Synthesis of Novel 3-substituted-1-(2'-hydroxyphenyl)propan-1-ones**

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Two novel ketonic Mannich bases that resulted through direct aminomethylation of 2'-hydroxyacetophenone with 4-methylpiperidine and 4-benzylpiperidine are reported in this paper. The replacement of the easily leaving dimethylamino moiety in the ketonic Mannich base derived from the same substrate with various nucleophiles has also been investigated. Thus, reaction of this ketonic Mannich base with thiophenols led to 3-(substituted phenylthio)-1-(2'-hydroxyphenyl)propan-1-ones, whereas 3-(substituted indol-3-yl)-1-(2' -hydroxyphenyl)propan-1-ones were obtained upon alkylation of the corresponding indoles at C-3. In addition, 4-bromo-3,5-dimethylpyrazole, 4-phenylimidazole, 1,2,4-triazole and benzotriazole were N-alkylated by the same ketonic Mannich base.

Keywords: Mannich reaction, Mannich base, 2'-hydroxypropiophenones, amine replacement, alkylation

Owing to the proximity of the phenolic hydroxyl and the carbonyl group, *ortho*-acylphenols are excellent starting materials in the synthesis of heterocyclic compounds such as benzofurans [2], chromanones [3,4], flavanones [5], coumarins [6], benzoxepins [7], 1,3-naphthoxazines [8] and benzisoxazoles [9,10]. 2'-Hydroxyacetophenones and the related derivatives of the carbonyl function, such as Schiff bases, oximes, hydrazones, semicarbazones, etc., are widely used as ligands in metal complexes with various applications [11–14]. In addition, diversely substituted 2'-hydroxyacetophenones and 2'-hydroxypropiophenones have been reported as antibacterial agents [15], antifungals [16], muscle relaxants [17], or substances acting as immunomodulators in inflammatory events [18]. On closer inspection, the structural diversity of the *ortho*-acylphenols employed in these studies is derived mostly from the substitution of the aromatic moiety or from the chemical modification of the carbonyl function. A brief examination of the literature showed that, with the notable exception of simple 2'-hydroxypropiophenones, all other *ortho*-acylphenols functionalized in the alkyl side chain are poorly represented in studies published on the aforementioned or related topics. The limited availability of commercial *ortho*-acylphenols is largely responsible for the lack of structural diversity of the compounds used in these investigations. However, the derivatization of the side alkyl chain in commercially available 2'-hydroxyacetophenones and 2'-hydroxypropiophenones may improve significantly the structural diversity of the *ortho*-acylphenols available for these studies. In order to achieve this goal, we developed a simple synthetic strategy that is based on a two-step reaction sequence comprising the Mannich reaction at the carbon atom α to the carbonyl function as the first stage, in conjunction with the replacement of the easily leaving dialkylamino group with various nucleophiles as the second stage. Several small libraries of 3-substituted-1-(2'-hydroxyphenyl)propan-1-ones have been so far created through the use of secondary aliphatic amines [19,20], arylamines [21,22], dithiocarbamates [23] and NH-heterocycles [24,25] as nucleophiles in the second stage of the reaction sequence. The present paper widens the scope of this synthetic strategy for the generation of *ortho*-acylphenols having diverse moieties in the side chain both by using 4-substituted piperidines as amine reagents in the first stage, and by exploring the use of novel nucleophiles in the second stage of the sequence.

Experimental part

Melting points were taken on a Mel-Temp II apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400-MHz spectrometer. The signals owing to residual protons in the deuterated solvents were used as internal standards for the ^{1}H NMR spectra. The chemical shifts for the carbon atoms are given relative to deuteriochloroform (δ = 77.16 ppm), d_4-methanol (δ = 49.00 ppm), or d_6-dimethyl sulfoxide (δ = 39.52 ppm). All chemical reagents were obtained from Sigma–Aldrich and were used without prior purification. 4-Methylpiperidine hydrochloride and 4-benzylpiperidine hydrochloride were obtained by treating an efficiently stirred, ice-cold 1M solution of the corresponding amine in diethyl ether with excess ethereal hydrogen chloride.

