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ORIGINAL PAPER

A concise route to 4-aminomethylpyrazoles and 4-aminomethylisoxazoles from acetylacetone-derived hexahydropyrimidines under mild conditions

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Acetylacetone was successfully used as a precursor of 4-aminomethylpyrazoles and 4-aminomethylisoxazoles in a two step process at ambient temperature. In the first step, acetylacetone was transformed to the corresponding hexahydropyrimidines (1,3-diazinanes) via two consecutive one-pot Mannich aminomethylations. Hexahydropyrimidines were then treated with hydrazine, phenylhydrazine, and hydroxylamine, respectively, to obtain the corresponding 4-aminomethylpyrazoles and 4-aminomethylisoxazoles in good yields. The hexahydropyrimidine ring decomposed providing the title compounds and a reasonable mechanism has been proposed.

Keywords: 4-aminomethylpyrazoles, 4-aminomethylisoxazoles, hexahydropyrimidines, 1,3-diazinanes, pyrazolone, aminomethylations, geminal diamines

Introduction

Development of the building blocks of biologically active heterocyclic compounds is still an active area in the organic synthesis research. Most notably, pyrazole and isoxazole units are usually associated with potent pharmaceutical agents. Several of these five-membered heterocyclic compounds have been found to possess valuable biological activity against various diseases (Jamwal et al., 2013). It has been reported that derivatives containing these units have interesting properties including anti-inflammatory (Shehata & Glennon, 1987), anticonvulsant (Uno et al., 1979), herbicidal (Jamwal et al., 2013), antibacterial (Gaikwad et al., 2013), anticancer (Nishida et al., 2012), antifungal (Brahmayya et al., 2013), anxiolytic (Wagner et al., 2004), and anti-HIV activities (Sechi et al., 2005). For example, the pyrazole derivative, celecoxib, and the isoxazole derivative, valdecoxib are approved and marketed drugs as selective inhibitors of cyclooxygenase-2 (COX-2), and they are prescribed for the treatment of arthritis and inflammatory diseases (Talley et al., 2000). Muscimol (Frølund et al., 2002), rimonabant (Fong & Heymsfield, 2009), fomepizole (WHO, 2013), oxacillin (Greenwood, 2008), and ibotenic acid (Becker et al., 1999) are also examples of approved drugs in which either the pyrazole or the isoxazole ring system is the key structural feature.

1,3-Dicarbonyl compounds are usually transformed to pyrazoles and isoxazoles through their treatment with hydrazines, arylhydrazines, hydroxylamine, and oximes (Katritzky et al., 1987; Heller & Natarajan, 2006; Gosselin et al., 2006; Nasu et al., 1998). Acetylacetone (ACAC) has been utilized as a precursor of biologically interested pyrazoles and isoxazoles (Bakharev et al., 2009). However, there is a lack of reports regarding the reaction of hexahydropyrimidines (1,3-diazinanes) (HHP) with hydrazines and hydroxylamines. It was our main objective to shed light on the reaction of hexahydropyrimidine–dicarbonyl conjugates obtained from acetylacetone (HHP–ACAC) with classical reagents used to produce pyrazoles and isoxazoles. Replication of the procedure established for ACAC on other β-dicarbonyl compounds, namely, hexahydropyrimidine conjugates with ethyl acetoac-

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etate (HHP–ETAA), resulted in different and interesting spiro-products.

Experimental

Column chromatography was performed on 230–400 mesh silica gel (Merck) and TLC plates with silica gel 60 F_{254} (Merck) were used. IR spectra of the samples as thin films were recorded on a Magna-IR 560 Nicolet FTIR spectrometer. ^{1}H (400 MHz) and ^{13}C (125 MHz) NMR spectra were recorded at ambient temperature on a Bruker Avance III spectrometer using $CDCl_3$ as the solvent and TMS as the internal standard. Elemental analyses were performed on a EuroEA3000 CHNS–O analyzer (EuroVector, Italy).

General method for preparation of HHP–ACAC conjugates: 1-(5-acetyl-1,3-dicyclohexyl-1,3-diazinan-5-yl)ethan-1-one (I), 1-[5-acetyl-1,3-bis(4-chlorophenyl)-1,3-diazinan-5-yl]ethan-1-one (II), 1-[5-acetyl-1,3-bis(4-bromophenyl)-1,3-diazinan-5-yl]ethan-1-one (III), 1-(5-acetyl-1,3-diphenyl-1,3-diazinan-5-yl)ethan-1-one (IV), 1-[5-acetyl-1,3-bis(4-methoxyphenyl)-1,3-diazinan-5-yl]ethan-1-one (V), 1-[5-acetyl-1,3-bis(4-methylphenyl)-1,3-diazinan-5-yl]ethan-1-one (VI)

A mixture of ACAC (1.0 mmol), primary amine (R—NH_2, 2.0 mmol), formaldehyde (37–41 % aqueous solution, 3 equiv,) and $FeCl_3$ (5 mole %) in dichloromethane (20 mL) was stirred at ambient temperature for 24 h. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography using EtOAc/hexane ($\varphi_r = 1 : 3$) as the solvent to afford the corresponding HHP–ACAC conjugate (Mukhopadhyay et al., 2011).

