-(4-chlorophenyl)-2,3-dihydro-1H-pyrazol-3-one (**6h**, $C_{16}H_{13}ClN_2O$)
Yield: 70 %; white solid; m.p.: 188–190 °C; IR (ATR): $\bar{\nu} = 1{,}702$, 1,613, 1,516, 1,229, 1,090, 836 cm^{-1}; ^{1}H NMR (250 MHz, MeOH-d_4): $\delta = 3.83$ (s, 2H), 7.08–7.24 (m, 5H), 7.30–7.37 (m, 4H) ppm; ^{13}C NMR (62.5 MHz, MeOH-d_4): $\delta = 28.7$, 102.4, 127.0, 129.2 (2C), 129.5 (2C), 129.9 (2C), 130.0 (2C), 130.8, 135.5, 142.5, 143.4, 162.7 ppm; HRMS (ESI$^+$): *m/z* calcd. for $C_{16}H_{14}ClN_2O$ 285.0795 ([M+H]$^+$), found 285.0787.

Acknowledgments The authors thank the São Paulo Research Foundation (FAPESP) and the Brazilian Council for Scientific and Technological Development (CNPq) for financial support. We also thank FAPESP for a post-doctoral fellowship to RCB (process FAPESP 2012/24783-1) and CNPq for fellowships to MTRJr and LAZ.

References

1. Baumanan M, Baxendale IR, Ley SV, Nikbin N (2011) Beilstein J Org Chem 7:442
2. Varvounis G, Fiamegos Y, Pilidis G (2008) Adv Heterocycl Chem 95:27
3. Burja B, Kocevar M, Slovenko P (2009) Tetrahedron 65:8690
4. Sonia G, Thachil KK, Parameswaran MK, Kochupappy RT (2014) Med Chem Res 23:1320
5. Ragab FA-F, Abdel-Gawad NM, Georgey HH, Said MF (2013) Chem Pharm Bull 61:834
6. Chen T, Benmohamed R, Kim J, Smith K, Amante D, Morimoto RI, Kirsch DR, Ferrante RJ, Silverman R (2012) J Med Chem 55:515
7. Markovic V, Eric S, Stanojkovic T, Gligorijevic N, Arandelovic S, Todorovoc N, Trifunovic S, Manojlovic N, Jelic R, Jaksovic MD (2011) Bioorg Med Chem Lett 21:4416
8. Girault P, Hagemann G (1972) Bactericidal and fungicidal compositions containing 3-amino-4,4-dichloro-2-pyrazolin-5-one. DE Patent 2,140,719, Feb 17, 1972; (1972) Chem Abstr 76:144856
9. Porter HD, Weissberger A (1945) Aminopyrazolones. U.S. Patent 2,376,380, May 22, 1945; (1945) Chem Abstr 39:29994
10. Singh J, Tripathy R (2001) Preparation of heterocyclylpyrazolinones as protein kinase inihibitors. WO Patent 2001032653, May 10, 2001; (2001) Chem Abstr 134:340503
11. Shamsuzzaman, Mashrai A, Ahmad A, Dar AM, Khanam HK, Danishuddin M, Khan AU (2014) Med Chem Res 23:348
12. Wang XH, Wang XK, Liang YJ, Shi Z, Zhang JY, Chen LM, Fu LW (2010) Chin J Cancer 29:980
13. Burja B, Cimbora-Zovko T, Tomic S, Jelusic T, Kocevar M, Polanc S, Osmak M (2010) Bioorg Med Chem 18:2375
14. Chiba P, Holzer W, Landau M, Bechmann G, Lorenz K, Plagens B, Hilzler M, Richter E, Ecker G (1998) J Med Chem 41:4001
15. Vijesh AM, Isloor AM, Isloor S, Shivananda KN, Shyma PC, Arulmoli T (2011) Pharm Chem 3:454
16. Aly HM, Saleh NM, Elhady HA (2011) Eur J Med Chem 46:4566
17. Padmavathi V, Subbaiah DRCV, Mahesh K, Lakshmi TR (2007) Chem Pharm Bull 12:1704
18. Gunasekaran P, Perumal S, Yogeeswari P, Sriram D (2011) Eur J Med Chem 46:4530
19. Nikolova I, Tencheva J, Voinikov J, Petkova V, Benbasat N, Danchev N (2012) Biotechnol Biotechnol Equip 26:3329

