***In situ* formed *tert*-butyl hypoiodite as an efficient oxidant for rapid, room temperature, metal-free dehydrogenation of Biginelli 3,4-dihydropyrimidin-2(1*H*)-ones under basic conditions**

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Abstract

A mild, highly efficient synthetic method was developed for the dehydrogenation of 3,4-dihydropyrimidin-2(1*H*)-ones employing *in situ* formed *tert*-butyl hypoiodite under basic conditions. The oxidant was prepared by the reaction of molecular iodine and potassium *tert*-butoxide. The reaction was carried out in dry tetrahydrofuran at room temperature and high purity products were isolated in high yields after simple work-up. The reaction times (3-10 min.) indicated the new method is superior in comparison to other literature oxidants employed under classical conditions or microwave promoted reactions. Two plausible mechanisms of dehydrogenation were proposed and the active species *tert*-butyl hypoiodite was characterized by UV/Vis spectroscopy method.

Keywords: Dehydrogenation, 3,4-dihydropyrimidin-2(1*H*)-ones, iodine, *tert*-butyl hypoiodite

Introduction

3,4-Dihydropyrimidin-2(1*H*)-ones (3,4-DHPM) are molecules that represent a diazaheterocyclic system with excellent pharmacological efficiency¹ and as such have become significant synthetic objects in organic and medicinal chemistry.² These compounds are also known as Biginelli compounds, after the Italian chemist Pietro Biginelli, who first reported the useful multicomponent acid-catalyzed cyclocondensation reaction of an aldehyde, a β -ketoester and urea³ some 120 years ago. The variation of all three starting components led to a high molecular diversity of products⁴ that may exhibit properties such as antiviral, antibacterial, antifungal, anticancer, antitubercular and antihypertensive properties, or act as calcium channel blockers.²

The heterocyclic 3,4-DHPM core has an intrinsic reactivity that allows many chemical transformations, such as oxidation (dehydrogenation/aromatization).² This type of transformation

has become one of the most popular reactions of 3,4-dihydropyrimidin-2(1*H*)-ones in the past two decades. Namely, the most accepted metabolic pathway of 3,4-DHPM drugs is *in vivo* oxidative dehydrogenation, which occurs in the liver.⁵ Unfortunately, most developed methods for the conversion of dihydropyrimidinones to their oxidized derivatives by oxidative dehydrogenation are far from *in vivo* physiological conditions.⁶ However, the study of those methods is important to facilitate an understanding of the metabolism of DHPM drugs. On the other hand, research on thermal and photochemical oxidation methods for organic molecules, especially those with pharmaceutical properties, is important to understand their stability and photochemical behavior.^{7,8} Finally, dehydrogenation of 3,4-DHPMs is a good way to obtain new heterocyclic, potentially biologically active molecules that contain the pharmacologically important pyrimidin-2(1*H*)-one scaffold.

The oxidative dehydrogenation of 3,4-DHPMs was found to be more difficult than that of Hantzsch 1,4-dihydropyridine due to their stable structure⁹ and the sensitivity of the methyl group at the C-6 position.^{10,11} Nevertheless, over the past two decades, different reagents and methods have been used, more or less successfully, for this type of reaction. Some are: *tert*-BHP/CuCl₂,¹² CAN/NaHCO₃,¹³ Co(NO₃)₂/K₂S₂O₈,¹¹ *tert*-BHP/PhI(OAc)₂,¹⁴ PCC,¹⁵ sono-thermal oxidation/K₂S₂O₈,¹⁶ O₂/activated carbon,¹⁷ microwave-assisted oxidation,¹⁸ NO⁺BF₄⁻,¹⁹ photocatalytic oxidation/TiO₂,^{20,21} thermal oxidation/K₂S₂O₈,²² UV light induced oxidation/Ar,^{7,8} ultrasound-assisted oxidation/K₂S₂O₈,²³ aerobic oxidative dehydrogenation/NHPI/Co^{II},²⁴ using Ca(OCl)₂ in aqueous media oxidation,⁶ photochemical oxidation using Re(I) complex,²⁵ CAN/HCl,²⁶ microwave-assisted oxidation/I₂,²⁷ light-induced free radical oxidation,²⁸ dehydrogenation with 1,4-bis(triphenylphosphonium)-2-butene peroxodisulfate²⁹ and others.³⁰⁻³³ However, despite best efforts, none of these methods have been found to be ideal with respect to prolonged reaction time, low yield, use of toxic reagents, complicated product isolation, etc. Therefore, there is still a need to seek out new and more efficient 3,4-DHPM dehydrogenation methods.

Results and Discussion

Initial studies were conducted on the simple model 3,4-DHPM **1**, employing different oxidants such as inorganic salts under a number of reaction conditions that are usually effective for the dehydrogenation of Hantzsch 1,4-DHPs, in order to determine the general type of oxidant and the reaction condition convenient for this type of reaction. The following reagents were tested under different reaction conditions: V₂O₅/K₂CO₃ in acetonitrile, Bi(NO₃)₃ x 5H₂O in acetic acid, VOCl₃ in dichloromethane, SeO₂ in acetic acid, MnO₂ in acetic acid, SnCl₄ in acetonitrile, SbCl₅ in toluene, Mn(OEt)₄ in acetic acid, NaClO₂ in acetic acid, NaNO₂ in acetic acid, NaIO₄ in acetic acid, ZrCl₄ in toluene/acetonitrile/acetic acid, KBrO₃ in acetic acid/trifluoroacetic acid, Pb(OAc)₄ in acetic acid, K₂S₂O₈/I₂ in acetic acid, FeCl₃ x 6H₂O in acetonitrile/acetic acid, FeCl₃ in acetonitrile/acetic acid, FeCl₃/Hünig's base in acetonitrile, iron(III) phthalocyanine chloride in

acetic acid and others. Surprisingly, none of these reagents gave a satisfactory result due to low chemoselectivity, low conversion, decomposition of starting material, or no reaction at all. Based on these negative results, we concluded that acid conditions do not support the aromatization of the model 3,4-DHPM **1**.

Further studies were focused on basic reaction conditions and molecular iodine as the oxidant. According to the literature, molecular iodine is used as a selective oxidant for many organic transformations. Previously, we utilized molecular iodine as an effective catalyst in a new method for acetoxylation of the 1,4-benzodiazepine ring and applied it to kilogram-scale production of lorazepam and oxazepam.³⁴ Under normal conditions or under ultrasound irradiation, molecular iodine selectively oxidizes 1,4-DHPs at elevated temperatures,³⁵ while in combination with the urea-hydrogen peroxide adduct (UHP), the same reaction is performed at room temperature.³⁶ In the case of 3,4-DHPMs, the UHP itself and in combination with molecular iodine, under different reaction conditions, did not afford a product with a satisfactory result.