General method for preparation of pyrazoles VII–XIII, isoxazoles XIV–XVIII and pyrazol-3-ones XIX and XX: 4-(cyclohexylmethyl)-3,5-dimethyl-1H-pyrazole (VII), 4-chloro-N-[(3,5-dimethyl-1H-pyrazol-4-yl)methyl]aniline (VIII), 4-bromo-N-[(3,5-dimethyl-1H-pyrazol-4-yl)methyl]aniline (IX), N-[(3,5-dimethyl-1H-pyrazol-4-yl)methyl]aniline (X), N-[(3,5-dimethyl-1H-pyrazol-4-yl)methyl]-4-methoxyaniline (XI), N-[(3,5-dimethyl-1H-pyrazol-4-yl)methyl]-4-methylaniline (XII), 4-chloro-N-[(3,5-dimethyl-1-phenyl-1H-pyrazol-4-yl)methyl]aniline (XIII), 4-chloro-N-[(dimethyl-1,2-oxazol-4-yl)methyl]aniline (XIV), 4-bromo-N-[(dimethyl-1,2-oxazol-4-yl)methyl]aniline (XV), N-[(dimethyl-1,2-oxazol-4-yl)methyl]aniline (XVI), N-[(dimethyl-1,2-oxazol-4-yl)methyl]-4-methoxyaniline (XVII), N-[(dimethyl-1,2-oxazol-4-yl)methyl]-4-methylaniline (XVIII), 7,9-bis(4-chlorophenyl)-4-methyl-2,3,7,9-tetraazaspiro[4.5]dec-3-en-1-one (XIX), 7,9-bis(4-bromophenyl)-4-methyl-2,3,7,9-tetraazaspiro[4.5]dec-3-en-1-one (XX)

A mixture of either HHP–ACAC conjugate (*I–VI*, 1.0 mmol) (for the preparation of *VII–XVIII*), HHP–ETAA conjugate (1 mmol) (for the preparation of *XIX* and *XX*), hydrazine (1.2 mmol) (for the preparation of *VII–XII*, *XIX* and *XX*), phenylhydrazine (1.2 mmol) (for the preparation *XIII*) or hydroxylamine (for the preparation of *XIV–XVIII*) and absolute EtOH (15 mL) was stirred at ambient temperature for 24 h. The solvent was evaporated under reduced pressure and the resulting residue was purified on a silica gel column using CH_2Cl_2 and CH_2Cl_2/EtOAc acetate ($\varphi_r = 1 : 1$) as the gradient elution solvents.

Results and discussion

HHP derivatives *I–VI* were synthesized from ACAC employing the double-Mannich annulations protocol (Mukhopadhyay et al., 2011). Their structures and spectral data are given in Fig. 1 and Table 1, respectively.

Both aliphatic and aromatic amines were applied as starting reaction components in the above synthesis. The resulting 1,3-dicarbonyl system in *I–VI* was used to provide heteroclycles using reagents with double nucleophilic centers such as hydrazine and hydroxylamine. Spiro products would be straightforward products of such strategy (Feng et al., 2014). From the pharmaceutical point of view, the newly prepared five-membered ring adds a favorable conformational restriction to the molecule.

Thus, when the HHP–ACAC conjugate *I* was stirred overnight with hydrazine in absolute ethanol at ambient temperature, unexpected decomposition of the hexahydropyrimidine ring took place with simultaneous formation of the 4-aminomethylpyrazole derivative *VII* in good yields. Analogously, 4-aminomethylpyrazole derivatives *VIII–XIII* were obtained starting from the HPP–ACC conjugates *II–VI* (Fig. 1). A similar reaction of *I–VI* with hydroxylamine under the same conditions afforded the corresponding 4-aminomethylisoxazoles *XIV–XVIII* (Fig. 1) in comparable yields. Spectral and analytical data of the prepared compounds are summarized in Tables 2 and 3.

The structure of all products was confirmed by NMR spectral data. As an example, the results for 4-aminomethylpyrazole derivative *VII* and 4-aminomethylisoxazole derivative *XIV* are discussed. For *VII*, the disappearance of the signal for the carbonyl carbon ($\delta_C = 204.8$) of the starting compound (*I*, Fig. 1) and the appearance of two new quaternary carbons ($\delta_C = 114.0$ and $\delta_C = 142.3$) (pyrazole carbons) are direct evidence of a pyrazole ring system