1-(2' -Hydroxyphenyl)-3-(4-methylpiperidin-1-yl)-1-propanone hydrochloride 2. A mixture of 2'-hydroxyacetophenone (1360 mg, 10 mmol), paraformaldehyde (600 mg, 20 mmol), 4-methylpiperidine hydrochloride (1355 mg, 10 mmol) and 37% HCl (4 drops) in 2-propanol (5 mL) was heated at reflux temperature for 4 h. The reaction mixture was allowed to cool to 40–50 °C, then acetone (20 mL) was gradually added under efficient stirring. The precipitate that formed after the mixture had been kept in a refrigerator overnight was filtered, washed with acetone, and air-dried. Recrystallization from ethanol (5 mL) yielded colorless crystals (1105 mg, 39%), mp 167–168 °C; ^{1}H NMR (D_2O, 400 MHz): δ 0.97 (d, J = 6.4 Hz, 3H), 1.35–1.50 (m, 2H), 1.62–1.80 (m, 1H), 1.95 (d, J = 14.4 Hz, 2H), 2.96–3.09 (m, 2H), 3.54 (t, J = 6.4 Hz, 2H), 3.56–3.69 (m, 4H), 6.97–7.09 (m, 2H), 7.55–7.65 (m, 1H), 7.89 (d, J = 8.0 Hz, 1H); ^{13}C NMR (D_2O, 100 MHz): δ 20.5, 28.3, 31.3, 33.0, 51.9, 53.8, 118.0, 119.3, 120.4, 130.8, 137.6, 160.4, 203.3.

1-(2' -Hydroxyphenyl)-3-(4-benzylpiperidin-1-yl)-1-propanone hydrochloride 3. A mixture of 2'-hydroxyacetophenone (680 mg, 5 mmol), paraformaldehyde (300 mg, 10 mmol), 4-benzylpiperidine hydrochloride (1058 mg, 5 mmol) and 37% HCl (3 drops) in 2-propanol (4 mL) was heated at reflux temperature for

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4 h. Addition of acetone (20 mL) to the slightly cooled reaction mixture under efficient stirring, followed by refrigeration overnight, afforded a precipitate. The solid was filtered, washed with acetone, air-dried, and recrystallized from ethanol (5 mL) to give colorless crystals (595 mg, 33%), mp 165–166 °C; ^{1}H NMR (CD_3OD, 400 MHz): δ 1.48–1.70 (m, 2H), 1.85–1.97 (m, 3H), 2.64 (d, *J* = 6.4 Hz, 2H), 3.03 (br s, 2H), 3.54 (t, *J* = 6.4 Hz, 2H), 3.58–3.72 (m, 4H), 6.94–7.02 (m, 2H), 7.16–7.23 (m, 3H), 7.25–7.32 (m, 2H), 7.49–7.57 (m, 1H), 7.94 (dd, *J* = 1.6 and 8.0 Hz, 1H); ^{13}C NMR (CD_3OD, 100 MHz): δ29.8, 30.5, 34.5, 36.6, 42.9, 45.3, 53.1, 54.6, 119.1, 120.5, 120.7, 127.4, 129.5, 130.2, 131.5, 137.9, 140.5, 163.0, 203.2.

3-Dimethylamino-1-(2'-hydroxyphenyl)-1-propanone hydrochloride 4. A mixture of 2'-hydroxyacetophenone (6.8 g, 50 mmol), paraformaldehyde (3 g, 100 mmol), dimethylamine hydrochloride (4.49 g, 55 mmol) and 37% HCl (0.5 mL) in 2-propanol (16 mL) was heated at reflux temperature for 4 h. The mixture was cooled in a water bath to 40–50 °C, then acetone (70 mL) was gradually added under efficient stirring. Refrigeration overnight afforded a precipitate, which was filtered, washed with acetone, air-dried and recrystallized to give off-white crystals (4.82 g, 42%), mp 175–176 °C (ethanol) (lit. mp 172–173 °C [26]; lit mp 174–175 °C [27]); ^{1}H NMR (d_6-DMSO, 400 MHz): δ 2.78 (s, 6H), 3.39 (t, *J* = 7.2 Hz, 2H), 3.65 (t, *J* = 7.2 Hz, 2H), 6.93–7.00 (m, 1H), 7.05 (dd, *J* = 0.8 and 8.4 Hz, 1H), 7.48–7.56 (m, 1H), 7.87 (dd, *J* = 1.6 and 8.0 Hz, 1H), 10.89 (br s, 1H, exchangeable with D), 11.48 (s, 1H, exchangeable with D); ^{13}C NMR (d_6-DMSO, 100 MHz): δ 35.0, 42.2, 51.6, 117.7, 119.2, 120.9, 130.4, 136.0, 160.0, 200.9.

