A simple synthesis of 4-aroyl-5-methyl-1*H*-imidazol-2(3*H*)-one derivatives (Enoxymone analogues) from aryl methyl ketones *via* enaminones

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Dedicated to Professor Rosa M. Claramunt on the occasion of her 65th anniversary

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Abstract

Aryl methyl ketones **1a-e** gave with *N*,*N*-dimethylacetamide dimethylacetal (DMADMA) (*E*)-1-aryl-3-(dimethylamino)-but-2-en-1-ones **2a-e**. Substitution of the *N*,*N*-(dimethylamino) group in the reaction with ammonium acetate afforded the corresponding (*Z*)-3-amino-1-aryl-but-2-en-1-ones **3a-e**. In the reaction of **3a-e** with diethyl azodicarboxylate intermediates **4a-e** were formed, which were, in most cases without isolation, cyclized into ethyl (5-aroyl-4-methyl-2-oxo-2,3-dihydro-1*H*-imidazol-1-yl)carbamates **5a-e**. Hydrolysis of the ester group, followed by the decarboxylation and deamination of intermediates **6a-c,e** produced 4-aroyl-5-methyl-1*H*-imidazol-2(3*H*)-ones **7a-c,e**.

Keywords: Aryl methyl ketones, enaminoines, 3-amino-1-arylbut-2-en-1-ones, (2-oxo-2,3-dihydro-1*H*-imidazol-1-yl)carbamates, 1*H*-imidazol-2(3*H*)-ones.

Introduction

Nitrogen containing heterocycles[1] are of special interest in organic synthetic chemistry, since they occur in wide variety of natural products. The imidazolone motif appears in many natural products,[2] which possess interesting biological activities.[3] They are inhibitors of V-RAF murine sarcoma viral oncogene homologue B1.[4] They are antagonists of many receptors including the neurokinin-1 receptor[5] and the dopamine receptor.[6] They were applied as intermediates in the synthesis of many natural products, such as biotin,[7] slagenins,[8] axinohydantoins,[9] oroidin-derived alkaloids,[10] aplysinopsins,[11] Lancetta-derived alkaloid carcaridine A,[12] and others. Due to their importance many methods have been developed for construction of imidazole ring.[13,14] Recently,

there has been a great progress in copper-catalyzed *N*-arylation.[15,16] 4-Aroyl-1,3-dihydro-2*H*-imidazol-2-ones, have been prepared by acylation of the appropriate 2*H*-imidazol-2-ones and evaluated as a new class of cardiotonic agents.[17] The most important compound in this series is 5-methyl-4-[4-(methylthio)benzoyl]-1*H*-imidazol-2(3*H*)-one (Perfan or Enoximone) (Figure 1), a selective phosphodiesterase inhibitor, has a significant inotropic and vasodilating properties that have proved useful in the postoperative management of infants and children having cardiac surgery.[18,19] Effects of phosphodiesterase (III/IV)-inhibitors and cytokines on mechanical properties of neutrophilic granulocytes in neonates and adults have been studied.[20]

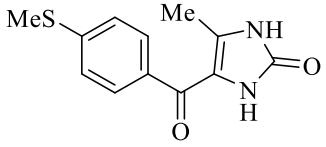


Figure 1. 5-Methyl-4-[4-(methylthio)benzoyl]-1*H*-imidazol-2(3*H*)-one (Perfan or Enoximone).

The wide applicability of 3-(dimethylamino)-propenoates and related enaminones as versatile reagents in heterocyclic synthesis,[21] parallel solution-phase and solid-phase synthesis of fused pyrimidinones,[22] and stereochemical synthesis,[23] including natural products and their analogues, e.g. the aplysinopsins,[24] meridianines,[25] dipodazines,[26] and triprostatines[27] has been demonstrated. Recently, a simple one-pot synthesis of ethyl 4-benzoyl-2-oxo-3-substituted-2,3-dihydro-1*H*-imidazol-1-yl)carbamates has been described.[28]

In this communication we report a simple synthesis of ethyl (5-aroyl-4-methyl-2-oxo-2,3-dihydro-1*H*-imidazol-1-yl)carbamate followed by hydrolysis of the ester group, decarboxylation and deamination to give 4-aroyl-5-methyl-1*H*-imidazol-2(3*H*)-ones.