Table 1. Characterization data of compounds *I–VI*

Compound	R	Yield	Spectral data
I	Cyclohexyl	85	IR, $\tilde{\nu}/cm^{-1}$: 1671 (C═O), 2950 ($CH_{aliphatic}$) ^1H NMR ($CDCl_3$), δ: 1.02–1.26, 1.54–1.57, 1.71–1.78 (m, 22H, $H_{cyclohexyl}$), 2.12 (s, 6H, CH_3), 2.32 (m, 2H, CH_2, $H_{cyclohexyl}$), 2.96 (s, 4H, CH_2), 3.26 (s, 2H, CH_2) ^{13}C NMR ($CDCl_3$), δ: 25.9, 26.1 (CH_2), 26.6 (CH_3), 28.8, 51.7 (CH_2), 62.1 (CH), 67.4 (C), 70.9 (CH_2), 204.8 (C)
II	4-Chlorophenyl	86	IR, $\tilde{\nu}/cm^{-1}$: 1669 (C═O), 2992 (CH), 3088 (CH_{aryl}) ^1H NMR ($CDCl_3$), δ: 2.17 (s, 6H, CH_3), 3.81 83(s, 4H, CH_2), 4.33 (s, 2H, CH_2), 7.01 (d, 4H, J = 8.8 Hz, H_{aryl}), 7.28 (d, 4H, J = 8.8 Hz, H_{aryl}) ^{13}C NMR ($CDCl_3$), δ: 26.6 (CH_3), 53.3 (CH_2), 67.1 (C), 69.2 (CH_2), 119.2, 126.6 (C), 129.3 (CH), 147.7, 203.2 (C)
III	4-Bromophenyl	83	IR, $\tilde{\nu}/cm^{-1}$: 1697 (C═O), 2929 (CH), 3016 (CH_{aryl}) ^1H NMR ($CDCl_3$), δ: 2.16 (s, 6H, CH_3), 3.79 (s, 4H, CH_2), 4.33 (s, 2H, CH_2), 6.93 (d, 4H, J = 8.8 Hz, H_{aryl}), 7.38 (d, 4H, J =8.8 Hz, H_{aryl}) ^{13}C NMR ($CDCl_3$), δ: 26.7 (CH_3), 53.0 (CH_2), 67.1 (C), 68.7 (CH_2), 113.9 (C), 119.5, 132.3 (CH), 148.1, 203.1 (C)
IV	Phenyl	87	IR, $\tilde{\nu}/cm^{-1}$: 1697 (C═O), 2822 ($CH_{aliphatic}$), 3026 (CH_{aryl}) ^1H NMR ($CDCl_3$), δ: 2.25 (s, 6H, CH_3), 3.90 (s, 4H, CH_2), 4.47 (s, 2H, CH_2), 7.06–7.41 (m, 10H, J = 8 Hz, H_{aryl}) ^{13}C NMR ($CDCl_3$), δ: 26.8 (CH_3), 53.4 (CH_2), 67.2 (C), 69.4 (CH_2), 118.0, 121.6, 129.5 (CH), 149.4, 203.7 (C)
V	4-Methoxyphenyl	88	IR, $\tilde{\nu}/cm^{-1}$: 1695 (C═O), 2833 ($CH_{aliphatic}$), 3036 (CH_{aryl}) ^1H NMR ($CDCl_3$), δ: 2.15 (s, 6H, CH_3), 3.73 (s, 6H, CH_3), 3.78 (s, 4H, CH_2), 4.56 (s, 2H, CH_2), 6.84 (d, 4H, J = 8.8 Hz, H_{aryl}), 7.02 (d, 4H, J = 8.8 Hz, H_{aryl}) ^{13}C NMR ($CDCl_3$), δ: 26.8, 55.7 (CH_3), 52.7 (CH_2), 67.3 (C), 69.8 (CH_2), 117.0 (CH), 127.1 (C), 130.0 (CH), 149.9, 203.5 (C)
VI	4-Tolyl	91	IR, $\tilde{\nu}/cm^{-1}$: 1693 (C═O), 2821 ($CH_{aliphatic}$), 3016 (CH_{aryl}) ^1H NMR ($CDCl_3$), δ: 2.21 (s, 6H, CH_3), 2.33 (s, 6H, CH_3), 3.78 (s, 4H, CH_2), 4.33 (s, 2H, CH_2), 7.02 (d, 4H, J = 8.6 Hz, H_{aryl}), 7.14 (d, 4H, J = 8.6 Hz, H_{aryl}) ^{13}C NMR ($CDCl_3$), δ: 21.7, 23.9 (CH_3), 52.9 (CH_2), 67.1 (C), 70.0 (CH_2), 113.7 (C), 114.3, 118.4 (CH), 126.7, 203.5 (C)