3-(4-Chlorophenylsulfanyl)-1-(2'-hydroxyphenyl)-1-propanone 5. A mixture of Mannich base **4** (689 mg, 3 mmol), 4-chlorothiophenol (434 mg, 3 mmol), ethanol (4 mL) and water (4 mL) was heated at reflux temperature for 1 h. The reaction mixture was then cooled in an ice bath with efficient stirring, when the heavy oil solidified. The solid was filtered, washed with a little 2-propanol, air-dried and recrystallized to give colorless crystals (632 mg, 72%), mp 100–101 °C (ethanol); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.25–3.35 (m, 4H), 6.84–6.92 (m, 1H), 6.98 (dd, *J* = 1.2 and 8.4 Hz, 1H), 7.24–7.34 (m, 4H), 7.44–7.51 (m, 1H), 7.64 (dd, *J* = 1.2 and 8.4 Hz, 1H), 12.10 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 28.3, 38.0, 118.8, 119.1, 119.2, 129.4, 129.8, 131.2, 132.7, 134.1, 136.8, 162.5, 203.9.

3-(4-Bromophenylsulfanyl)-1-(2'-hydroxyphenyl)-1-propanone 6. A mixture of Mannich base **4** (459 mg, 2 mmol), 4-bromothiophenol (378 mg, 2 mmol), ethanol (3 mL) and water (3 mL) was heated at reflux temperature for 1 h. The reaction mixture was then cooled in an ice bath with efficient stirring, when the heavy oil solidified. The solid was filtered, washed with a little 2-propanol, air-dried and recrystallized to give colorless crystals (472 mg, 70%), mp 89–90 °C (ethanol); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.26–3.36 (m, 4H), 6.84–6.92 (m, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 7.20–7.26 (m, 2H), 7.39–7.45 (m, 2H), 7.44–7.51 (m, 1H), 7.65 (dd, *J* = 1.6 and 8.0 Hz, 1H), 12.08 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 28.2, 38.0, 118.8, 119.2, 119.3, 120.6, 129.8, 131.4, 132.3, 134.9, 136.8, 162.6, 203.9.

1-(2'-Hydroxyphenyl)-3-(1*H*-indol-3-yl)-1-propanone 7. A mixture of Mannich base **4** (689 mg, 3 mmol), indole (351 mg, 3 mmol), ethanol (4 mL) and water (4 mL) was heated at reflux temperature for 4 h. The reaction mixture was then cooled in an ice bath with efficient stirring, when the heavy oil solidified. The solid was filtered, washed with a little 2-propanol, air-dried and recrystallized from ethanol (4 mL) to give off-white crystals (382 mg, 48%), mp 119–120 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.24 (t, *J* = 7.4 Hz, 2H), 3.42 (t, *J* = 7.4 Hz, 2H), 6.83–6.91 (m, 1H), 7.00 (dd, *J* = 1.2 and 8.4 Hz, 1H), 7.02–7.07 (m, 1H), 7.13–7.19 (m, 1H), 7.20–7.27 (m, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.42–7.51 (m, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.75 (dd, *J* = 1.6 and 8.4 Hz, 1H), 7.99 (br s, 1H), 12.42 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ19.8, 39.1, 111.4, 115.1, 118.6, 118.7, 119.0, 119.6, 121.8, 122.3, 127.3, 130.1, 136.4, 162.6, 206.2.