20. Kimata A, Nakagawa H, Ohyama R, Fukuuchi T, Ohta S, Suzuki T, Miyata N (2007) J Med Chem 50:5053
21. Uramaru N, Shigematsu H, Toda A, Eyanagi R, Kitamura S, Ohta S (2010) J Med Chem 53:8727
22. Huang H, Yu Y, Gao Z, Zhang Y, Li C, Xu X, Jin H, Yan W, Ma R, Zhu J, Shen X, Jiang H, Chen L, Li JJ (2012) J Med Chem 55:7037
23. Mahajan SS, Scian M, Sripathy S, Posakony J, Lao U, Loe TK, Leko V, Thalhofer A, Schuler AD, Bedalov A, Simon JA (2014) J Med Chem 57:3283
24. Resmi SR, Babu G, Biju CR (2013) J Drug Discov Ther 1:50
25. Pal S, Mareddy J, Devi NS (2008) J Braz Chem Soc 19:1207
26. Mariappan G, Saha BP, Sutharson L, Haldar A (2010) Indian J Chem B 49:1671
27. Cucciolito ME, D'Amora A, Vitagliano A (2010) Organometallics 29:5878
28. Zhang Z, Liu Y, Gong M, Zhao X, Zhang Y, Wang J (2010) Angew Chem Int Ed 49:1139
29. Sato K, Isoda M, Ohata S, Morita S, Tarui A, Omote M, Kumadaki I, Ando A (2012) Adv Synth Catal 354:510
30. Ragavan RV, Kumar KM, Vijayakumar V, Sarveswari S, Ramaiah S, Anbarasu A, Karthikeyan S, Giridharan P, Kumari NS (2013) Org Med Chem Lett 3:1
31. Li W, Wang J, Hu X, Shen K, Wang W, Chu Y, Lin L, Liu X, Feng X (2010) J Am Chem Soc 132:8532
32. Akita H, Chen CY, Nagumo S (1994) Tetrahedron Asymmetry 5:1207
33. Srensen US, Falch E, Stensbl TB, Jaroszewski JW, Madsen U, Krogsgaard-Larsen P (2001) Arch Pharm 334:62
34. Kadota H, Fukazawa N, Nagase H, Maruyama K, Nakao T, Asada N, Hachimaki T, Kibayashi K, Uta H, Morikawa M (2001) Preparation of quinolone derivatives as nuclear proliferator-activated receptor antagonists. WO 2001070698 A1, Sep 27, 2001; (2001) Chem Abstr 135:272892
35. Bouziane A, Carboni B, Bruneau C, Carreaux F, Renaud J-L (2008) Tetrahedron 64:11745
36. Matsumoto K, Suzuki M, Iwasaki T, Miyoshi M (1972) J Org Chem 37:2731
37. Katritzky AR, Wang Z, Wang M, Wilkerson CR, Hall CD, Akhmedov NG (2004) J Org Chem 69:6617
38. Coelho F, Almeida WP, Veronese D, Mateus CR, Lopes ECS, Rossi RC, Silveira GPC, Pavam CH (2002) Tetrahedron 58:7437
39. Ferreira BRV, Pirovani RV, Souza-Filho LG, Coelho F (2009) Tetrahedron 65:7712 (for reviews on the Morita–Baylis–Hillman reaction, see)
40. Shi M, Wang F-J, Zhao M-X, Wei Y (2011) The chemistry of the Morita–Baylis–Hillman Reaction. RSC Publishing, Cambrigde
41. Liu TY, Xie M, Chen YC (2012) Chem Soc Rev 41:4101
42. Basavaiah D, Veeraraghavaiah G (2012) Chem Soc Rev 41:68
43. Basavaiah D, Reddy BS, Badsara SS (2010) Chem Rev 110:5447
44. Singh V, Sanjay B (2008) Tetrahedron 64:4511
45. Almeida WP, Coelho F (2000) Quim Nova 23:98
46. Santos MS, Coelho F (2012) RSC Adv 2:3237
47. Beug GT, Meesala R, Mordi MN, Mansor SM (2014) Synth Commun 44:1291
48. Takacz D, Nagy I, Bombicz P, Egyed O, Jemnitz K, Riedl Z, Molnar J, Maral L, Hajos G (2012) Bioorg Med Chem 20:4258
49. Tan MX, Zhang Y (2009) Tetrahedron Lett 50:4912
50. Borghese A, Antoine L, Stephenson G (2002) Tetrahedron Lett 43:8087