Table 1. Dehydrogenation of 3,4-DHPM **1** with molecular iodine (1.1 equiv) under different reaction conditions at room temperature

Entry	Base ^a	Solvent	t (min.)	Yield (%) ^b
1	<i>tert</i> -BuOK	toluene	15	97
2	<i>tert</i> -BuOK	THF	2	96
3	<i>tert</i> -BuOK	<i>tert</i> -BuOH	10	96
4	NaH	THF	15	95
5	NaOH	MeOH	10	60
6	KOH	MeOH	10	59
7	K ₂ CO ₃	MeOH	10	31
8	EtN(<i>i</i> -Pr) ₂	CH ₂ Cl ₂	120	- ^c
9	<i>tert</i> -BuOK	<i>tert</i> -BuOAc	150	- ^c

^aBase (3 equiv). ^bIsolated yield.

^cLow chemoselectivity and low yield (< 10%).

Surprisingly, the reaction of model compound **1** with a stoichiometric amount of molecular iodine in the presence of a strong base such as potassium *tert*-butoxide, in THF as the solvent, at room temperature, selectively afforded product **2** in several minutes. Encouraged by this result, further studies were focused on finding the best combination of base/solvent for the reaction performed at room temperature. The results presented in Table 1 indicated excellent conversion in short reaction times with the use of potassium *tert*-butoxide (*tert*-BuOK) in toluene (Entry 1), dry tetrahydrofuran (THF, Entry 2) or *tert*-butanol (*tert*-BuOH, Entry 3). Due to the highest reaction speed and isolated yield (2 minutes, 96%), the combination potassium *tert*-butoxide/dry THF was selected for further study. The same reaction, using *tert*-butanol or toluene as a solvent, also gave excellent yields (96% and 97%), though these reactions required a longer reaction time, likely due to the lower solubility of base in these solvents, Table 2.³⁷ Interestingly, by employing sodium hydride (NaH) as a base in THF (Entry 4) as a solvent, a high yield was achieved (95%) in only 15 minutes, though product isolation was challenging due to the presence of mineral oil in sodium hydride. Other bases were inefficient (Table 1, Entries 5-9) and hence not tested further.

Table 2. Solubility of potassium *tert*-butoxide in different solvents

Entry	Solvent	Solubility ^a
1	THF	25 g/100 ml
2	<i>tert</i> -BuOH	18 g/100 ml
3	toluene	2 g/100 ml

^aSolubility at 20 °C.

Further optimization of the reaction was carried out in order to find the optimal amount of oxidant, molecular iodine (Table 3). According to the obtained results, a 1.1 equivalent of I₂ (Table 3, Entry 4) was found to be the optimal amount due to the complete conversion of the reaction, high yield (96%) and short reaction time of just 3 minutes. At lower quantities of iodine (Table 3, Entries 1-3), the conversions were not completed.

In the next step, our aim was to define the optimal amount of base in the reaction. According to the results presented in Table 4, a 2.8 equivalent of base (Entry 6) was optimal, with no loss of reaction speed, conversion and yield. An increased amount of base did not improve the reaction, while lower amounts did not afford a product in satisfactory results (lower yields and higher reaction times).

In order to explore the scope and limitations of this new oxidation method, employing molecular iodine under basic conditions, we tested it on a series of substituted 3,4-DHPMs with a variety of substituents at all positions of the 3,4-DHPM ring. Under optimized reaction conditions with 1.1 equivalent of molecular iodine and 2.8 equivalent of potassium *tert*-butoxide in dry THF at room temperature, dehydrogenation of differently substituted 3,4-DHPMs was carried out.

Table 3. Dehydrogenation of 3,4-DHPM **1** with different amounts of molecular iodine in the presence of potassium *tert*-butoxide (3 equiv)

Entry	I ₂ (equiv)	Yield (%) ^{a,b}
1	0.95	91
2	1	94
3	1.05	95
4	1.1	96
5	2	97
6	3	97

^aIsolated yield.^bReactions were carried out at room temperature, in THF, during 3 minutes.**Table 4.** Dehydrogenation of 3,4-DHPM **1** with molecular iodine (1.1 equiv) in the presence of different amounts of potassium *tert*-butoxide

Entry	<i>tert</i> -BuOK (equiv)	Yield (%) ^{a,b}
1	1	50
2	2	84
3	2.5	93
4	2.6	94
5	2.7	94
6	2.8	96
7	2.9	96
8	3	96

^aIsolated yield.^bReactions were carried out at room temperature, in THF, during 3 minutes.

The results presented in Table 5 show that new method is generally applicable for the oxidation of different 3,4-DHPMs. The main characteristics of the reaction are excellent selectivity, high speed, good to excellent yields and high product purity. The reactions were completed in 3-10 minutes, making this system faster than to other known literature methods for the oxidation of 3,4-DHPMs employing classical reaction conditions. The reaction speed of the presented method is comparable to microwave promoted reactions which, in turn, require high temperatures. Product yields ranged from 68-96%, except for compound **5** (Table 5, Entry 4), due to the presence of the *ortho*-nitro group on the aromatic ring, which gave product at a yield of 55%. Both electron-withdrawing (Table 5, Entries 4-6) and electron-donating substituents (Table 5, Entries 7, 8, 15-17, 24) on the aromatic ring were well tolerated and had no considerable influence on the reaction rate. The oxidation of all sterically constrained derivatives

with an isopropyl group instead of a methyl group at position 6 of the 3,4-DHPM ring conveyed product in slightly higher yields, due to its lower acidity compared to the methyl group.

Table 5. Dehydrogenation of substituted 3,4-DHPMs with molecular iodine (1.1 equiv) in the presence of potassium *tert*-butoxide (2.8 equiv) at room temperature