1-(2'-Hydroxyphenyl)-3-(1-methyl-1*H*-indol-3-yl)-1-propanone 8. A mixture of Mannich base **4** (689 mg, 3 mmol), 1-methylindole (393 mg, 3 mmol), ethanol (4 mL) and water (4 mL) was heated at reflux temperature for 4 h. The reaction mixture was then cooled in an ice-salt bath with efficient stirring until the heavy oil solidified. The solid was filtered, washed with a little 2-propanol, air-dried and recrystallized to yield off-white crystals (427 mg, 51%), mp 56–57 °C (ethanol); ^{1}H NMR ($CDCl_3$, 400 MHz): δ3.23 (t, *J* = 7.6 Hz, 2H), 3.41 (t, *J* = 7.6 Hz, 2H), 3.76 (s, 3H), 6.84–6.94 (m, 2H), 7.01 (dd, *J* = 0.8 and 8.4 Hz, 1H), 7.11–7.19 (m, 1H), 7.22–7.35 (m, 2H), HHH), 7.43–7.51 (m, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.76 (dd, *J* = 1.6 and 8.0 Hz, 1H), 12.42 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.7, 32.7, 39.4, 109.4, 113.5, 118.6, 118.8, 118.9, 119.0, 119.5, 121.8, 126.6, 127.7, 130.0, 136.4, 137.3, 162.6, 206.2.

3-(5-Bromo-1*H*-indol-3-yl)-1-(2'-hydroxyphenyl)-1-propanone 9. A mixture of Mannich base **4** (689 mg, 3 mmol), 5-bromoindole (588 mg, 3 mmol), ethanol (4 mL) and water (4 mL) was heated at reflux temperature for 4 h. The reaction mixture was then cooled in an ice bath with efficient stirring to afford a crystalline solid, that was filtered, washed with a little 2-propanol, air-dried and recrystallized to give reddish crystals (296 mg, 29%), mp 137–138 °C (ethanol); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.17 (t, *J* = 7.2 Hz, 2H), 3.38 (t, *J* = 7.2 Hz, 2H), 6.83–6.91 (m, 1H), 6.99 (dd, *J* = 0.8 and 8.4 Hz, 1H), 7.05 (d, *J* = 2.4 Hz, 1H), 7.19–7.31 (m, 2H), 7.41–7.50 (m, 1H), 7.69–7.78 (m, 2H), 8.03 (br s, 1H), 12.35 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.5, 38.9, 112.8, 112.9, 114.9, 118.7, 119.1, 119.5, 121.4, 123.1, 125.1, 129.1, 130.0, 135.0, 136.5, 162.5, 205.9.

3-(4-Bromo-3,5-dimethyl-1*H*-pyrazol-1-yl)-1-(2'-hydroxyphenyl)-1-propanone 10. A mixture of Mannich base **4** (689 mg, 3 mmol), 5-bromo-3,5-dimethylpyrazole (525 mg, 3 mmol), ethanol (4 mL) and water (4 mL) was heated at reflux temperature for 1 h. The reaction mixture was then cooled in an ice-salt bath with efficient stirring until the heavy oil solidified. The solid was filtered, washed with a little 2-propanol, air-dried and recrystallized to yield off-white crystals (387 mg, 40%), mp 143–144 °C (2-propanol); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.18 (s, 3H), 2.31 (s, 3H), 3.60 (t, *J* = 6.6 Hz, 2H), 4.40 (t, *J* = 6.6 Hz, 2H), 6.84–6.92 (m, 1H), 6.97 (d, *J* = 8.4 HZ, 1H), 7.43–7.51 (m, 1H), 7.71 (dd, *J* = 1.2 and 8.0 Hz, 1), 12.01 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 10.5, 12.4, 38.1, 43.8, 94.0, 118.7, 119.3, 130.0, 136.9, 137.7, 146.6, 162.5, 203.3.