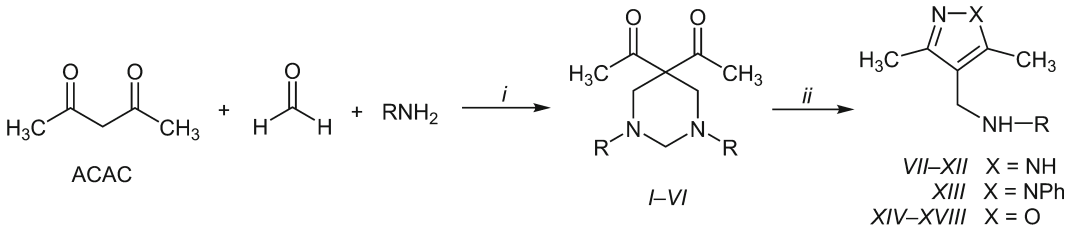

Fig. 1. Synthesis of HHP–ACAC conjugates *I–VI* (for R, see Table 1) and their conversion into pyrazoles *VII–XIII* and isoxazoles *XIV–XVIII* (for R, see Table 2). Reaction conditions: *i*) ACAC (1 equiv), formaldehyde (3 equiv), amine (2 equiv), 5 mole % $FeCl_3$, dichloromethane, ambient temperature, 24 h; *ii*) hydrazine or phenylhydrazine or hydroxylamine, abs. EtOH, ambient temperature, 24 h.

formation. Additionally, the decomposition of a hexahydropyrimidine ring can be confirmed by comparing the signals at δ_H = 2.96 (s, 4H) and δ_C = 51.7 for the CH_2—C—CH_2 group and at δ_H = 3.26 (s, 2H) and δ_C = 70.9 for the N—CH_2—N group present in the starting compound with those at δ_H = 3.52 and δ_C = 39.3 for the only one CH_2 group in the product. Clearly, ^{13}C DEPT-135 assignments combined with the integration associated with the NMR signals, strongly suggest the pyrimidine ring decomposition (note that due to the symmetry of methyl groups, a six-proton singlet was identified in both the starting material and the product).

A similar analysis revealed the same conclusion for isoxazole *XIV* formation. Specifically, symmetric methyl groups of the starting compound *II* (δ_H and δ_C respectively) (δ_H = 2.17, s, 6H; δ_C = 26.6) became asymmetric in the product *XIV* (δ_H = 2.28, s, 3H; δ_C = 10.1; δ_H = 2.40, s, 3H; δ_C = 11.1). The formation of an isoxazole ring system is evident due to the disappearance of the signal for the carbonyl carbon (δ_C = 203.2) of reactant *II*, and the appearance of new three quaternary carbons (confirmed by ^{13}C DEPT-135 spectra) of the isoxazole ring (δ_C: 111.1, 159.6, 166.7) of product *XIV*. The hexahydropyrimidine ring decomposition was also confirmed by the dis-

Table 2. Characterization data of compounds *VII–XX*

Compound	R	X	Formula	M_r	w_i(calc.)/% w_i(found)/%			Yield/%
					C	H	N	
VII	Cyclohexyl	NH	$C_{12}H_{21}N_3$	207.32	69.52	10.21	20.27	75
					69.77	10.24	20.35	
VIII	4-Chlorophenyl	NH	$C_{12}H_{14}ClN_3$	235.71	61.15	5.99	17.83	86
					60.91	6.01	17.89	
IX	4-Bromophenyl	NH	$C_{12}H_{14}BrN_3$	280.16	51.44	5.04	15.00	60
					51.64	5.06	15.05	
X	Phenyl	NH	$C_{12}H_{15}N_3$	201.16	71.61	7.51	20.88	66
					71.79	7.49	20.91	
XI	4-Methoxyphenyl	NH	$C_{13}H_{17}N_3O$	231.29	67.51	7.41	18.17	79
					66.87	7.59	17.95	
XII	4-Tolyl	NH	$C_{13}H_{17}N_3$	215.29	72.52	7.96	19.52	81
					71.79	8.05	19.11	
XIII	4-Chlorophenyl	NPh	$C_{18}H_{18}ClN_3$	311.81	69.34	5.82	13.48	83
					69.14	5.84	13.53	
XIV	4-Chlorophenyl	O	$C_{12}H_{13}ClN_2O$	236.70	60.89	5.54	11.84	87
					60.65	5.52	11.79	
XV	4-Bromophenyl	O	$C_{12}H_{13}BrN_2O$	281.15	51.26	4.66	9.96	90
					51.11	4.67	9.98	
XVI	Phenyl	O	$C_{12}H_{14}N_2O$	202.25	71.26	6.98	13.85	64
					71.44	7.00	13.90	
XVII	4-Methoxyphenyl	O	$C_{13}H_{16}N_2O_2$	232.28	67.22	6.94	12.06	85
					66.45	7.00	11.90	
XVIII	4-Tolyl	O	$C_{13}H_{16}N_2O$	216.28	72.19	7.46	12.95	81
					73.01	7.71	13.08	
XIX	–	–	$C_{19}H_{18}Cl_2N_4O$	389.28	58.62	4.66	14.39	85
					59.01	4.69	14.53	
XX	–	–	$C_{19}H_{18}Br_2N_4O$	478.18	47.72	3.79	11.72	87
					48.05	3.81	11.77	