Entry	3,4-DHPM	Ar	R ¹ ; R ²	Product	T (min.)	Yield (%) ^a	Mp (°C)
1	1	<i>p</i> -FC ₆ H ₄	CH ₃ ; CH(CH ₃) ₂	2	3	96	196-197, (lit. mp not reported ¹²)
2	3	C ₆ H ₅	CH ₃ ; CH ₃	26	5	74	192-194, (195-197) ¹⁵
3	4	<i>p</i> -ClC ₆ H ₄	CH ₃ ; CH ₃	27	5	94	176-177, (lit. mp not reported ¹²)
4	5	<i>o</i> -NO ₂ C ₆ H ₄	CH ₃ ; CH ₃	28	3	55	235-236
5	6	<i>m</i> -NO ₂ C ₆ H ₄	CH ₃ ; CH ₃	29^c	5 ^b	74	201-203
6	7	<i>p</i> -NO ₂ C ₆ H ₄	CH ₃ ; CH ₃	30	3	71	230-231
7	8	<i>p</i> -CH ₃ C ₆ H ₄	CH ₃ ; CH ₃	31	5	72	191-192, (lit. mp not reported ¹²)
8	9	<i>p</i> -CH ₃ OC ₆ H ₄	CH ₃ ; CH ₃	32	5	72	178-180, (180-181) ¹³
9	10	1-naphthyl	CH ₃ ; CH ₃	33^c	10	74	173-174
10	11	C ₆ H ₅	CH ₃ ; CH(CH ₃) ₂	34	5	71	189-191, (lit. mp not reported ¹²)
11	12	<i>o</i> -ClC ₆ H ₄	CH ₃ ; CH(CH ₃) ₂	35	5	78	173-174
12	13	<i>m</i> -ClC ₆ H ₄	CH ₃ ; CH(CH ₃) ₂	36	5	77	190-192
13	14	<i>p</i> -ClC ₆ H ₄	CH ₃ ; CH(CH ₃) ₂	37	5	92	210-211
14	15	<i>o</i> -NO ₂ C ₆ H ₄	CH ₃ ; CH(CH ₃) ₂	38	5	78	238-239
15	16	2,4-(CH ₃) ₂ C ₆ H ₃	CH ₃ ; CH(CH ₃) ₂	39	5	68	215-216
16	17	<i>p</i> -CH ₃ C ₆ H ₄	CH ₃ ; CH(CH ₃) ₂	40	5	70	194-196
17	18	<i>p</i> -CH ₃ OC ₆ H ₄	CH ₃ ; CH(CH ₃) ₂	41	5	91	226-228
18	19	C ₆ H ₅	CH ₂ CH ₃ ; CH ₃	42^c	10	70	130-131, (130-132) ^{7,16,22}
19	20	C ₆ H ₅	CH(CH ₃) ₂ ; CH ₃	43	10	86	191-192
20	21	C ₆ H ₅	CH ₂ CH(CH ₃) ₂ ; CH ₃	44^c	5	78	151-152
21	22	C ₆ H ₅	CH ₂ C ₆ H ₅ ; CH ₃	45^c	5	77	138-140
22	23	2-naphthyl	CH ₂ CH ₃ ; CH ₃	46^c	5	72	83-85
23	24	1-naphthyl	CH ₃ ; CH(CH ₃) ₂	47	5	73	188-190
24	25	<i>o</i> -CH ₃ OC ₆ H ₄	CH ₃ ; CH(CH ₃) ₂	48	5	94	169-171

^aIsolated yield. ^bReaction with *tert*-BuOK (3 equiv). ^cPurification by column chromatography.

The ^1H NMR spectrum of products showed peaks of all protons present in the molecule. However, certain quaternary carbons of dehydrogenated products in the ^{13}C NMR spectrum were missing. This effect is well known in the literature for this type of compound.^{12,13,15,24} Shanmugam et al.¹³ provided the explanation that this phenomenon was caused by the tautomerization of N1-H to N3 in a solution of *N*(1)-alkyl unsubstituted dehydrogenated product. In the case of the ^{13}C NMR spectrum of *N*(1)-alkyl substituted derivatives, which have no tautomerization in solution, all peaks are present.

Figure 1. UV/Vis spectra of molecular iodine in THF and the mixture of potassium *tert*-butoxide and molecular iodine in THF.

In order to determine the reason for the high reaction speed, further studies were performed to clarify the reaction mechanism and determine which oxidation species are formed in the reaction. Even during preliminary studies, a loss of colorization was observed during the mixing of molecular iodine and the base, suggesting the formation of a new, highly reactive species that is capable of oxidizing stable 3,4-DHPMs at room temperature. According to the UV/Vis spectra of the THF solution of molecular iodine, which shows maximum absorbance at 460 nm, and the mixture of potassium *tert*-butoxide and molecular iodine, with maximum absorbance at 370 nm, it was clear that the maximum absorbance is shifted from the visible area to the UV area of the spectrum (Figure 1). This spectral change is due to the formation of *tert*-butyl hypoiodite (*tert*-BuOI) from molecular iodine and the base, according to the equation.

Tert-butyl hypoiodite and other organic hypoiodites have been used in many organic transformations.³⁸ For example, Barton used this species to prepare *N*-iodoamides³⁹ and to decarboxylate carboxylic acids.⁴⁰ Other authors have used it in the preparation of esters from carboxylic acids and alkyl iodides,⁴¹ and in the iodination of aromatics with strong electron donor substituents. The usual literature method for the preparation of *tert*-butyl hypoiodite is the reaction of *tert*-butyl hypochlorite with either molecular iodine or metal iodides, or by the reaction of potassium *tert*-butoxide with molecular iodine. According to Tanner et al.,³⁸ such

obtained species differ due to their high reactivity and low stability. According to the literature, *tert*-butyl hypoiodite obtained by the reaction of potassium *tert*-butoxide and molecular iodine is seldom used in organic synthesis in comparison to reagents prepared by other methods. Moreover, based on Tanner's results,³⁸ *tert*-butyl hypoiodite contained 10% free iodine, and testing was only performed in carbon tetrachloride as the solvent. In our method, *tert*-butyl hypoiodite was prepared in dry THF with excess potassium *tert*-butoxide to allow complete consumption of molecular iodine, which was observed as a rapid color change. Based on this data, *tert*-butyl hypoiodite prepared by our method was unique in comparison to literature data and was characterized by maximum absorption at 370 nm (Figure 1).

Scheme 1. Possible mechanism of 3,4-DHPM dehydrogenation via base catalysed substitution and elimination.

We proposed two plausible mechanisms of 3,4-DHPMs dehydrogenation employing our method. Strong anhydrous basic conditions of reaction facilitates mechanism presented in Scheme 1. In the first step, the deprotonation of N1-H in **I** occurs, rather than the deprotonation of N3-H, due to the presence of conjugated enamino ester moiety. The thus formed N1-anion **II** further reacts with *in situ* formed *tert*-butyl hypoiodite to give an N-iodo derivative **III**. By deprotonation of the C4 hydrogen with the *tert*-butoxy anion, and subsequent elimination of the iodide anion and *tert*-butanol, product **IV** is formed.

Scheme 2. Radical mechanism of 3,4-DHPM dehydrogenation.

Due to the fact that *tert*-butyl hypoiodite as well as other organic hypoiodites easily undergo homolytic cleavage^{42,43} to produce *tert*-butoxy and iodine radicals, radical mechanism was also proposed (Scheme 2). In a first step *tert*-butoxy radical abstracts hydrogen from C4-H position, leading to a radical **V** that is both benzylic and allylic. Addition of an iodine radical may lead to the compound **VI**, with iodine in C4, that upon E1cB elimination reaction leads to the final compound **IV**.

Conclusions

A mild, highly efficient synthetic method was developed for the dehydrogenation of 3,4-dihydropyrimidin-2(1*H*)-ones employing *in situ* formed *tert*-butyl hypoiodite under basic conditions. The reaction times (3-10 min.) show the superiority of the new method compared to other literature oxidants employed under classical conditions or microwave promoted reactions. Two plausible reaction mechanisms were proposed, via N1-iodo derivative obtained by substitution reaction of anion obtained by deprotonation of 3,4-DHPM and radical mechanism initiated by homolytic cleavage of *tert*-butyl hypoiodite.