1-(2'-Hydroxyphenyl)-3-(1*H*-1,2,4-triazol-1-yl)-1-propanone 11. A mixture of Mannich base **4** (459 mg, 2 mmol), 1,2,4-triazole (138 mg, 2 mmol), ethanol (4 mL) and water (4 mL) was heated at reflux temperature for 1 h. The mixture was refrigerated for 2 days, then the solid was filtered, washed with water, air-dried and recrystallized from ethanol (3 mL) to afford colorless crystals (165 mg, 38%), mp 91–92 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.63 (t, *J* = 6.2 Hz, 2H), 4.63 (t, *J* = 6.2 Hz, 2H), 6.84–6.93 (m, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 7.42–7.51 (m, 1H), 7.68 (dd, *J* = 1.2 and 8.0 Hz, 1H), 7.91 (s, 1H), 8.21 (s, 1H), 11.87 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 37.6, 43.7, 118.8, 119.0, 119.4, 129.7, 137.1, 144.1, 152.2, 162.5, 202.3.

1-(2'-Hydroxyphenyl)-3-(4-phenyl-1*H*-imidazol-1-yl)-1-propanone 12. A mixture of Mannich base **4** (459 mg, 2 mmol), 4-phenylimidazole (288 mg, 2 mmol), ethanol (4 mL) and water (4 mL) was heated at reflux temperature for 1 h. The solid that formed upon cooling was filtered, washed with 2-propanol, and recrystallized to give colorless crystals (362 mg, 62%), mp 142–143 °C (ethanol); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.51 (t, *J* = 6.4 Hz, 2H), 4.43 (t, *J* = 6.4 Hz, 2H), 6.85–6.92 (m, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 7.19–7.26 (m, 2H), 7.32–7.39 (m, 2H), 7.44–7.52 (m, 1H), 7.62–7.69 (m, 2H), 7.75 (d, *J* = 7.6 Hz, 2H), 11.95 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 39.6, 41.3, 115.0, 118.9, 119.1, 119.4, 124.9, 127.0, 128.7, 129.6, 134.1, 137.1, 137.8, 142.6, 162.6, 202.3.

3-(1*H*-Benzotriazol-1-yl)-1-(2'-hydroxyphenyl)-1-propanone 13. A mixture of Mannich base **4** (1377 mg, 6 mmol), benzotriazole (714 mg, 6 mmol), ethanol (7 mL) and water (11 mL) was heated at reflux temperature for 1 h. The solid obtained upon cooling in an ice bath was filtered, washed with little 2-propanol, air-died, and recrystallized from ethanol (12 mL) to give colorless crystals (945 mg, 59%), mp 130–131 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ3.85 (t, *J* = 6.6 Hz, 2H), 5.05 (t, *J* = 6.6 Hz, 2H), 6.83–6.92 (m, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 7.33–7.41 (m, 1H), 7.42–7.56 (m, 2H), 7.65–7.74 (m, 2H), 8.04 (d, *J* = 8.4 Hz, 1H), 11.90 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 37.9, 42.3, 109.8, 118.7, 119.0, 119.4, 120.0, 124.2, 127.7, 129.8, 133.3, 137.1, 145.9, 162.5, 202.4.