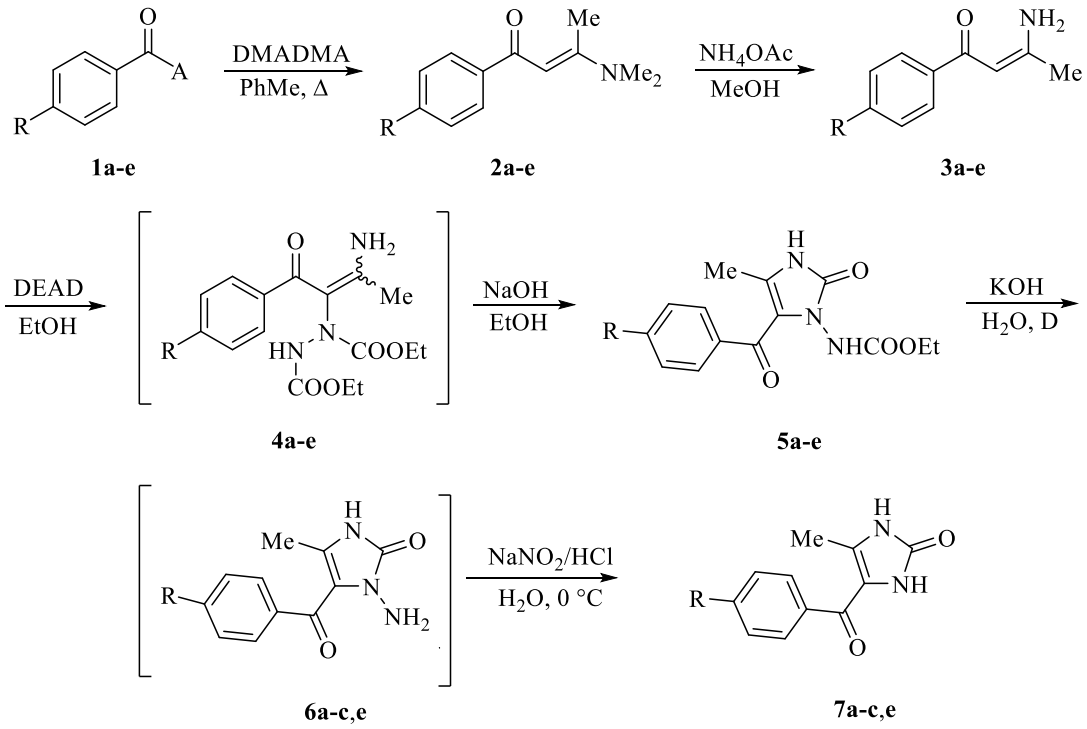
Results and Discussion

In this paper we report the preparation of 5-methyl-4-(aroyl substituted)imidazol-2(1*H*)-ones starting from aryl methyl ketones **1a-e**, which were transformed by treatment with *N*,*N*-dimethyl acetamide dimethylacetal (DMADMA) into (*E*)-3-(dimethylamino)-1-(4-substituted-phenyl)but-2-en-1-ones **2a-e.** These were treated with ammonium acetate to form (*Z*)-3-amino-1-(4-substituted-phenyl)but-2-en-1-ones **3a-e**. By further reaction with diethyl azodicarboxylate (DEAD) intermediates **4a-e** were formed which cyclize after addition of sodium hydroxide under experimental conditions into ethyl [5-aroyl-4-methyl-2-oxo-2,3-dihydro-1*H*-imidazol-1-yl]carbamates **5a-e**. After hydrolysis of the ester group, followed by decarboxylation and deamination, 4-aroyl-5-methyl-1*H*-imidazol-2(3*H*)-ones **7a-c,e** were isolated.

In our first attempt to synthesize 5-methyl-4-[(4-methylthio)benzoyl]-1*H*-imidazol-2(1*H*)-one (**7a**) (Enoximone or Perfan) we treated 1-[(4-methylthio)phenyl]ethanone (**1a**) with

dimethylacetamide dimethylacetal (DMADMA) in dry toluene to afford (*E*)-3(dimethylamino)-[(4-methylthio)phenyl]but-2-en-1-one (**2a**) as an yellow oil in ~5 % yield. By further treatment of this compound with ammonium acetate in MeOH for 18 h at room temperature the corresponding (*Z*)-3-amino-1-[(4-methylthio)phenyl]but-2-en-1-one (**3a**) was obtained practically quantitatively as a yellow solid. In the reaction of **3a** with diethyl azodicarboxylate (DEAD) in EtOH for 2 h at room temperature, without the isolation of the intermediate **4a**, ethyl [4-methyl-5-(4-methylthio)benzoyl]-2-oxo-2,3-dihydro-1*H*-imidazol-1-yl]carbamate (**5a**) was isolated in 68 % yield upon addition of NaOH to **4a**. At the end **5a** was hydrolyzed and decarboxylated by heating at reflux temperature in an aqueous ethanolic KOH solution for 20 h to afford 1-amino-4-methyl--(4-methylthio)benzoyl)-1*H*-imidazol-2(3*H*)-one (**6a**) which was directly deaminated to 5-methyl-4-(4-(methylthio)benzoyl)-1*H*-imidazol-2(3*H*)-one (**7a**) in 93 % overall yield. However, the overall yield starting from **1a** was very low (< 3%).

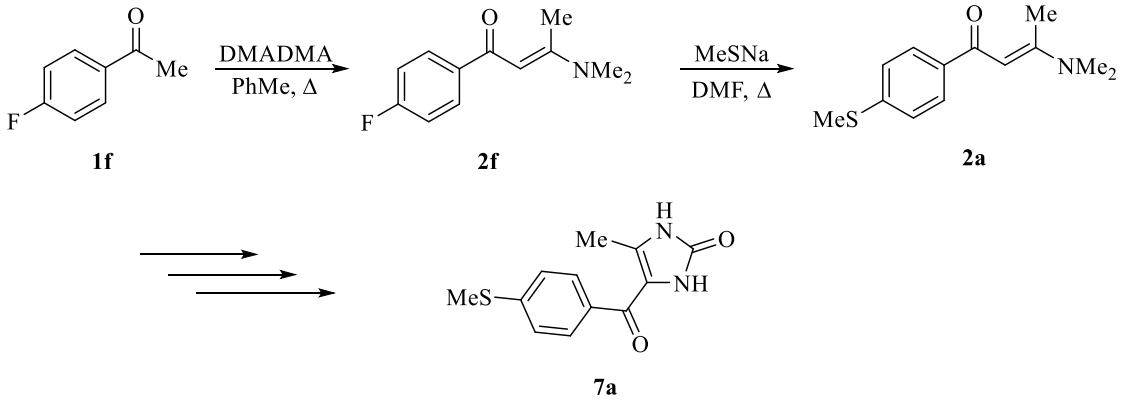
In order to avoid the extremely poor yield in the transformation of **1a** into **2a**, we extended the reaction to a number of aryl ketones **1b-f** and prepared the corresponding analogues of enoximone **7a**. (Scheme 1, Table 1). We found that 1-(4-fluorophenyl)ethanone (**1f**) could be transformed with DMADMA into (*E*)-3-(dimethylamino)-1-1(4-fluorophenyl)but-2-en-1-one (**2f**) in 67 % yield. The substitution of fluorine with MeSNa afforded (*E*)-3-(dimethylamino)-1-1-(4-(methylthio)phenyl)but-2-en-1-one (**2a**) in 80 % yield. In this way, following the reaction sequence **1f** → **2f** → **2a** → **3a** → **4a** → **5a** → **6a** → **7a**, the overall yield was 32 % (Scheme 2).



Scheme 1.