Experimental Section

General. All IR spectra were recorded on a Perkin-Elmer Spectrum One spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on an AV Bruker (600 MHz) spectrometer, and shifts were given in ppm downfield from TMS as an internal standard. TLC analyses were performed on Merck's (Darmstadt, Germany) DC-alufolien with Kieselgel 60F₂₅₄. Melting points were determined using a Büchi B-540 instrument. UV/Vis analyses were performed with a Varian Cary 100 spectrophotometer (Walnut Creek, CA, SAD). HPLC analyses were performed with a Thermo Separation Products (TSP) instrument equipped with vacuum membrane degasser SCM 1000, quaternary gradient pump P 4000, autosampler AS 3000, scanning detector UV 3000HR, controller SN 4000 and software Chromquest (Ver. 2.51). HPLC MS analysis was performed on HPLC Waters Alliance 2795 with PDA detector Waters 996 (210-350 nm) and MS detector Micromass ZMD 4000 (ESI 3.50 kV). All reagents and solvents were obtained from commercial sources (Sigma Aldrich, Merck) and used without further purification. Dry tetrahydrofuran was prepared by the usual method (using benzophenone and sodium wire) and distilled under a nitrogen atmosphere. Compounds **1** and **3-25** were efficiently prepared by a method developed in our laboratory⁴⁴ employing antimony(III) chloride as a catalyst.

General procedure for the dehydrogenation of 3,4-DHPMs. Potassium *tert*-butoxide (1.60 g, 98%, 0.014 mol, 2.8 equiv) was added at once while stirring to a suspension of the corresponding 3,4-DHPM (5 mmol) in dry tetrahydrofuran (16 mL). The temperature of the reaction mixture was maintained at 20-25 °C (ice + water), and molecular iodine (1.40 g, 5 mmol, 1.1 equiv) was added. The reaction mixture was stirred at 25 °C for the time indicated in Table 5. The progress of reactions was monitored by TLC. After completion of the reaction, dichloromethane (8 mL) and diluted hydrochloric acid (6 mL of 37% HCl + 10 mL of distilled water) were added to the reaction mixtures. A few drops of the saturated sodium thiosulphate solution were added to complete decoloration. The phases were separated and the aqueous phase was additionally extracted with dichloromethane (2x8 mL). The combined organic layers were dried over anhydrous sodium sulphate, filtered and evaporated to dryness. The crude products were crystallized from 96% ethanol. The obtained products were filtered and air dried to a constant weight to obtain the corresponding products. In the case of products that did not crystallize from 96% ethanol (**29**, **33**, **42**, **44**, **45**, **46**), the crude product was purified by column chromatography on SiO₂ using the CH₂Cl₂/MeOH (9:1) system.

Methyl 6-methyl-4-(2-nitrophenyl)-2-oxo-1,2-dihydropyrimidine-5-carboxylate (28). Yellowish solid, yield 55%, 0.80 g. R_f (CH₂Cl₂/MeOH, 9:1) 0.42; IR (KBr) ν_{max} 3001, 2893, 2829, 2736, 1736, 1646, 1600, 1539, 1447, 1429, 1370, 1287, 1208, 1136, 1112 cm⁻¹. ^1H NMR (600 MHz, DMSO): δ_{H} 2.52 (3H, s, CH₃), 3.41 (3H, s, OCH₃), 7.43 (1H, d, J 7.0 Hz, arom.), 7.70 (1H, t, J 8.1 Hz, arom.), 7.82 (1H, t, J 7.5 Hz, arom.), 8.20 (1H, d, J 7.8 Hz, arom.), 12.70 (1H, br s, NH). ^{13}C NMR (600 MHz, DMSO): δ_{C} 13.2 (CH₃), 51.7 (OCH₃), 60.5, 124.1, 129.2,

130.0, 134.1, 146.3, 164.5 (C=O, ester). MS (ES): m/z 290.01 (MH^+). Anal. Calcd. for $C_{13}H_{11}N_3O_5$: C 53.98, H 3.83, N 14.53. Found: C 54.10, H 3.74, N 14.40.

Methyl 6-methyl-4-(3-nitrophenyl)-2-oxo-1,2-dihydropyrimidine-5-carboxylate (29).

Yellowish solid, yield 74%, 1.07 g. R_f ($CH_2Cl_2/MeOH$, 9:1) 0.45; IR (KBr) ν_{max} 2946, 2919, 2849, 2734, 1718, 1661, 1594, 1531, 1448, 1435, 1419, 1353, 1289, 1273, 1212, 1139, 1114 cm^{-1} . 1H NMR (600 MHz, DMSO): δ_H 2.47 (3H, s, CH_3), 3.52 (3H, s, OCH_3), 7.79 (1H, t, J 8.0 Hz, arom.), 7.87-7.91 (1H, m, arom.), 8.27-8.28 (1H, m, arom.), 8.35-8.39 (1H, m, arom.), 12.65 (1H, br s, NH). ^{13}C NMR (600 MHz, DMSO): δ_C 17.0 (CH_3), 52.0 (OCH_3), 122.2, 124.7, 130.0, 133.9, 147.5, 165.8 (C=O, ester). MS (ES): m/z 290.02 (MH^+). Anal. Calcd. for $C_{13}H_{11}N_3O_5$: C 53.98; H 3.83; N 14.53. Found: C 53.80, H 3.75, N 14.60.

Methyl 6-methyl-4-(4-nitrophenyl)-2-oxo-1,2-dihydropyrimidine-5-carboxylate (30).

Pale yellow solid, yield 71%, 1.03 g; R_f ($CH_2Cl_2/MeOH$, 9:1) 0.44; IR (KBr) ν_{max} 3037, 2950, 2903, 2810, 2755, 1716, 1664, 1609, 1597, 1520, 1431, 1348, 1286, 1209, 1132, 1108 cm^{-1} . 1H NMR (600 MHz, DMSO): δ_H 2.46 (3H, s, CH_3), 3.34 (3H, s, OCH_3), 7.69 (2H, d, J 8.7 Hz, arom.), 8.32 (2H, d, J 8.7 Hz, arom.), 12.62 (1H, br s, NH). ^{13}C NMR (600 MHz, DMSO): δ_C 20.9 (CH_3), 52.0 (OCH_3), 60.9, 123.5, 128.9, 148.1, 165.6 (C=O, ester). MS (ES): m/z 290.01 (MH^+). Anal. Calcd. for $C_{13}H_{11}N_3O_5$: C 53.98; H 3.83; N 14.53. Found: C 53.95, H 3.80, N 14.40.

Methyl 6-methyl-4-(1-naphthyl)-2-oxo-1,2-dihydropyrimidine-5-carboxylate (33).