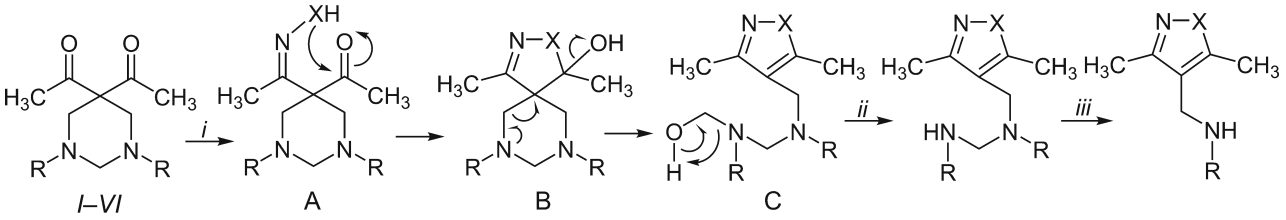

Fig. 2. Proposed mechanism of the formation of products *VII–XVIII* (for R and X, see Table 2); *i*) H_2NXH; *ii*) loss of H_2CO; *iii*) loss of $RN{=}CH_2$.

appearance of the two CH_2 groups (CH_2—C—CH_2) (δ_H = 3.81, s, 4H; δ_C = 53.3) and one CH_2 group (N—CH_2—N) (δ_H = 4.33, s, 2H; δ_C = 69.2) present in the starting compound and the appearance of a signal (δ_H = 4.00, s, 2H; δ_C = 37.1) for only one CH_2 group (C—CH_2—N) in the product.

The above conclusions are supported by the FTIR spectral analysis. The characteristic C=O bands of the starting compounds disappeared and the corresponding bands associated with the newly formed hetero-ring systems were observed.

Mechanistically, the HHP–ACAC conjugates *I–VI* react with hydrazine via its nucleophilic addition to the carbonyl group forming the corresponding intermediate hydrazones (A, Fig. 2). Cyclization of hydrazones leads to the pyrazole ring system forming intermediates B and C. It is assumed that the spiro-intermediate B undergoes a hexahydropyrimidine ring opening. The cleavage of bond between the spiro carbon and the CH_2 group at the adjacent nitrogen is accompanied by either hydroxyl group migration or progression through a charged intermediate leading to the formation of the pyrazole ring system in intermediate C. Under these circumstances, aromatization of the hetero-ring on the expense of the HHP ring system degradation is the driving force of this conversion. The subsequent loss of the formaldehyde molecule and decomposition of the resulting geminal diamine interme-