Table 1. Yields of 4-aroyl-5-methyl-1*H*-imidazol-2(3*H*)-ones (**7**)

Compounds 1-7	R	Yield (%)	Yield (%)
a	SMe	**1**→**7** (5)	**2**→**7**, 48
b	H	**1**→**7** (23)	
c	Cl	**1**→**7** (31)	
d	SO_2Me	/	**1**→**5**, 16
e	Br	**1**→**7** (27)	
f	F	**1**→**2** (67)	



Scheme 2

The structure of (*E*)-1-aryl-3-(dimethylamino)but-2-en-1-ones **2a-e** is supported by X-ray analysis for compound **2d** (Figure 2). The orientation around the double bond in compounds **2** and **3** was determined on the basis of chemical shifts. In compounds **2** the methyl group appear downfield (δ = 2.50-2.67 ppm) in comparison to the chemical shift of methyl group in compounds **3** (δ = 2.05-2.09 ppm). Furthermore, in (*Z*)-3-amino-1-aryl-but-2-en-1-ones (**3**) a large difference in chemical shifts (~5ppm) for both protons attached to the amino group was observed, due to the strong intramolecular hydrogen bond of one proton to carbonyl group (Figure 2).

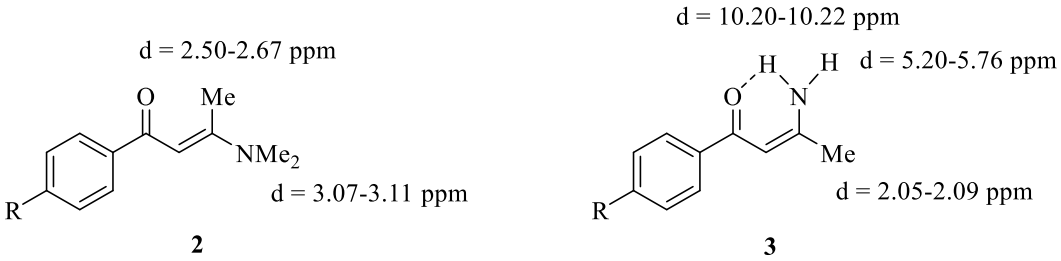


Figure 2. Characteristic ^{1}H chemical shifts for compounds **1** and **2**.

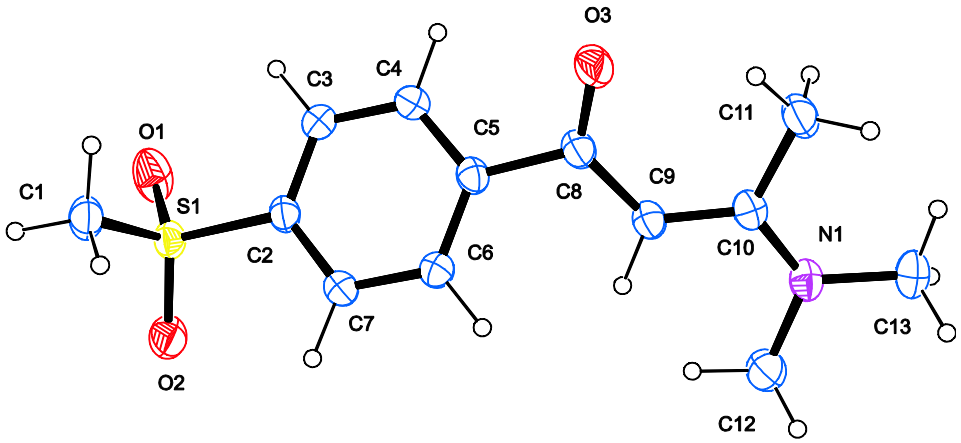


Figure 3. ORTEP plot of (*E*)-3-(dimethylamino)-1-((4-methylsulfonyl)phenyl)but-2-en-one (**2d**) at the 50 % probability level of ellipsoids.

Conclusions

In summary, a new synthetic method for the preparation of 4-aroyl-5-methyl-1*H*-imidazol-2(3*H*)-ones (**7a**-c,**e**) (Enoximone analogues) was developed. The synthesis started with commercially available methyl ketones **1a-f** which were transformed with DMADMA into (*E*)-1-aryl-3-(dimethylamino)-but-2-en-1-ones **2a-e**. Substitution of the *N*,*N*-(dimethylamino) group with NH_4OAc afforded the corresponding (*Z*)-3-amino-1-aryl-but-2-en-1-ones **3a-e**. In the reaction of **3a-e** with diethyl azodicarboxylate intermediates **4a-e** were formed, which were cyclized into ethyl 5-aroyl-4-methyl-2-oxo-2,3-dihydro-1*H*-imidazol-1-yl)carbamates **5a-e**. Hydrolysis of the ester group, followed by the decarboxylation and deamination of 1-amino-5-aroyl-4-methyl-1*H*-imidazol-2(3*H*)-ones **6a-c,e** as intermediates produced 4-aroyl-5-methyl-1*H*-imidazol-2(3*H*)-ones **7a-c,e** (Enoximone analogues).

Experimental Section

General. Melting points were determined on a Kofler micro hot stage and on a SRS OptiMelt MPA100-Automated Melting Point System. NMR spectra were obtained on a Bruker Avance DPX 300 at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C, and a Bruker UltraShield 500 plus at 500 MHz for ^{1}H and 126 MHz for ^{13}C, using DMSO-d_6 and $CDCl_3$ with TMS as the internal standard, as solvents. Mass spectra were recorded on an AutoSpecQ spectrometer and Agilent 6224 Accurate Mass TOF LC/MS**,** IR spectra on a Perkin-Elmer Spectrum BX FTIR spectrophotometer. The microanalyses for C, H, and N were performed on a Perkin-Elmer CHN Analyser 2400 II. Column chromatography (CC) was performed on silica gel (Fluka, Silica gel 60, particle size: 0.035-0.070 mm).