Yellowish solid, yield 74%, 1.10 g. R_f ($CH_2Cl_2/MeOH$, 9:1) 0.46; IR (KBr) ν_{max} 3110, 3046, 2949, 2928, 2855, 1720, 1655, 1599, 1508, 1433, 1421, 1320, 1284, 1256, 1220, 1111 cm^{-1} . 1H NMR (600 MHz, DMSO): δ_H 2.48 (3H, s, CH_3), 3.36 (3H, s, OCH_3), 7.40 (1H, d, J 6.6 Hz, arom.), 7.49-7.61 (3H, m, arom.), 7.76 (1H, d, J 7.7 Hz, arom.), 7.99-8.03 (2H, m, arom.), 12.56 (1H, br s, NH). ^{13}C NMR (600 MHz, DMSO): δ_C 22.0 (CH_3), 51.4 (OCH_3), 124.7, 125.0, 126.1, 126.6, 128.2, 129.7, 132.7, 165.5 (C=O, ester). MS (ES): m/z 295.07 (MH^+). Anal. Calcd. for $C_{17}H_{14}N_2O_3$: C 69.38; H 4.79; N 9.52. Found: C 69.50, H 4.69, N 9.40.

Methyl 6-isopropyl-4-(2-chlorophenyl)-2-oxo-1,2-dihydropyrimidine-5-carboxylate (35).

White solid, yield 78%, 1.19 g; R_f ($CH_2Cl_2/MeOH$, 9:1) 0.50; IR (KBr) ν_{max} 2981, 2928, 2868, 2837, 2748, 1722, 1655, 1597, 1585, 1554, 1471, 1430, 1348, 1318, 1272, 1249, 1130, 1108, 1080, 1047 cm^{-1} . 1H NMR (600 MHz, DMSO): δ_H 1.28 (6H, d, J 6.0 Hz, $CH(CH_3)_2$), 3.28-3.37 (1H, m, $CH(CH_3)_2$), 3.46 (3H, s, OCH_3), 7.43-7.62 (4H, m, arom.), 12.48 (1H, br s, NH). ^{13}C NMR (600 MHz, DMSO): δ_C 18.8 (CH_3), 19.2 (CH_3), 26.9, 52.0 (OCH_3), 96.7, 127.0, 127.8, 128.3, 129.2, 131.7, 141.4, 151.9, 157.3, 165.5 (C=O, ester). MS (ES): m/z 307.03 (MH^+). Anal. Calcd. for $C_{15}H_{15}ClN_2O_3$: C 58.73, H 4.93, N 9.13. Found: C 58.80, H 4.85, N 9.25.

Methyl 6-isopropyl-4-(3-chlorophenyl)-2-oxo-1,2-dihydropyrimidine-5-carboxylate (36).

White solid, yield 77%, 1.18 g; R_f ($CH_2Cl_2/MeOH$, 9:1) 0.60; IR (KBr) ν_{max} 2998, 2979, 2944, 2903, 2883, 2842, 1722, 1653, 1596, 1542, 1444, 1436, 1414, 1383, 1337, 1278, 1263, 1204, 1126 cm^{-1} . 1H NMR (600 MHz, DMSO): δ_H 1.24 (6H, d, J 6.8 Hz, $CH(CH_3)_2$), 3.07-3.16 (1H, m, $CH(CH_3)_2$), 3.55 (3H, s, OCH_3), 7.41 (1H, d, J 7.6 Hz, arom.), 7.50-7.61 (3H, m, arom.), 12.34 (1H, br s, NH). ^{13}C NMR (600 MHz, DMSO): δ_C 20.5 (CH_3), 52.4 (OCH_3), 126.2, 127.5, 130.3,

130.4, 133.2, 166.9 (C=O, ester). MS (ES): m/z 307.04 (MH^+). Anal. Calcd. for $C_{15}H_{15}ClN_2O_3$: C 58.73, H 4.93, N 9.13. Found: C 58.80, H 4.85, N 9.20.

Methyl 6-isopropyl-4-(4-chlorophenyl)-2-oxo-1,2-dihydropyrimidine-5-carboxylate (37). White solid, yield 92%, 1.41 g. R_f ($CH_2Cl_2/MeOH$, 9:1) 0.58; IR (KBr) ν_{max} 2993, 2969, 2944, 2885, 2838, 1719, 1655, 1591, 1570, 1431, 1404, 1387, 1340, 1318, 1279, 1203, 1123, 1108, 1087 cm^{-1} . 1H NMR (600 MHz, DMSO): δ_H 1.23 (6H, d, J 6.8 Hz, $CH(CH_3)_2$), 3.04-3.18 (1H, m, $CH(CH_3)_2$), 3.57 (3H, s, OCH_3), 7.54 (4H, q, J_1 8.6 Hz, J_2 18.6 Hz, arom.), 12.27 (1H, br s, NH). ^{13}C NMR (600 MHz, DMSO): δ_C 20.5 (CH_3), 52.5 (OCH_3), 128.6, 129.5, 135.4, 167.0 (C=O, ester). MS (ES): m/z 306.97 (MH^+). Anal. Calcd. for $C_{15}H_{15}ClN_2O_3$: C 58.73, H 4.93, N 9.13. Found: C 58.75, H 4.85, N 9.25.

Methyl 6-isopropyl-4-(2-nitrophenyl)-2-oxo-1,2-dihydropyrimidine-5-carboxylate (38). Yellowish solid, yield 78%, 1.24 g. R_f ($CH_2Cl_2/MeOH$, 9:1) 0.57; IR (KBr) ν_{max} 3004, 2980, 2919, 2883, 1726, 1654, 1599, 1527, 1429, 1403, 1390, 1351, 1311, 1277, 1259, 1203, 1129 cm^{-1} . 1H NMR (600 MHz, DMSO): δ_H 1.26 (6H, d, J 6.8 Hz, $CH(CH_3)_2$), 3.23-3.35 (1H, m, $CH(CH_3)_2$), 3.41 (3H, s, OCH_3), 7.53 (1H, d, J 7.5 Hz, arom.), 7.76 (1H, t, J 7.8 Hz, arom.), 7.86 (1H, t, J 7.5 Hz, arom.), 8.24 (1H, d, J 7.7 Hz, arom.). ^{13}C NMR (600 MHz, DMSO): δ_C 20.5 (CH_3), 31.5, 52.1 (OCH_3), 124.4, 129.7, 130.8, 134.2, 146.5, 165.3 (C=O, ester). MS (ES): m/z 318.01 (MH^+). Anal. Calcd. for $C_{15}H_{15}N_3O_5$: C 56.78, H 4.76, N 13.24. Found: C 56.85, H 4.85, N 13.35.