Results and discussions

The Mannich reaction is a remarkable synthetic tool for the derivatization of alkyl aryl ketones at the carbon atom α to the carbonyl function. Acylphenols behave in a particular manner in aminomethylations, because they are bifunctional substrate having two activating groups, namely the carbonyl function and the phenolic hydroxyl, that could potentially lead either a ketonic Mannich base or a phenolic Mannich base, respectively [28]. In the case of monohydroxilic acylphenols, chemoselectivity of aminomethylation can be achieved through the selection of the appropriate reaction conditions. Thus, ketonic Mannich bases are the usual reaction product when aminomethylation is conducted at low *p*H (by using amine hydrochloride as the amine reagent), whereas phenolic Mannich bases are obtained at high pH (the free amine is the amine reagent). In addition, several *ortho*-acylphenols are known to undergo a ring-closure reaction to chromanone simultaneously with the Mannich reaction, both at low [29] and high *p*H [30,31]. At low *p*H, the course of aminomethylation of 2'-hydroxyacetophenones appears to be steered towards either ketonic Mannich bases or chromanone Mannich bases by the nature of the reaction medium, as the use lower alcohols affords the former [19], whereas the use of a high boiling point solvent such as DMF gives good yields of the latter [29]. Consequently, the Mannich reaction of 2'-hydroxyaceto-phenone **1** at low *p*H in refluxing 2-propanol should yield the ketonic Mannich bases **2**–**4**, and not chromanone Mannich bases (fig. 1). Generally, the formation of ketonic Mannich bases derived from acetophenones can be confirmed by the presence of two triplets within 3 to 4 ppm range in the ^{1}H NMR spectrum, which correspond to the protons in the two methylene groups bridging the carbonyl function and the amine moiety. In contrast, the formation of a chromanone Mannich base from 2'-hydroxyacetophenone translates into a proton spectrum that has a more complex aliphatic region than the proton spectrum of the corresponding ketonic Mannich base. In addition, the aliphatic region of the proton spectrum of a chromanone Mannich base displays proton signals having chemical shift values higher than 4 ppm owing to the hydrogen atoms of the methylene group adjacent to the oxygen atom in chromanone. Compound **4** is without a doubt the ketonic Mannich base of 2'-hydroxyacetophenone, as the aforementioned two triplets are easily noticeable in its ^{1}H NMR spectrum. In the case of compounds **2** and **3**, only one triplet is evident, the second triplet being obscured by superimposition with signals of protons in the piperidine ring. Nonetheless, the structure of a chromanone Mannich base is ruled out for compounds **2** and **3** based on the absence of any signals above 4 ppm in the aliphatic region of the ^{1}H NMR spectra, and also based on the number of protons recorded in the spectra, which is accurate only for a ketonic Mannich base (the corresponding chromanone Mannich base should present extra signals in its proton spectrum at δ values above 4 ppm [30]). Further confirmation for the structure of compounds **2**–**4** as ketonic Mannich bases is offered by their ^{13}C NMR spectra, which present in the aliphatic region the correct number of peaks for the proposed structure; in addition, all of the peaks associated with aliphatic carbon atoms have chemical shift values lower than 60 ppm. If compounds **2**–**4** were chromanone Mannich bases instead, their ^{13}C NMR spectra would display an extra peak at δ value higher than 60 ppm. The yields of ketonic Mannich bases **2**–**4** are modest, but no attempts have been made at this stage to optimize the process and improve them. Compound **4** has been preferred over Mannich bases **2** or **3** as starting material for the next stage of the reaction sequence because the amine hydrochloride required for

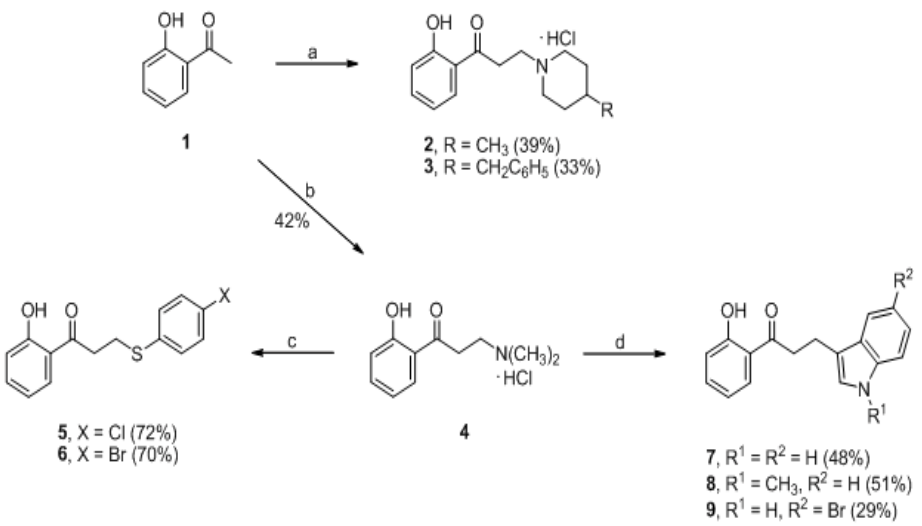

Fig. 1. Aminomethylation of 2'-hydroxyacetophenone **1** with 4-substituted piperidines and replacement of the amine moiety in Mannich base **4** by thiophenols and indoles. Conditions: a) paraformaldehyde, 4-substituted piperidine hydrochloride, 2-propanol, reflux, 4 h; b) paraformaldehyde, dimethylamine hydrochloride, 2-propanol, reflux, 4 h; c) thiophenol, ethanol–water, reflux 1 h; d) indole, ethanol–water, reflux 4 h