(*E*)-3-(Dimethylamino)-1-(4-(methylthio)phenyl)but-2-en-1-one (2a)

Method A. 1-(4-(Methylthio)phenyl)ethanone (**1a**) (1.52 g, 9.1 mmol) was dissolved in dry PhMe (200 mL) and DMADMA (1.3 mL, 9 mmol) was added. Reaction mixture was refluxed for 48 h. Volatile components were evaporated and the product isolated by column chromatography (EtOAc/petroleum ether). Yield: 110 mg (5.1 %), yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.50 (3H, s, C*H*$_3$); 2.66 (3H, s, SC*H*$_3$); 3.07 (6H, s, N*Me*$_2$); 5.65 (1H, s, C*H*); 7.22-7.25 (2H, m, Ph); 7.79-7.81 (2H, m, Ph). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 15.4, 16.6, 40.2, 92.3, 125.3, 127.8, 139.5, 141.5, 163.8, 187.3. EI-HRMS: *m/z* = 236.1105 (MH^+); $C_{13}H_{18}NOS$ calculated: m/z = 236.1104 (MH^+); ν_{max} (KBr) 3279, 3143, 1580, 1548, 1522, 1485, 1433, 1400, 1367, 1323, 1290, 1271, 1217, 1184, 1108, 1092, 1010, 951, 846 cm^{-1}

Method B. (*E*)-3-(dimethylamino)-1-(4-fluorophenyl)but-2-en-1-one (**2f**) (2 mmol, 412 mg) was dissolved in dry DMF (3 mL) and MeSNa (2 mmol, 140 mg) was added. Reaction mixture was stirred for 24 h at 70 °C. Volatile components were evaporated and the product isolated by column chromatography (EtOAC/petroleum ether = 1:1). Yield: 376 mg (80 %). ^{1}H NMR is in agreement with ^{1}H NMR spectra of the product prepared by the method A.

(*E*)-3-(Dimethylamino)-1-(4-(methylsulfonyl)phenyl)but-2-en-1-one (2d)

1-(4-(Methylsulfonyl)phenyl)ethanone (**1d**) (1.98 g, 10 mmol) was dissolved in dry PhMe (20 mL) and DMADMA (2.19 mL, 15 mmol) was added to reaction mixture. Reaction mixture was refluxed for 3 h. Upon cooling the product precipitated from reaction mixture and was filtered of. Recrystallization from EtOAc. Yield: 1.69 g (63 %), yellow solid, mp 168.1-170.0 ˚C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.67 (3H, s, C*H*$_3$); 3.12 (3H, s, C*H*$_3$); 3.11 (6H, s, N*Me*$_2$); 5.60 (1H, s, C*H*); 7.92-8.00 (4H, m, Ph). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 16.7, 40.4, 44.5, 92.3, 127.2, 128.1, 141.3, 148.2, 165.4, 185.8. ($C_{13}H_{17}NO_3S$ calculated: C, 58.40; H, 6.41; N, 5.24. found C, 58.41; H, 6.58; N, 5.20); EI-HRMS: *m/z* = 268.1003 (MH^+); $C_{13}H_{18}NO_3S$ calculated: m/z = 268.1007 (MH^+); ν_{max} (KBr) 3011, 2997, 2917, 1608, 1538, 1477, 1434, 1385, 1353, 1306, 1290, 1223, 1179, 1153, 1082, 1026, 973, 918, 863, 851 cm^{-1}.

(*E*)-1-(4-Bromophenyl)-3-(dimethylamino)but-2-en-1-one (2e)[29]

1-(4-Bromophenyl)ethanone (**1e**) (4.00 g, 20 mmol) was dissolved in dry PhMe (50 mL) and DMADMA (3.8 mL, 26 mmol) was added. The reaction mixture was refluxed for 3 h and chilled. When petroleum ether was added the product precipitated from the reaction mixture and was recrystallized from EtOAc. Yield: 2.81 g (53 %), yellow solid, mp 118.8-120.4 ˚C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.65 (3H, s, C*H*$_3$); 3.08 (6H, s, N*Me*$_2$); 5.60 (1H, s, C*H*); 7.48-7.53 (2H, m, Ph); 7.70-7.74 (2H, m, Ph). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 16.8, 40.4, 92.4, 124.9, 129.1, 131.4, 142.1, 164.6, 187.0.

(*E*)-3-(Dimethylamino)-1-(4-fluorophenyl)but-2-en-1-one (2f)[29]

1-(4-Fluorophenyl)ethanone (**1f**) (6.06 mL, 50 mmol) was dissolved in dry PhMe (100 mL) and DMADMA (11.00 mL, 75 mmol) was added to reaction mixture. Reractiom mixture was

refluxed for 48 h volatile components were evaporated and the product was isolated by column chromatography (EtOAC/petroleum ether = 1:1). Yield: 6.93 g (67 %), yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.65 (3H, s, C*H*$_3$); 3.08 (6H, s, N*Me*$_2$); 5.62 (1H, s, C*H*); 7.03-7.07 (2H, m, Ph); 7.84-7.88 (2H, m, Ph).

(*Z*)-3-Amino-1-(4-(methylthio)phenyl)but-2-en-1-one (3a)

(*E*)-3-(Dimethylamino)-1-(4-(methylthio)phenyl)but-2-en-1-one (**2a**) (108 mg, 0.46 mmol) was dissolved in MeOH (3 mL) NH_4OAc (308 mg, 4 mmol) was added and the reaction mixture stirred for 18 h at room temperature. Volatile components were evaporated and the product isolated by column chromatography (EtOAc/petroleum ether = 1:1). Recrystallization from MeOH. Yield: 95 mg (99 %), yellow solid, mp 154.0-156.2 ˚C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.05 (3H, s, C*H*$_3$); 2.51 (3H, s, SC*H*$_3$); 5.20 (1H, br s, N*H* from NH_2); 5.71 (1H, s, C*H*); 7.24-7.26 (2H, m, Ph); 7.80-7.82 (2H, m, Ph); 10.20 (1H, br s, N*H* from NH_2). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 15.3, 23.1, 92.1, 125.4, 127.7, 136.7, 142.5, 162.8, 188.7. ($C_{11}H_{13}NOS$ calculated: C, 63.74; H, 6.23; N, 6.76. found C, 63.53; H, 6.27; N, 6.70); EI-HRMS: *m/z* = 208.0790 (MH^+); $C_{11}H_{14}NOS$ calculated: m/z = 208.00791 (MH^+); ν_{max} (KBr) 3280, 3140, 1600, 1583, 1559, 157, 1477, 1443, 1396, 1370, 1314, 1288, 273, 1171, 1119, 1104, 1069, 1007, 845 cm^{-1}.