Methyl 6-isopropyl-4-(2,4-dimethylphenyl)-2-oxo-1,2-dihydropyrimidine-5-carboxylate (39). White solid, yield 68%, 1.02 g. R_f ($CH_2Cl_2/MeOH$, 9:1) 0.55; IR (KBr) ν_{max} 2971, 2954, 2932, 2872, 2754, 1730, 1651, 1598, 1549, 1439, 1319, 1268, 1200, 1122 cm^{-1} . 1H NMR (600 MHz, DMSO): δ_H 1.20 (6H, d, J 6.7 Hz, $CH(CH_3)_2$), 2.16 (3H, s, CH_3), 2.31 (3H, s, CH_3), 3.05-3.14 (1H, m, $CH(CH_3)_2$), 3.40 (3H, s, OCH_3), 7.02-7.08 (2H, m, arom.), 7.13 (1H, s, arom.), 12.23 (1H, br s, NH). ^{13}C NMR (600 MHz, DMSO): δ_C 19.0 (CH_3), 20.8 (CH_3), 32.6, 52.1 (OCH_3), 126.1, 127.5, 130.8, 135.0, 139.2, 166.3 (C=O, ester). MS (ES): m/z 301.35 (MH^+). Anal. Calcd. for $C_{17}H_{20}N_2O_3$: C 67.98, H 6.71, N 9.33. Found: C 67.80, H 6.80, N 9.45.

Methyl 6-isopropyl-4-(4-methylphenyl)-2-oxo-1,2-dihydropyrimidine-5-carboxylate (40). Yellowish solid, yield 70%, 1.00 g. R_f ($CH_2Cl_2/MeOH$, 9:1) 0.52; IR (KBr) ν_{max} 2972, 2885, 2840, 2747, 1716, 1654, 1597, 1429, 1404, 1388, 1341, 1277, 1205, 1189, 1126, 1075 cm^{-1} . 1H NMR (600 MHz, DMSO): δ_H 1.22 (6H, d, J 6.8 Hz, $CH(CH_3)_2$), 2.37 (3H, s, CH_3), 3.02-3.11 (1H, m, $CH(CH_3)_2$), 3.56 (3H, s, OCH_3), 7.31 (2H, d, J 8.1 Hz, arom.), 7.40 (2H, d, J 8.2 Hz, arom.), 12.20 (1H, br s, NH). ^{13}C NMR (600 MHz, DMSO): δ_C 20.5 (CH_3), 20.9 (CH_3), 31.8, 52.4 (OCH_3), 127.6, 129.1, 140.6, 167.3 (C=O, ester). MS (ES): m/z 287.07 (MH^+). Anal. Calcd. for $C_{16}H_{18}N_2O_3$: C 67.12, H 6.34, N 9.78. Found: C 67.05, H 6.41, N 9.65.

Methyl 6-isopropyl-4-(4-methoxyphenyl)-2-oxo-1,2-dihydropyrimidine-5-carboxylate (41). White solid, yield 91%, 1.37 g. R_f ($CH_2Cl_2/MeOH$, 9:1) 0.56; IR (KBr) ν_{max} 3017, 2977, 2950, 2910, 1717, 1643, 1591, 1516, 1434, 1398, 1387, 1300, 1278, 1257, 1208, 1178, 1124, 1021 cm^{-1} . 1H NMR (600 MHz, DMSO): δ_H 1.23 (6H, d, J 6.8 Hz, $CH(CH_3)_2$), 3.02-3.11 (1H, m, $CH(CH_3)_2$), 3.60 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 7.06 (2H, d, J 8.8 Hz, arom.); 7.49 (2H, d, J

8.7 Hz, arom.), 12.14 (1H, br s, NH). ^{13}C NMR (600 MHz, DMSO): δ_{C} 20.6 (CH_3), 27.7, 52.4 (OCH_3), 55.4 (OCH_3), 114.0, 129.5, 161.3, 167.5 ($\text{C}=\text{O}$, ester). MS (ES): m/z 303.10 (MH^+). Anal. Calcd. for $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_4$: C 63.56, H 6.00, N 9.27. Found: C 63.65, H 6.05, N 9.35.

Isopropyl 6-methyl-4-phenyl-2-oxo-1,2-dihydropyrimidine-5-carboxylate (43). Yellowish solid, yield 86%, 1.17 g. R_f ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 9:1) 0.40; IR (KBr) ν_{max} 2982, 2933, 2898, 2829, 2734, 1723, 1646, 1601, 1457, 1430, 1284, 1209, 1090 cm^{-1} . ^1H NMR (600 MHz, DMSO): δ_{H} 0.92 (6H, d, J 6.2 Hz, $\text{OCH}(\text{CH}_3)_2$), 2.39 (3H, s, CH_3), 4.73-4.86 (1H, m, $\text{OCH}(\text{CH}_3)_2$), 7.45-7.47 (3H, m, arom.), 7.49-7.52 (2H, m, arom.), 12.30 (1H, br s, NH). ^{13}C NMR (600 MHz, DMSO): δ_{C} 20.9 (CH_3), 68.7 (OCH), 127.5, 128.3, 130.1, 166.3 ($\text{C}=\text{O}$, ester). MS (ES): m/z 273.03 (MH^+). Anal. Calcd. for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_3$: C 66.16, H 5.92, N 10.29. Found: C 66.30, H 5.80, N 10.10.

Isobutyl 6-methyl-4-phenyl-2-oxo-1,2-dihydropyrimidine-5-carboxylate (44). Yellowish solid, yield 78%, 1.11 g. R_f ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 9:1) 0.44; IR (KBr) ν_{max} 2960, 2936, 2873, 2741, 1719, 1662, 1645, 1599, 1580, 1553, 1455, 1422, 1377, 1279, 1208, 1137, 1105, 1081 cm^{-1} . ^1H NMR (600 MHz, DMSO): δ_{H} 0.57 (6H, d, J 6.8 Hz, $\text{CH}(\text{CH}_3)_2$), 1.47-1.52 (1H, m, $\text{CH}(\text{CH}_3)_2$), 2.41 (3H, s, CH_3), 3.69 (2H, d, J 6.5 Hz, OCH_2), 7.46-7.48 (5H, m, arom.). ^{13}C NMR (600 MHz, DMSO): δ_{C} 13.2 (CH_3), 18.4 (CH_3), 26.5, 60.8 (OCH_2), 70.9, 127.4, 128.2, 128.3, 130.1, 130.2, 166.1 ($\text{C}=\text{O}$, ester). m/z 287.08 (MH^+). Anal. Calcd. for $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_3$: C 67.12; H 6.34; N 9.78. Found: C 67.20, H 6.45, N 9.60.