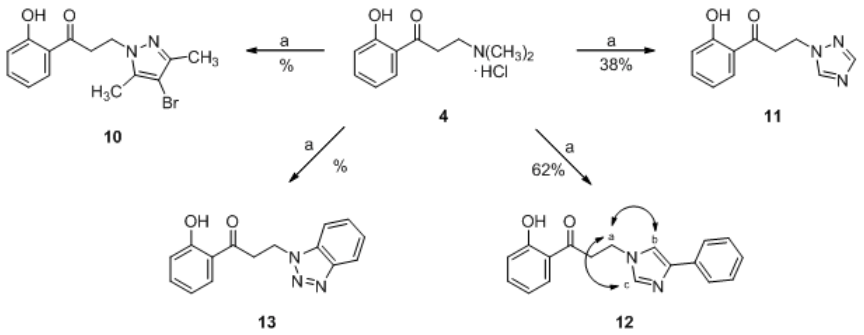

Fig. 2. Substitution of the amine moiety in Mannich base 4 with NH-heterocycles. Conditions: a) NH-heterocycle, ethanol–water, reflux 1 h

its synthesis is commercially available, and the yield of amino ketone **4** is marginally higher than the yields of compounds **2** or **3**. Mannich bases **2**–**4** are colorless to off-white solids, with high melting points, very soluble in water and DMSO, less soluble in lower alcohols, practically insoluble in acetone, ethyl acetate, diethyl ether and petroleum ether.

Literature indicates two slightly different experimental methodologies for the substitution of the amine moiety in Mannich bases by nucleophiles [32]. The major difference between these methodologies consists in the nature of the solvent employed (either aprotic or protic), which in turn determines the nature of the Mannich base (as a free base or as a salt, respectively) used in the reaction. In the case of ketonic Mannich bases as substrates, the yields for the isolated reaction products cannot be factored into deciding which methodology is best, as they appear to be very similar in both. However, because ketonic Mannich bases are usually isolated as hydrochlorides, the approach that uses protic solvents has been preferred in this study. A mixture of water and ethanol is preferable to either water or ethanol as a protic medium for the substitution of the amine moiety in ketonic Mannich bases with nucleophiles, because an ethanol–water mixture dissolves both the ketonic Mannich base hydrochloride and the nucleophile, and provides a homogeneous reaction medium, but it is not a good solvent for the reaction product, which separates easily upon cooling. Therefore, all of the amine replacement reactions with ketonic Mannich base **4** as a substrate reported in this study have been conducted in a mixture of ethanol and water.

Under these reaction conditions, replacement of dimethylamino residue in Mannich base **4** by thiophenols leads to thioethers **5** and **6** (fig. 1). Upon slow cooling, sulfides **5** and **6** separate initially from the reaction mixture as heavy oils, which turn into solids upon further cooling in an ice bath. One recrystallization from small volumes of ethanol, in which they are quite soluble, affords good yields of pure thioethers **5** and **6**. The protons in the two methylene groups in compounds **5** and **6** do not appear as well resolved triplets in their proton NMR spectra, but rather coalesce into a single multiplet in the range of 3.25 to 3.35 ppm. The phenolic proton gives a sharp peak in the offset, at approximately 12 ppm, owing to its involvement in an intramolecular hydrogen bond with the neighbouring oxygen atom from the carbonyl function.