(*Z*)-3-Amino-1-(4-(methylsulfonylphenyl)but-2-en-1-one (3d)

(*E*)-3-(dimethylamino)-1-(4-(methylsulfonylphenyl)but-2-en-1-one (**2d**) (1.5 g, 5.65 mmol) was dissolved in MeOH (30 mL) NH_4OAc was added (4.35 g, 50 mmol) and reaction mixture stirred for 14 h at room temperature. Volatile components were evaporated and the product was isolated by column chromatography (EtOAc). Recrystallization from EtOAc/petroleum ether. Yield: 1.33 g (99 %), yellow solid, mp 150.2-151.3 ˚C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.09 (3H, s, C*H*$_3$); 3.08 (3H, s, C*H*$_3$); 5.71 (1H, s, C*H*); 5.76 (1H, br s, N*H* from NH_2); 7.95-8.04 (4H, m, Ph); 10.32 (1H, br s, N*H* from NH_2). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 23.2, 44.8, 92.8, 127.7, 128.3, 142.2, 145.5, 165.3, 187.2. ($C_{11}H_{13}NO_3S$ calculated: C, 55.21; H, 5.48; N, 5.85. found C, 55.18; H, 5.33; N, 5.79); EI-HRMS: *m/z* = 240.0699 (MH^+); $C_{11}H_{14}NO_3S$ calculated: m/z = 240.0694 (MH^+); ν_{max} (KBr) 3282, 3142, 1617, 1560, 1531, 1398, 1319, 1307, 1288, 1214, 1178, 1151, 1106, 1014, 962, 846 cm^{-1}.

(*Z*)-3-Amino-1-(4-bromophenyl)but-2-en-1-one (3e)

(*Z*)-1-(4-bromophenyl)-3-(dimethylamino)but-2-en-1-one (**2e**) (2.81 g, 10.5 mmol) was dissolved in MeOH (50 mL) NH_4OAc was added (7.7 g, 100 mmol) and the reaction mixture was stirred for 2 h at room temperature. Volatile components were evaporated and the product was isolated by column chromatography (EtOAc/petroleum ether = 1:1). Recrystallization from EtOAc/petroleum ether. Yield: 2.47 g (99 %), yellow solid, mp 129.6-131.2 ˚C (mp^{30} = 126-128 ˚C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.06 (3H, s, C*H*$_3$); 5.27 (1H, br s, N*H* from NH_2); 5.67 (1H, s, C*H*); 7.51-7.55 (2H, m, Ph); 7.72-7.76 (2H, m, Ph); 10.22 (1H, br s, N*H* from NH_2). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 23.1, 92.2, 125.7, 129.0, 131.6, 139.2, 163.6, 188.3. ($C_{10}H_{10}NOBr$

calculated: C, 50.02; H, 4.20; N, 5.83. found C, 50.00; H, 4.10; N, 5.82); EI-HRMS: *m/z* = 240.0019 (MH^+); $C_{11}H_{11}NOBr$ calculated: m/z = 240.0019 (MH^+); ν_{max} (KBr) 3280, 3140, 1600, 1583, 1559, 157, 1477, 1443, 1396, 1370, 1314, 1288, 273, 1171, 1119, 1104, 1069, 1007, 845 cm^{-1}.

Diethyl 1-(3-amino-1-(4-(methylsulfonylphenyl)-1-oxobut-2-en-2-yl)hydrazine-1,2-dicarboxylate (4d)

(*Z*)-3-amino-1-(4-(methylsulfonylphenyl)but-2-en-1-one (**3d**) (570 mg, 2.38 mmol) was dissolved in MeCN (10 mL) DEAD was added (408 μL, 2.6 mmol) and reaction mixture stirred for 12 h at room temperature Volatile components were evaporated and the product was isolated by column chromatography (EtOAc/petroleum ether = 1:1). Yield: 450 mg (46 %), yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.17-1.27 (6H, m 2xC*H*$_3$); 2.39 (3H, s, C*H*$_3$); 3.06 (3H, s, C*H*$_3$); 4.02-4.27 (4H, m, 2xC*H*$_2$); 5.66 (1H, br s, N*H*); 5.72-5.88 (1H, m, N*H*); 7.49-7.54 (1H, m, Ph); 7.57-7.62 (1H, m, Ph); 7.94-8.00 (2H, m, Ph); 10.42-10.59 (1H, m, N*H*). EI-HRMS: *m/z* = 414.1329 (MH^+); $C_{17}H_{24}N_3O_7S$ calculated: m/z = 414.1329 (MH^+); ν_{max} (NaCl) 3382, 2982, 2919, 2357, 1716, 1610, 1478, 1393, 1375, 1341, 1284, 1236, 1155, 1135, 1069, 1088, 958, 908, 841 cm^{-1}.

Diethyl 1-(3-amino-1-(4-bromophenyl)-1-oxobut-2-en-2-yl)hydrazine-1,2-dicarboxylate (4e)

(*Z*)-3-amino-1-(4-bromophenyl)but-2-en-1-one (**3e**) (670 mg, 2.80 mmol) was dissolved in MeCN (10 mL) DEAD was added (486 μL, 3.1 mmol) and the reaction mixture was stirred 14 h at room temperature. Volatile components were evaporated and the product was isolated by column chromatography (EtOAc/petroleum ether = 1:1). Yield: 1.00 mg (87 %), yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.18-1.26 (6H, m, 2xC*H*$_3$); 2.33-2.40 (3H, s, C*H*$_3$); 4.05-4.30 (4H, m, 2xC*H*$_2$); 5.53 (1H, br s, N*H*); 5.81-5.86 (1H, m, N*H*); 7.17-7.21 (1H, m, Ph); 7.26-7.63 (1H, m, Ph); 7.48-7.53 (2H, m, Ph); 10.35-10.56 (1H, m, N*H*). EI-HRMS: *m/z* = 412.0505 ($M\text{-}H^-$); $C_{16}H_{19}N_3O_5Br$ calculated: m/z = 412.0514 ($M\text{-}H^-$); ν_{max} (NaCl) 3354, 2981, 2925, 2358, 1713, 1608, 1584, 1480, 1374, 1320, 1286, 1228, 1140, 1093, 1070, 1012, 861, 837 cm^{-1}.