Benzyl 6-methyl-4-phenyl-2-oxo-1,2-dihydropyrimidine-5-carboxylate (45). Yellowish solid, yield 77%, 1.22 g; R_f ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 9:1) 0.42; IR (KBr) ν_{max} 3060, 3032, 2925, 2852, 1720, 1655, 1600, 1496, 1454, 1420, 1377, 1276, 1202, 1132, 1098 cm^{-1} . ^1H NMR (600 MHz, DMSO): δ_{H} 2.41 (3H, s, CH_3), 4.99 (2H, s, OCH_2), 7.24-7.24 (1H, m, arom.), 7.26-7.27 (3H, m, arom.), 7.28-7.28 (1H, m, arom.), 7.42-7.43 (1H, m, arom.), 7.45-7.45 (3H, m, arom.), 7.47-7.48 (1H, m, arom.), 12.42 (1H, br s, NH). ^{13}C NMR (600 MHz, DMSO): δ_{C} 25.9 (CH_3), 67.3 (OCH_2), 126.8, 128.0, 128.6, 128.7, 128.8, 130.8, 135.3, 166.3 ($\text{C}=\text{O}$, ester). MS (ES): m/z 321.11 (MH^+). Anal. Calcd. for $\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}_3$: C 71.24; H 5.03; N 8.74. Found: C 71.35, H 5.15, N 8.70.

Ethyl 6-methyl-4-(2-naphthyl)-2-oxo-1,2-dihydropyrimidine-5-carboxylate (46). Yellowish solid, yield 72%, 1.11 g. R_f ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 9:1) 0.49; IR (KBr) ν_{max} 3420, 2981, 2918, 1725, 1638, 1588, 1444, 1424, 1388, 1367, 1286, 1242, 1120, 1097 cm^{-1} . ^1H NMR (600 MHz, DMSO): δ_{H} 2.46 (3H, s, CH_3), 3.33 (3H, s, OCH_2CH_3), 3.95 (2H, q, J 14.2 Hz, OCH_2CH_3), 7.55-7.58 (1H, m, arom.), 7.59-7.62 (2H, m, arom.), 7.98-8.02 (2H, m, arom.), 8.03-8.05 (2H, m, arom.), 12.44 (1H, br s, NH). ^{13}C NMR (600 MHz, DMSO): δ_{C} 13.2 (CH_3), 14.0 (CH_3), 60.8 (OCH_2), 124.8, 126.8, 127.6, 127.7, 128.5, 132.2, 133.4, 166.0 ($\text{C}=\text{O}$, ester). MS (ES): m/z 309.12 (MH^+). Anal. Calcd. for $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_3$: C 70.12; H 5.23; N 9.09. Found: C 69.95, H 5.30, N 9.15.

Methyl 6-isopropyl-4-(1-naphthyl)-2-oxo-1,2-dihydropyrimidine-5-carboxylate (47). Yellowish solid, yield 73%, 1.17 g. R_f ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 9:1) 0.60; IR (KBr) ν_{max} 2987, 2975, 2959, 2932, 2909, 1722, 1651, 1571, 1540, 1433, 1333, 1273, 1255, 1214, 1140, 1114 cm^{-1} . ^1H NMR (600 MHz, DMSO): δ_{H} 1.27 (6H, d, J 6.7 Hz, $\text{CH}(\text{CH}_3)_2$), 3.14 (3H, s, OCH_3), 3.18-3.25 (1H, m, $\text{CH}(\text{CH}_3)_2$), 7.47 (1H, d, J 6.9 Hz, arom.), 7.53-7.60 (3H, m, arom.), 7.72 (1H, d, J 6.9

Hz, arom.), 8.00-8.07 (2H, m, arom.), 12.40 (1H, br s, NH). ^{13}C NMR (600 MHz, DMSO): δ_{C} 21.3 (CH₃), 52.3 (OCH₃), 125.2, 125.5, 126.9, 127.4, 128.8, 130.3, 130.4, 133.3, 166.6 (C=O, ester). MS (ES): m/z 323.12 (MH⁺). Anal. Calcd. for C₁₉H₁₈N₂O₃: C 70.79, H 5.63, N 8.69. Found: C 70.85, H 5.70, N 8.60.

Methyl 6-isopropyl-4-(2-methoxyphenyl)-2-oxo-1,2-dihydropyrimidine-5-carboxylate (48).

White solid, yield 94%, 1.41 g. R_{f} (CH₂Cl₂/MeOH, 9:1) 0.50; IR (KBr) ν_{max} 3075, 2986, 2970, 2948, 1726, 1692, 1646, 1605, 1592, 1572, 1538, 1498, 1459, 1431, 1342, 1318, 1293, 1263, 1124, 1019 cm⁻¹. ^1H NMR (600 MHz, DMSO): δ_{H} 1.22 (6H, d, J 6,8 Hz, CH(CH₃)₂), 3.19-3.33 (1H, m, CH(CH₃)₂), 3.46 (3H, s, OCH₃), 3.74 (3H, s, OCH₃), 7.01-7.10 (2H, m, arom.), 7.30 (1H, d, J 7.5 Hz, arom.), 7.46 (1H, t, J 7.9 Hz, arom.), 11.99 (1H, br s, NH). ^{13}C NMR (600 MHz, DMSO): δ_{C} 21.2 (CH₃), 32.4, 52.0 (OCH₃), 55.9 (OCH₃), 111.6, 120.7, 130.0, 132.1, 156.6, 157.2, 166.5 (C=O, ester). MS (ES): m/z 303.08 (MH⁺). Anal. Calcd. for C₁₆H₁₈N₂O₄: C 63.56, H 6.00, N 9.27. Found: C 63.40, H 6.10, N 9.35.

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References

1. Kappe, C. O. *Acc. Chem. Res.* **2000**, *33*, 879.
<http://dx.doi.org/10.1021/ar000048h>
2. Matache, M.; Dobrota, C.; Bogdan, N. D.; Funeriu, D. P. *Curr. Org. Synth.* **2011**, *8*, 356.
<http://dx.doi.org/10.2174/157017911795529218>
3. Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360.
4. Suresh; Sandhu, J. S. *Arkivoc* **2012**, (i), 66.
<http://dx.doi.org/10.3998/ark.5550190.0013.103>
5. Guengerich, F. P.; Martin, M. V.; Beaune, P. H.; Kremers, P.; Wolf, T.; Waxman, D. J. *J. Biol. Chem.* **1986**, *261*, 5051.
6. Tamaddon, F.; Razmi, Z.; *Synth. Commun.* **2011**, *41*, 485.
<http://dx.doi.org/10.1080/00397911003587523>
7. Memarian H. R.; Farhadi A. *Monatsh. Chem.* **2009**, *140*, 1217.
<http://dx.doi.org/10.1007/s00706-009-0156-0>
8. Memarian, H. R.; Farhadi, A.; Sabzyan, H.; Soleymani, M. *J. Photochem. Photobiol. A Chem.* **2010**, *209*, 95.
<http://dx.doi.org/10.1016/j.jphotochem.2009.10.012>