Table 3. Spectral data of compounds *VII–XX*

Compound	Spectral data
VII	IR, $\tilde{\nu}$/cm^{-1}: 1592 (C═N), 2927 (CH), 3206 (NH) ^{1}H NMR ($CDCl_3$), δ: 1.02–1.20, 1.53–1.85 (m, 10H, $H_{cyclohexyl}$), 2.15 (s, 6H, CH_3), 2.38–2.40 (m, 1H, $CH_{cyclohexyl}$), 3.52 (s, 2H, CH_2) ^{13}C NMR ($CDCl_3$), δ: 10.7 (CH_3), 25.0, 26.0, 33.3, 39.3 (CH_2), 56.0 (CH), 114.0, 142.3 (C)
VIII	IR, $\tilde{\nu}$/cm^{-1}: 1638 (C═N), 2926 (CH), 3419 (NH) ^{1}H NMR ($CDCl_3$), δ: 2.29 (s, 6H, CH_3), 4.02 (s, 2H, CH_2), 6.59 (d, 2H, J = 8.8 Hz, H_{aryl}), 7.16 (d, 2H, J = 8.8 Hz, H_{aryl}) ^{13}C NMR ($CDCl_3$), δ: 10.8 (CH_3), 37.8 (CH_2), 112.7 (C), 113.7 (CH), 122.0 (C), 129.1 (CH), 143.2, 146.8 (C)
IX	IR, $\tilde{\nu}$/cm^{-1}: 1640 (C═N), 2930 (CH), 3027 (CH_{aryl}), 3448 (NH) ^{1}H NMR ($CDCl_3$), δ: 2.29 (s, 6H, CH_3), 4.01 (s, 2H, CH_2), 6.55 (d, 2H, J = 8.8 Hz, H_{aryl}), 7.29 (d, 2H, J = 8.8 Hz, H_{aryl}) ^{13}C NMR ($CDCl_3$), δ: 10.8 (CH_3), 37.7 (CH_2), 109.0, 112.6 (C), 114.2, 131.9 (CH), 143.8, 147.2 (C)
X	IR, $\tilde{\nu}$/cm^{-1}: 1638 (C═N), 3445 (NH) ^{1}H NMR ($CDCl_3$), δ: 2.31 (s, 6H, CH_3), 4.07 (s, 2H, CH_2), 6.69–7.25 (m, 5H, H_{aryl}) ^{13}C NMR ($CDCl_3$), δ: 10.8 (CH_3), 37.7 (CH_2), 112.7 (CH), 113.0 (C), 117.5, 129.3 (CH), 143.3, 148.4 (C)
XI	IR, $\tilde{\nu}$/cm^{-1}: 1660 (C═N), 3454 (NH) ^{1}H NMR ($CDCl_3$), δ: 2.28 (s, 6H, CH_3), 3.79 (s, 3H, CH_3), 4.02 (s, 2H, CH_2), 6.65 (d, 2H, J = 9.2 Hz, H_{aryl}), 6.85 (d, 2H, J = 9.2 Hz, H_{aryl}) ^{13}C NMR ($CDCl_3$), δ: 10.8 (CH_3), 38.7 (CH_2), 55.9 (CH_3), 113.3, 114.0 (C), 114.6, 115.0 (CH), 142.8, 152.2 (C)
XII	IR, $\tilde{\nu}$/cm^{-1}: 1617 (C═N), 3495 (NH) ^{1}H NMR ($CDCl_3$), δ: 2.00 (s, 3H, CH_3), 2.28 (s, 6H, CH_3), 4.51 (s, 2H, CH_2), 6.38 (d, 2H, J = 8.8 Hz, H_{aryl}), 6.92 (d, 2H, J = 8.8 Hz, H_{aryl}) ^{13}C NMR ($CDCl_3$), δ: 10.7 (CH_3), 20.4 (CH_3), 38.6 (CH_2), 114.5, 115.3 (CH), 113.4, 114.0, 141.8, 152.3 (C)
XIII	IR, $\tilde{\nu}$/cm^{-1}: 1634 (C═N), 3445 (NH) ^{1}H NMR ($CDCl_3$), δ: 2.32 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 4.08 (s, 2H, CH_2), 6.61–7.40 (m, 9H, H_{aryl}) ^{13}C NMR ($CDCl_3$), δ: 10.9, 11.87 (CH_3), 38.3 (CH_2), 113.7 (CH), 114.9, 121.0 (C), 122.1, 124.9, 127.5, 129.1 (CH), 137.9, 139.8, 146.8, 148.3 (C)
XIV	IR, $\tilde{\nu}$/cm^{-1}: 1638 (C═N), 3404 (NH) ^{1}H NMR ($CDCl_3$), δ: 2.28 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 4.00 (s, 2H, CH_2), 6.58 (d, 2H, J = 8.6 Hz, H_{aryl}), 7.17 (d, 2H, J = 8.6 Hz, H_{aryl}) ^{13}C NMR ($CDCl_3$), δ: 10.1, 11.1 (CH_3), 37.1 (CH_2), 111.1 (C), 113.0 (CH), 122.9 (C), 129.2 (CH), 146.2, 159.6, 166.7 (C)
XV	IR, $\tilde{\nu}$/cm^{-1}: 1638 (C═N), 3444 (NH) ^{1}H NMR ($CDCl_3$), δ: 2.26 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 3.99 (s, 2H, CH_2), 6.54 (d, 2H, J = 8.8 Hz, H_{aryl}), 7.29 (d, 2H, J = 8.8 Hz, H_{aryl}) ^{13}C NMR ($CDCl_3$), δ: 10.2, 11.1 (CH_3), 37.0 (CH_2), 109.9, 111.1 (C), 114.4, 132.1 (CH), 146.7, 159.6, 166.7 (C)
XVI	IR, $\tilde{\nu}$/cm^{-1}: 1639 (C═N), 3447 (NH) ^{1}H NMR ($CDCl_3$), δ: 2.34 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 4.25 (s, 2H, CH_2), 6.72–7.27 (m, 5H, H_{aryl}) ^{13}C NMR ($CDCl_3$), δ: 10.1, 11.1 (CH_3), 37.1 (CH_2), 111.7 (C), 113.1, 118.4, 129.4 (CH), 147.7, 159.9, 166.9 (C)
XVII	IR, $\tilde{\nu}$/cm^{-1}: 1637 (C═N), 3347 (NH) ^{1}H NMR ($CDCl_3$), δ: 2.28 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 3.78 (s, 3H, CH_3), 3.99 (s, 2H, CH_2), 6.65 (d, 2H, J = 8.8 Hz, H_{aryl}), 6.83 (d, 2H, J = 8.8 Hz, H_{aryl}) ^{13}C NMR ($CDCl_3$), δ: 10.2, 11.1 (CH_3), 38.1 (CH_2), 111.6 (C), 114.6, 115.0 (CH), 141.8, 152.8, 159.8, 166.6 (C)
XVIII	IR, $\tilde{\nu}$/cm^{-1}: 1618 (C═N), 3457 (NH) ^{1}H NMR ($CDCl_3$), δ: 2.28 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 4.01 (s, 2H, CH_2), 6.60 (d, 2H, J = 8.4 Hz, H_{aryl}), 7.05 (d, 2H, J = 8.4 Hz, H_{aryl}) ^{13}C NMR ($CDCl_3$), δ: 10.2, 11.1, 20.4 (CH_3), 37.4 (CH_2), 111.6 (C), 113.1, 129.84 (CH), 127.5, 145.5, 159.7, 166.5 (C)
XIX	IR, $\tilde{\nu}$/cm^{-1}: 1639 (C═N), 1790 (C═O), 3503 (NH) ^{1}H NMR ($CDCl_3$), δ: 2.03 (s, 3H, CH_3), 3.38 (d, 2H, J = 12.4 Hz), 3.60 (d, 2H, J = 12.4 Hz), 4.10 (d, 1H, J = 11.2 Hz), 5.12 (d, 1H, J = 11.2 Hz), 6.92 (d, 4H, J = 8.4 Hz), 7.29 (d, 4H, J = 8.4 Hz), 9.34 (brs, 1H) ^{13}C NMR ($CDCl_3$), δ: 17.8 (CH_3), 51.3 (C), 53.1, 69.1 (CH_2), 118.7, 129.6 (CH), 126.5, 147.3, 165.0, 175.4 (C)
XX	IR, $\tilde{\nu}$/cm^{-1}: 1638 (C═N), 1794 (C═O), 3500 (NH) ^{1}H NMR ($CDCl_3$), δ: 2.02 (s, 3H, CH_3), 3.39 (d, 2H, J = 12.6 Hz), 3.61 (d, 2H, J = 12.6 Hz), 4.10 (d, 1H, J = 11.6 Hz), 5.14 (d, 1H, J = 11.6 Hz), 6.86 (d, 4H, J = 8.8 Hz), 7.43 (d, 4H, J = 8.8 Hz), 8.70 (brs, 1H) ^{13}C NMR ($CDCl_3$), δ: 17.8 (CH_3), 51.1 (C), 53.0, 68.6 (CH_2), 113.8 (C), 119.0, 132.5 (CH), 147.6, 164.9, 175.0 (C)