Ethyl [4-methyl-5-(4-(methylthiobenzoyl)-2-oxo-2,3-dihydro-1*H*-imidazol-1-yl]carbamate (5a)

(*Z*)-3-amino-1-(4-(methylthiophenyl)but-2-en-1-one (**3a**) (93 g, 0.45 mmol) was dissolved in (2 mL) DEAD (80 μL, 0.5 mmol) was added and reaction mixture stirred for 2 h at room temperature. Intermediate diethyl 1-(3-amino-1-(4-(methylthio)phenyl)-1-oxobut-2-en-2-yl)hydrazine-1,2-dicarboxylate (**4a**) was used directly in the cyclisation step without purification. NaOH (60 mg, 1.5 mmol) was added to the reaction mixture and it was stirred for 48 h at room temperature. Volatile components were evaporated and the product isolated by column chromatography ($CHCl_3$/MeOH = 15:1). Yield: 103 mg (68 %), white solid, mp 234.3-237.4 ˚C. ^{1}H NMR (DMSO-*d*$_6$, 500 MHz): δ 1.15 (3H, t, *J* = 7.1 Hz, C*H*$_3$); 1.85 (3H, s, C*H*$_3$); 2.53 (3H, s, SC*H*$_3$); 4.02 (2H, s, J = 7.1 Hz, C*H*$_2$); 7.33-7.35 (2H, m, Ph); 7.56-7.58 (2H, m, Ph); 9.85 (1H, s,

N*H*); 11.12 (1H, br s, N*H*). ^{13}C NMR (DMSO-d_6, 126 MHz): δ 12.2, 14.0, 14.4, 61.0, 119.7, 124.8, 128.8, 129.3, 134.9, 144.4, 151.8, 155.4, 182.5. EI-HRMS: *m/z* = 336.1008 (MH^+); $C_{15}H_{18}N_3O_4S$ calculated: m/z = 336.1013 (MH^+); ν_{max} (KBr) 3185, 2991, 1740, 1723, 1686, 1625, 1585, 1542, 1431, 1368, 1350, 1272, 1243, 1201, 1180, 1111, 1086, 1064, 1019, 978, 957, 914, 864, 829 cm^{-1}.

Ethyl [5-(4-chlorobenzoyl)-4-methyl-2-oxo-2,3-dihydro-1*H*-imidazol-1-yl]carbamate (5c)

(Z)-3-amino-1-(4-chlorophenyl)but-2-en-1-one[30] (**3c**) (3.74 g, 19.2 mmol) was dissolved in EtOH (50 mL) DEAD (3.57 mL, 22 mmol) was added and the reaction mixture was stirred for 4 h at room temperature. Intermediate diethyl 1-(3-amino-1-(4-chlorophenyl)-1-oxobut-2-en-2-yl)hydrazine-1,2-dicarboxylate (**4c**) was directly used in next step without isolation. To **4c** was added NaOH (1.6 g, 40 mmol) and reaction mixture was stirred for 15 h at room temperature. Product **5c** was isolated by column chromatography ($CHCl_3$/MeOH = 8:1). Yield: 4.73 g (76 %), white solid, mp 238.3-240.0 ˚C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.15 (3H, t, *J* = 7.1 Hz, CH_3); 1.85 (3H, s, CH_3); 4.02 (2H, s, J = 7.1 Hz, CH_2); 7.55-7.59 (2H, m, Ph); 7.61-7.66 (2H, m, Ph); 9.87 (1H, s, N*H*); 11.25 (1H, br s, N*H*). ^{13}C NMR (DMSO-d_6, 126 MHz): δ 12.2, 14.4, 61.0, 119.5, 128.7, 130.3, 130.4, 137.0, 137.7, 151.7, 155.4, 182.2. ($C_{14}H_{14}N_3O_4Cl$ calculated: C, 51.94; H, 4.36; N, 12.98. found C, 51.93; H, 4.14; N, 12.98); EI-HRMS: *m/z* = 324.0748 (MH^+); $C_{14}H_{15}N_3O_4Cl$ calculated: m/z = 324.0746 (MH^+); ν_{max} (KBr) 3193, 3067, 3005, 2982, 1738, 1722, 1687, 1619, 1585, 1536, 1474, 1435, 1412, 1369, 1344, 1279, 1261, 1197, 1177, 1109, 1065, 1011, 980, 956, 914, 870, 833 cm^{-1}.

Ethyl [4-methyl-5-(4-(methylsulfonyl)benzoyl)-2-oxo-2,3-dihydro-1*H*-imidazol-1-yl]carbamate (5d)