9. Vanden Eynde, J. J.; Audiart, N.; Canonne, V.; Michel, S.; Van Haverbeke Y.; Kappe, C. O. *Heterocycles* **1997**, *45*, 1967.
<http://dx.doi.org/10.3987/COM-97-7931>
10. Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937.
[http://dx.doi.org/10.1016/S0040-4020\(01\)87971-0](http://dx.doi.org/10.1016/S0040-4020(01)87971-0)
11. Shanmugam, P.; Perumal, P. T. *Tetrahedron* **2007**, *63*, 666.
<http://dx.doi.org/10.1016/J.TET.2006.11.010>
12. Yamamoto, K.; Chen, Y. G.; Buono, F. G. *Org. Lett.* **2005**, *7*, 4673.
<http://dx.doi.org/10.1021/ol051879w>
13. Shanmugam, P.; Perumal, P. T. *Tetrahedron* **2006**, *62*, 9726.
<http://dx.doi.org/10.1016/j.tet.2006.07.063>
14. Karade, N. N.; Gampawar, S. V.; Kondre, J. M.; Tiwari, G. B. *Tetrahedron Lett.* **2008**, *49*, 6698.
<http://dx.doi.org/10.1016/j.tetlet.2008.09.045>
15. Singh, K.; Singh, K. *Aust. J. Chem.* **2008**, *61*, 910.
<http://dx.doi.org/10.1071/CH07432>
16. Memarian, H. R.; Farhadi, A. *Ultrasonics Sonochem.* **2008**, *15*, 1015.
<http://dx.doi.org/10.1016/j.ultsonch.2008.02.014>
17. Kawashita, Y.; Hayashi, M. *Molecules* **2009**, *14*, 3073.
<http://dx.doi.org/10.3390/molecules14083073>
18. Memarian, H. R.; Sabzyan, H.; Farhadi A. *Z. Naturforsch.* **2009**, *64b*, 532.
19. Liang, R. R.; Wu, G. L.; Wu, W. T.; Wu, L. M. *Chin. Chem. Lett.* **2009**, *20*, 1183.
<http://dx.doi.org/10.1016/j.cclet.2009.04.039>
20. Nasr-Esfahani, M.; Montazerzohori, M.; Abdi, K. *Arkivoc* **2009**, (x), 255.
<http://dx.doi.org/10.3998/ark.5550190.0010.a23>
21. Memarian, H. R.; Ranjbar, M. *J. Mol. Catal. Chem.* **2012**, *356*, 46.
<http://dx.doi.org/10.1016/j.molcata.2011.12.026>
22. Memarian, H. R.; Farhadi, A. *J. Iran. Chem. Soc.* **2009**, *6*, 638.
23. Memarian, H. R.; Farhadi, A.; Sabzyan, H. *Ultrasonics Sonochem.* **2010**, *17*, 579.
<http://dx.doi.org/10.1016/j.ultsonch.2009.11.014>
24. Han, B.; Han, R.-F.; Ren, Y.-W.; Duan, X.-Y.; Xu, Y.-C.; Zhang, W. *Tetrahedron* **2011**, *67*, 5615.
<http://dx.doi.org/10.1016/j.tet.2011.05.105>
25. Liu, Q.; Li, Y.-N.; Zhang, H.-H.; Chen, B.; Tung, C.-H.; Wu, L.-Z. *J. Org. Chem.* **2011**, *76*, 1444.
<http://dx.doi.org/10.1021/jo102062u>
26. Karade, H. N.; Acharya, J.; Kaushik, M. P. *Tetrahedron Lett.* **2012**, *53*, 5541.
<http://dx.doi.org/10.1016/j.tetlet.2012.08.017>
27. Kodape M. M.; Aswar A. S.; Gawhale, N. D.; Humne, V. T.; Mir, B. A. *Chin. Chem. Lett.* **2012**, *23*, 1339.

- <http://dx.doi.org/10.1016/j.cclet.2012.10.015>
28. Memarian, H. R.; Hejazi, L.; Farhadi, A. Z. *Naturforsch.* **2012**, 67b, 263.
29. Gorjizadeh, M. *Bull. Korean Chem. Soc.* **2013**, 34, 1751.
<http://dx.doi.org/10.5012/bkcs.2013.34.6.1751>
30. Bhong, B. Y.; Shelke, A. V.; Karade N. N. *Tetrahedron Lett.* **2013**, 54, 739.
<http://dx.doi.org/10.1016/j.tetlet.2012.10.131>
31. Bhong, B. Y.; Thorat, P. B.; Karade N. N. *Tetrahedron Lett.* **2013**, 54, 1862.
<http://dx.doi.org/10.1016/j.tetlet.2013.01.099>
32. Phan, N. H. T.; Sohn J.-H. *Tetrahedron* **2014**, 70, 7929.
<http://dx.doi.org/10.1016/j.tet.2014.08.057>
33. Memarian, H. R.; Ranjbar, M.; Sabzyan, H.; Kiani A. C. R. *Chimie* **2012**, 15, 1001.
<http://dx.doi.org/10.1016/j.crci.2012.09.009>
34. Cepanec, I.; Litvić, M.; Pogorelić, I. *Org. Process Res. Dev.* **2006**, 10, 1192.
<http://dx.doi.org/10.1021/op068009u>
35. Zeynizadeh, B.; Dilmaghani, K. A.; Roozijoy, A. J. *Chin. Chem. Soc.* **2005**, 52, 1001.
<http://dx.doi.org/10.1002/jccs.200500139>
36. Filipan-Litvić M.; Litvić, M.; Vinković, V. *Tetrahedron* **2008**, 64, 5649.
<http://dx.doi.org/10.1016/j.tet.2008.04.040>
37. Potassium *tert*-butoxide (KTB), powder, Rockwood Lithium, Date of Issue: 09/2012,
www.rockwoodlithium.com
38. Tanner, D. D.; Gidley, G. C.; Das, N.; Rowe, J. E.; Potter, A. *J. Am. Chem. Soc.* **1984**, 106, 5261.
<http://dx.doi.org/10.1021/ja00330a038>
39. Barton, D. H. R.; Beckwith, A. L. J.; Goosen, A. J. *J. Chem. Soc.* **1965**, 181.
<http://dx.doi.org/10.1039/JR9650000181>
40. Barton, D. H. R.; Faro, H. P.; Serebryakov, E. P.; Woolsey, N. F. *J. Chem. Soc.* **1965**, 2438.
<http://dx.doi.org/10.1039/JR9650002438>
41. Britten-Kelly M. R.; Goosen, A.; Lovelock, J.; Scheffer, A. *J. Chem. Soc., Perkin Trans I*, **1977**, 945.
<http://dx.doi.org/10.1039/P19770000945>
42. Togo, H. *Advanced Free Radical Reactions for Organic Synthesis*; Elsevier: Amsterdam, 2004; p 172.
43. Zard, S. Z. *Radical Reactions in Organic Synthesis*; Oxford University Press, Inc.: New York, 2003; pp 181-184.
44. Cepanec, I.; Litvić, M.; Filipan-Litvić, M.; Grüngold, I. *Tetrahedron* **2007**, 63, 11822.
<http://dx.doi.org/10.1016/j.tet.2007.09.045>