diate lead to the formation of the products obtained. The geminal diamine decomposition occurs as a result of inherent instability of such intermediates, leading to the formation of the respective by-product that was confirmed by the NMR spectra. This decomposition is a well established phenomenon and it has been found

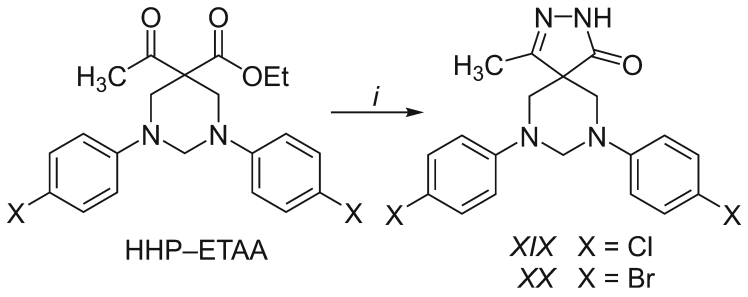

Fig. 3. Synthesis of pyrazol-3-one derivatives from HHP–ETAA conjugates (Saleh et al., 2014). Reaction conditions: *i*) hydrazine hydrate, abs. EtOH, ambient temperature, 24 h (85 % and 87 % yield of *XIX* and *XX*, respectively).

to occur in both biological reactions and in certain synthetic transformations (Moad & Benkovic, 1978).

It is clear that both the starting HHP derivative and the intermediate C are considered to be geminal diamines. However, HHP rings are known to be stable and they have been found in several natural and synthetic biologically active compounds, while geminal diamines with their structure similar to that of intermediate C are unstable (Moad & Benkovic, 1978).

It is highly probable that the formation of 4-aminomethylisoxazole products by the reaction of *II*–*VI* with hydroxylamine follows the same mechanism as described above. The products obtained through this route either with hydrazine or hydroxylamine forming pyrazole and isoxazole ring systems, respectively, is not entirely unusual. The formation of indazoles by the reaction of azabicyclononanones with hydrazine, hydroxylamine, or methylhydrazine has been explained on a similar mechanistic background (Neochoritis et al., 2011). Also in this case, the driving force of such transformations is the aromatization of the hetero-ring system. Theoretical calculations performed for this system indicate that the aromatization step is thermodynamically favorable.

There have been several attempts to apply the above mechanism designed for HHP–ACAC conjugates to other substrates, in particular, hexahydropyrimidines conjugated with dibenzoylmethane (HHP–DBM) and ethyl acetoacetate (HHP–ETAA), respectively. Efforts to prepare HHP–DBM analogs under the same conditions reported herein resulted in the formation of monocarbonyl derivatives (5-benzoyl-1,3-diazinans) (Saleh et al., 2014) which are unsuitable for the current protocol.