Diethyl 1-(3-amino-1-(4-(methylsulfonyl)phenyl)-1-oxobut-2-en-2-yl)hydrazine-1,2-dicarboxylate (**4d**) (450 mg, 1.09 mmol) was dissolved in EtOH (5 mL) and NaOH was added (110 mg, 2.18 mmol). Reaction mixture was stirred for 15 h at room temperature and product isolated by column chromatography ($CHCl_3$/MeOH = 10:1). Yield: 220 mg (55 %), yellow solid, mp 196.5-201.1 ˚C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.14 (3H, t, *J* = 7.0 Hz, CH_3); 1.85 (3H, s, CH_3); 3.28 (3H, s, CH_3); 3.97-4.04 (2H, m, CH_2); 7.81 (2H, d, *J* = 8.0 Hz, Ph); 8.03 (2H, d, *J* = 8.0 Hz, Ph); 9.88 (1H, s, N*H*); 11.36 (1H, br s, N*H*). ^{13}C NMR (DMSO-d_6, 126 MHz): δ 12.4, 14.4, 43.3, 61.1, 119.3, 127.3, 129.1, 131.7, 143.2, 151.6, 155.4, 182.1. ($C_{15}H_{17}N_3O_6$ calculated: C, 49.04; H, 4.66; N, 11.44. found C, 49.08; H, 4.59; N, 11.20); EI-HRMS: *m/z* = 368.0900 (MH^+); $C_{15}H_{18}N_3O_6S$ calculated: m/z = 368.0911 (MH^+); ν_{max} (KBr) 3412, 1742, 1713, 1626, 1430, 1315, 1266, 1198, 1153, 1117, 1089, 1064, 1013, 967, 907, 870, 768, 756, 694 cm^{-1}.

Ethyl [5-(4-bromobenzoyl)-4-methyl-2-oxo-2,3-dihydro-1*H*-imidazol-1-yl]carbamate (5e)

Diethyl 1-(3-amino-1-(4-bromophenyl)-1-oxobut-2-en-2-yl)hydrazine-1,2-dicarboxylate (**4e**) (1.00 g, 2.44 mmol) was dissolved in EtOH (10 mL) and NaOH was added (260 mg, 6.5 mmol). Reaction mixture was stirred for 14 h at room temperature and product isolated by column

chromatography ($CHCl_3$/MeOH = 10:1). Yield: 610 mg (68 %), white solid, mp 247.7-249.9 ˚C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.14 (3H, t, J = 7.1 Hz, CH_3); 1.84 (3H, s, CH_3); 4.01 (2H, q, J = 7.1 Hz, CH_2); 7.54 (2H, d, J = 8.4 Hz, Ph); 7.70 (2H, d, J = 8.4 Hz, Ph); 9.85 (1H, s, N*H*); 11.24 (1H, br s, N*H*). ^{13}C NMR (DMSO-d_6, 126 MHz): δ 12.3, 14.4, 61.0, 119.4, 126.0, 130.4, 130.5, 131.7, 138.0, 151.6, 155.4, 182.3. ($C_{14}H_{14}N_3O_4Br$ calculated: C, 45.67; H, 3.83; N, 11.41. found C, 45.91; H, 3.61; N, 11.26); EI-HRMS: *m/z* = 368.0236 (MH^+); $C_{14}H_{15}N_3O_4Br$ calculated: m/z = 368.0240 (MH^+); ν_{max} (KBr) 3414, 3240, 1744, 1692, 1637, 1584, 1540, 1418, 1283, 1196, 1179, 1068, 1010, 981, 914, 869 cm^{-1}.

5-Methyl-4-(4-(methylthio)benzoyl)-1*H*-imidazol-2(3*H*)-one or Enoxymone (7a)

Ethyl (4-methyl-5-(4-(methylthio)benzoyl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)carbamate (**5a**) (95 mg, 0.28 mmol) was dissolved in EtOH (5 mL) KOH was added (220 mg, 3.4 mmol) and the reaction mixture was reflxed for 20 h. Volatile components were evaporated the solid residue dissolved in H_2O (1 mL) and concentrated solution of $HCl_{(aq)}$ (3 mL) was added. Reaction mixture was than chilled to 0 °C and 2 M $NaNO_{2(aq)}$ (5 mL) was slowly added during 20 min. When all $NaNO_{2(aq)}$ was added the reaction mixture was stirred further for 20 min at room temperature. White solid precipitated which was filtered and washed with Et_2O (3x5 mL). Yield: 65 mg (93 %), white solid, mp 251.0-254.3 ˚C (mp[17] 255-258 ˚C). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.89 (3H, s, CH_3); 2.53 (3H, s, SCH_3); 7.32-7.34 (2H, m, Ph); 7.55-7.57 (2H, m, Ph); 10.27 (1H, br s, N*H*); 10.85 (1H, br s, N*H*). ^{13}C NMR (DMSO-d_6, 126 MHz): δ 12.2, 14.0, 119.0, 124.8, 128.9, 131.5, 135.1, 143.3, 152.8, 182.8. EI-HRMS: *m/z* = 249.0690 (MH^+); $C_{12}H_{13}N_2O_2S$ calculated: m/z = 249.0692 (MH^+); ν_{max} (KBr) 3156, 6023, 2917, 2854, 1744, 1694, 1610, 1588, 1547, 1488, 1465, 1434, 1372, 1328, 1368, 1201, 1180, 1114, 1087, 1067, 1026, 994, 971, 952, 935, 865, 813 cm^{-1}.

4-Benzoyl-5-methyl-1*H*-imidazol-2(3*H*)-one (7b)

(*E*)-3-(dimethylamino)-1-phenylbut-2-en-1-one[29] (**2b**) (3.78 g, 20 mmol) was disolved in MeOH (50 mL) NH_4OAc was added (15.4 g, 200 mmol) and the reaction mixture was stirred for 3 h at room temperature. Volatile components were evaporated and the product, (*Z*)-3-amino-1-phenylbut-2-en-1-one,[30] was isolated by column chromatography (EtOAc/petroleum ether = 1:1) and used directly in the next step. EtOH (50 mL) and DEAD was added (2.98 mL, 19.0 mmol) and the reaction mixture was stirred 14 h at room temperature when NaOH (1.90 g, 47.5 mmol) was added. The reaction mixture was stirred further for 24 h. Precipitated product was used directly in the next step. Ethyl (5-benzoyl-4-methyl-2-oxo-2,3-dihydro-1*H*-imidazol-1-yl)carbamate (**5b**) (662 mg, 2.3 mmol) was dissolved in the mixture of H_2O/THF = 1:1 (20 mL) and KOH was added to solution (560 mg, 10 mmol). The reaction mixture was refluxed for 24 h, volatile components were evaporated and intermediate 1-amino-5-benzoyl-4-methyl-1H-imidazol-2(3*H*)-one (**6b**) was isolated by column chromatography ($CHCl_3$/MeOH = 7:1). Intermediate **6a** was suspended in H_2O (10 mL) and $HCl_{(aq)}$ (2 mL) was added to a suspension. Reaction mixture was chilled to 0 °C and 1.5 M solution of $NaNO_{2(aq)}$ (8 mL) was added during