51. Ling I, Podanyl B, Hassori T, Solyon S (1995) J Chem Soc Perkin Trans 1:1423
52. Keglevich G, Fekete M, Chuluuanbaatar T, Dobo A, Bocski Z, Töke L (2000) Synth Commun 30:4221
53. Keglevich G, Gaumont A-C, Denis J-M (2001) Heteroatom Chem 12:161
54. Brown HC, Keblys KA (1964) J Am Chem Soc 86:1795
55. Akita H, Chen CY, Nagumo S (1995) J Am Chem Soc 17:2159
56. Bertogg A, Hintermann L, Huber DP, Perseghini M, Sanna M, Togni A (2012) Helv Chim Acta 95:353
57. Li M, Liu C-L, Yang JI-C, Zhang J-BO, Li Z-N, Zhang H, Li Z-M (2010) J Agric Food Chem 58:2664
58. Muraoka T, Hiraiwa E, Abe M, Ueno K (2013) Tetrahedron Lett 54:4309
59. Vita MV, Wasen J (2013) Org Lett 15:3246
60. Matsumo K, Suzu M, Iwasa T, Muneji M (1972) J Org Chem 87:2731
61. Evans DE, Carter PH, Carreira EM, Charette EB, Prunet JA, Lautens MJ (1999) J Am Chem Soc 121:7540
62. Temba ESC, de Oliveira IMF, Donnici CL (2003) Quim Nova 26:112
63. Kim H, Yun J (2010) Adv Synth Cat 352:1881
64. Pirovani RV, Ferreira BRV, Coelho F (2009) Synlett 2009:2333–2337
65. Basavaiah D, Muthukumaran K (1998) Tetrahedron 54:4943
66. Sundar N, Bhat SV (1998) Synth Commun 28:2311
67. Perkin WH, Bellenot G (1886) J Chem Soc 49:447
68. Yoshida Y, Matsumoto N, Hamasaki R, Tanabe Y (1999) Tetrahedron Lett 40:4227
69. Yoshida Y, Hayashi R, Sumihara H, Tanabe Y (1997) Tetrahedron Lett 38:8727
70. Tanabe Y, Mukaiyama T (1984) Chem Lett (11):1867–1870
71. Kumareswaran V, Yashwant D (1998) Synth Commun 28:2291
72. Gomez V, Perez-Medrano A, Muchowski JM (1994) J Org Chem 59:1219
73. Taber DF, Sheth RB, Joshi PV (2005) J Org Chem 70:2851
74. Kim JM, Kim KH, Kim TH, Kim JN (2008) Tetrahedron Lett 49:3248
75. Han HO, Kim SH, Kim KH, Hur GC, Yim HJ, Chung HK, Woo SH, Koo KD, Lee CS, Koh JS, Kim GT (2007) Bioorg Med Chem Lett 17:937
76. Katrizky AR, Barczynski P, Ostercamp DL (1987) J Chem Soc Perkin Trans 2:969
77. Whitehouse CM, Dreyer CN, Yamashita M, Fenn JB (1985) Anal Chem 57:675
78. Fenn JB, Mann M, Meng CK, Wong SF, Whitehouse CM (1989) Science 246:64
79. Cole RB (1997) Electrospray Ionization Mass Spectrometry. Wiley, New York
80. Yunker LPE, Stoddard RL, McIndoe JS (2014) J Mass Spectrom 49:1
81. Coelho F, Eberlin MN (2011) Angew Chem Int Ed 50:5261
82. Santos VG, Regiani T, Dias FFG, Ramão W, Jara LP, Klitzke CF, Coelho F, Eberlin MN (2011) Anal Chem 83:1375
83. dos Santos MR, Gomes AF, Gozzo FC, Suarez PAZ, Neto BAD (2012) ChemSusChem 5:2383
84. Metzger JO, Santos LS (2008) Rapid Commun Mass Spectrom 22:898
85. Santos LS, Pavam CH, Almeida WP, Coelho F, Eberlin MN (2004) Angew Chem Int Ed 43:4330
86. Amarante GW, Milagre HMS, Vaz BG, Ferreira BVR, Eberlin MN, Coelho F (2009) J Org Chem 74:3031
87. Amarante GW, Benassi M, Milagre HMS, Braga AAC, Maseras F, Eberlin MN, Coelho F (2009) Chem Eur J 15:12460
88. Amarante GW, Benassi M, Pascoal RN, Eberlin MN, Coelho F (2010) Tetrahedron 66:4370
89. Dess DB, Martin JC (1983) J Org Chem 48:4155