Despite the fact that indoles are known to be ambident nucleophiles (at N and C-3), several members of this class of heterocycles were selectively C-alkylated at position 3 by Mannich base **4**, under the same reaction conditions as thiophenols, to give indole–ketones **7**–**9** (fig. 1). Taking into consideration the lower nucleophilicity of indoles compared to thiophenols, the reaction time has been extended from 1 hour to 4 hours with the view to obtain good yields of reaction products. Nonetheless, even an extended reaction period afforded only moderate yields of reaction products in the case of indole and 1-methylindole, and poor yields when 5-bromoindole was used as a nucleophile. The proton spectra of compounds **7**–**9** presented two distinct triplets centered at approximately 3.2 and 3.4 ppm, which correspond to the protons in the methylene groups. Besides the signal in the offset associated with the phenolic proton, ^{1}H NMR spectra of indole–ketones **7** and **9** exhibit a broad singlet at approximately 8 ppm, which can be assigned to the hydrogen at the nitrogen atom in indole. The presence of this signal in the spectra of indole–ketones **7** and **9** proves that alkylation of N-unsubstituted indoles takes place selectively at C-3. This broad signal is absent from the proton spectrum of indole–ketone **8** derived from 1-methylindole.

The alkylation of various NH-heterocycles by Mannich base **4** has also been investigated. 4-Bromo-3,5-dimethylpyrazole, 1*H*-1,2,4-triazole, 4-phenylimidazole and benzotriazole served as nucleophiles from different classes of azoles, and all of them underwent N-alkylation with compound **4** smoothly to yield azole–ketones **10**–**13** (fig. 2). The yields of the reaction products were very good, except for compound **11** derived from 1*H*-1,2,4-triazole. However, as the yield for the crude azole–ketone **11** isolated from the reaction mixture was 61%, it is the high solubility of compound **11** in the recrystallization solvent that is responsible for the modest yield recorded for pure **11**, rather than the reduced reactivity of 1*H*-1,2,4-triazole compared to that of the other azoles that were employed in this study.

4-Bromo-3,5-dimethylpyrazole affords a single product in reaction with Mannich base **4**, but all other azoles used in this study could potentially lead to mixture of two regioisomers arising from different tautomeric forms of the same azole. However, the N-alkylation of 1*H*-1,2,4-triazole, 4-phenylimidazole and benzotriazole proceeded regioselectively, as only one regioisomer could be detected in crude reaction product by NMR. Compound **11** was assigned the structure of a 1,2,4-triazole alkylated at N-1 based on the presence of two singlets integrating

for one proton at 7.91 and 8.21 ppm; these singlets are associated with the two magnetically non-equivalent protons in the structure of a 1-substituted 1,2,4-triazole. The structure of azole–ketone **12** as a derivative of 4-phenylimidazole alkylated at N-1 was established using heteronuclear correlation spectroscopy. First, an HMQC experiment was performed with a view to assign the correct chemical shift values for H_a (4.43 ppm) (fig. 3a) and C_b (115.0 ppm) and C_c (137.8 ppm) (fig. 3b). Next, an HMBC experiment clearly showed that H_a strongly correlates with both C_b and C_c (fig. 3c), thus confirming that compound **12** is a derivative of 4-phenylimidazole alkylated at N-1. If azole–ketone **12** had been a derivative of 5-phenylimidazole alkylated at N-1, H_a would have correlated strongly with C_c, but there would have been only a weak correlation or no correlation at all between H_a and C_b. In the case of compound **13**, the presence in its proton spectrum of four distinct sets of signals found in the 7.33 to

8.04 ppm range rather than of two individual doublets of doublets is supportive for the structure of a benzotriazole substituted at N-1 [33].

Conclusions

Starting from 2' -hydroxyacetophenone, a series of novel 3-substituted-1-(2'-hydroxyphenyl)propan-1-ones have been synthesized through a two-step synthetic strategy comprising the aminomethylation of the starting material, followed by the replacement of the amino moiety with various nucleophiles. Two 3-(4-substituted-1-piperidinyl)-1-(2'-hydroxyphenyl)propan-1-ones have been obtained by the direct Mannich reaction of 2'-hydroxyacetophenone with 4-substituted piperidines as an example of the first step in the aforementioned synthetic strategy. The use in second step of the synthetic strategy of thiophenols, indoles and various NH-heterocycles as nucleophiles afforded nine novel 3-substituted-1-(2'-hydroxyphenyl)propan-1-ones that are potentially useful in the synthesis of heterocyclic compounds, the development of new ligands in metal complexes intended for various applications, or as biologically active compounds.

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