30 minutes. Reaction mixture was than stirred for 2 h at room temperature. Volatile components were evaporated and the product was isolated using Soxhlet's extraction (EtOAc). Yield: 353 mg (76 %), yellow solid, mp 243-246 ˚C (mp[17] 253-255 ˚C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.81 (3H, s, CH_3); 7.45-7.52 (2H, m, Ph); 7.54-7.61 (3H, m, Ph); 10.27 (1H, br s, N*H*); 10.84 (1H, br s, N*H*).

4-(4-Chlorobenzoyl)-5-methyl-1*H*-imidazol-2(3*H*)-one (7c)

Ethyl (5-(4-chlorobenzoyl)-4-methyl-2-oxo-2,3-dihydro-1H-imidazol-1-yl)carbamate (**5c**) (1.62 g, 5 mmol) was dissolved in EtOH (20 mL) KOH was added (3.00 g, 53.5 mmol) and the reaction mixture was refluxed for 15 h. Volatile components were evaporated, solid residue dissolved in H_2O (5 mL) and concentrated $HCl_{(aq)}$ (3 mL) was added. Reaction mixture was than chilled to 0 °C and 6 M $NaNO_{2(aq)}$ (5 mL) was slowly added during 20 min. When all $NaNO_{2(aq)}$ was added the reaction mixture was stirred further for 20 min at room temperature. White solid precipitated which was filtered and washed with Et_2O (3x5 mL). Recrystallization from EtOH. Yield: 944 mg (80 %), white solid, mp 284.3-286.9 ˚C (mp[17] 291-293 ˚C). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.86 (3H, s, CH_3); 7.55 (2H, d, J = 8.5 Hz, Ph); 7.63 (2H, d, J = 8.5 Hz, Ph); 10.34 (1H, br s, N*H*); 10.94 (1H, br s, N*H*). ^{13}C NMR (DMSO-d_6, 126 MHz): δ 12.1, 118.9, 128.6, 130.0, 132.7, 136.2, 137.9, 152.7, 182.2. ($C_{11}H_9N_2O_2Cl$ calculated: C, 55.83; H, 3.83; N, 11.84. found C, 55.63; H, 3.62; N, 11.70); EI-HRMS: *m/z* = 237.0430 (MH^+); $C_{11}H_{10}N_2O_2Cl$ calculated: m/z = 237.0425 (MH^+); ν_{max} (KBr) 2967, 1661, 1614, 1592, 1488, 1437, 1437, 1394, 1373, 1316, 1267, 1182, 1127, 1086, 1013, 949, 936, 836 cm^{-1}.

4-(4-Bromobenzoyl)-5-methyl-1*H*-imidazol-2(3*H*)-one (7e)

Ethyl (5-(4-bromobenzoyl)-4-methyl-2-oxo-2,3-dihydro-1*H*-imidazol-1-yl)carbamate (**5e**) (421.5 mg, 1.5 mmol) was dissolver in EtOH (5 mL) KOH was added (1.00 g, 17.85 mmol) and reaction mixture refluxed for 12 h. Volatile components were evaporated the solid residue dissolved in H_2O (5 mL) and concentrated solution of $HCl_{(aq)}$ (2 mL) was added. Reaction mixture was than chilled to 0 °C and 6 M $NaNO_{2(aq)}$ (5 mL) was slowly added during 20 min. When all $NaNO_{2(aq)}$ was added the reaction mixture was stirred further for 20 min at room temperature. White solid precipitated which was filtered and washed with Et_2O (3x5 mL). Recrystallization from H_2O. Yield: 279 mg (87 %), white solid, mp 246.7-249.9 ˚C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.86 (3H, s, CH_3); 7.54 (2H, d, J = 8.4 Hz, Ph); 7.69 (2H, d, J = 8.4 Hz, Ph); 10.30 (1H, br s, N*H*); 10.91 (1H, br s, N*H*). ^{13}C NMR (DMSO-d_6, 75.5 MHz): δ 12.1, 118.8, 125.0, 130.1, 131.4, 132.6, 138.2, 152.7, 182.3. ($C_{11}H_9N_2O_2Brx1/4H_2O$ calculated: C, 46.26; H, 3.35; N, 9.81. found C, 4.32; H, 3.06; N, 9.75); EI-HRMS: *m/z* = 280.9916 (MH^+); $C_{11}H_{10}N_2O_2Br$ calculated: m/z = 280.9920 (MH^+); ν_{max} (KBr) 3413, 1702, 1617, 1465, 1438, 1393, 1329, 1269, 1170, 1124, 1067, 1044, 1011, 936, 836 cm^{-1}.

X-ray structure analysis for compound 2d

The reflection data were collected on a Nonius Kappa CCD diffractometer using monochromated Mo Ka radiation at room temperature by using Nonius Collect software.[32] Data reduction and integration were performed with the software package DENZO-SMN.[33] The coordinates of all of the nonhydrogen atoms were found *via* direct methods using the SIR97 structure solution program.[34] A full-matrix least-squares refinement on F^2 magnitudes with anisotropic displacement parameters for all non-hydrogen atoms using SHELXL-97 was employed.[35] All H atoms were initially located in difference Fourier maps and subsequently treated as riding atoms in geometrically idealized positions with bond lengths C−H 0.96 Å for methyl and 0.93 Å for aromatic hydrogens with Uiso(H)=1.5Ueq(C,methyl) and Uiso(H)=1.2Ueq(C,aromatic), respectively. Figures depicting the structures were prepared by ORTEP3.[36] CCDC-939062 contains the supplementary crystallographic data for structure **2d**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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