However, recent reports have introduced high-yielding procedures for the reaction of ethyl acetoacetate with formaldehyde and primary amines to furnish the corresponding hexahydropyrimidines in comparable yields (Latypova et al., 2013; Mukhopadhyay et al., 2011). HHP–ETAA conjugates (Saleh et al., 2014) have shown a different mechanism when treated with hydrazine and, subsequently, different products were obtained (Fig. 3). The products obtained in comparable yields were characterized as spiroheterocyclic pyrazol-3-one compounds *XIX* and *XX* (Fig. 3). Their analytical and spectral data are summarized in Tables 2 and 3. It is worth mentioning that the slightly different chemical shift of the aromatic ring protons observed for compounds *XIX* and *XX* might be due to the differences in size, electronegativity, and the degree of overlapping with aromatic π-electrons of Cl versus Br substituents (the same phenomenon has been observed for the corresponding anilines substituted in the para position).

The possibility of the HHP ring survival, unlike the HHP–ACAC conjugates reported herein, can be explained similarly. Specifically, aromatization of the pyrazole/isoxazole ring systems causes the HHP ring destruction, whereas the same factor is less pronounced or even absent in the spiro-heterocyclic compounds *XIX* and *XX*. Accordingly, the following mechanism can be proposed for such systems (Fig. 4) (Cocivera et al., 1978; Katritzky et al., 1987).

In the first step, nucleophilic addition of a hydrazine nitrogen atom to the ketone group of the β-ketoester proceeds to form a carbinolamine (Fig. 4, route a) followed by the ring closure via hydrazone as the intermediate. Alternatively, the carboxylate group is attacked via the nucleophilic addition/elimination mechanism (Fig. 4, route b) followed by the pyrazolone ring closure. For symmetrically substituted hydrazine, both routes ultimately produce the same pyrazolone product. However, Cocivera et al. (1978) demonstrated that route a is the main pathway for HHP–ETAA conjugates.

Conclusions

A concise and good yielding procedure for the preparation of 4-aminomethylpyrazoles and 4-aminomethylisoxazoles from acetylacetone using reagents with double nucleophilic centers, namely, hydrazine, phenylhydrazine and hydroxylamine in two steps under mild conditions has been proposed (Fig. 1). Additionally, a suitable mechanism has been provided (Fig. 2) and confirmed by a literature report considering a similar system (Neochoritis et al., 2011). A different mechanism was observed when hexahydropyrimidines conjugated with ethyl acetoacetate were used under the same conditions. This difference is, proba-

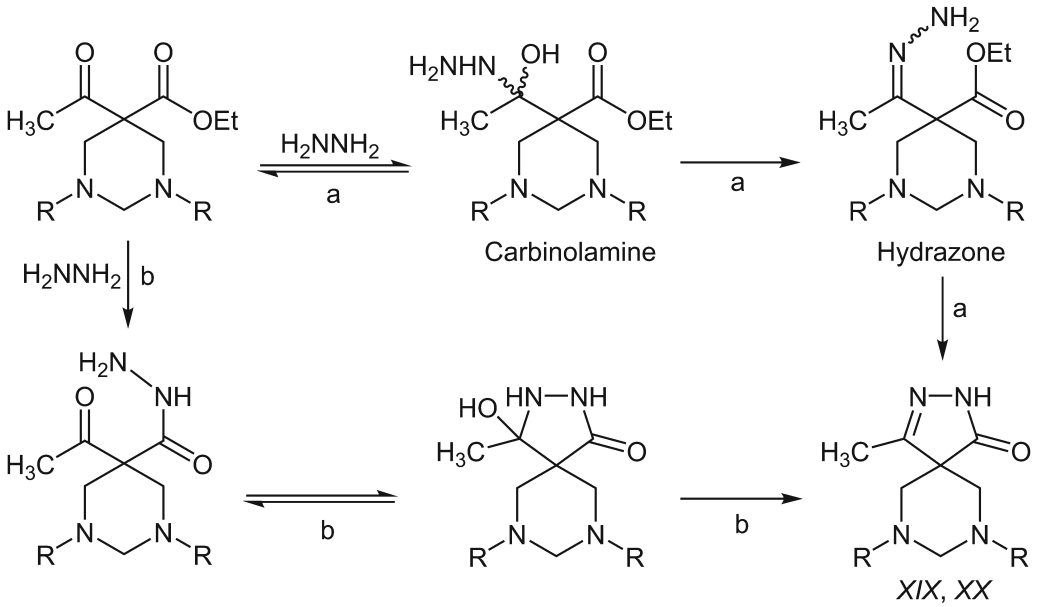

Fig. 4. Proposed mechanism for the formation of compounds *XIX* (R = 4-chlorophenyl) and *XX* (R = 4-bromophenyl).

bly, due to the presence of an ester group in the HHP–ETAA conjugates.

Attempts to prepare the corresponding hexahydropyrimidines conjugated with dibenzoylmethane (HHP–DBM) have resulted in 5-benzoyl-1,3-diazinans. Consequently, the dibenzoylmethane-system was not studied. On the other hand, hexahydropyrimidines conjugated with asymmetric β-diketones (such as 1-phenylbutane-1,3-dione) have been avoided at this stage to focus rather on the mechanism than on regio- or stereochemical complications possibly arising from the reaction.

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