Tetrahedron Letters 55 (2014) 1229–1233

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Chemoselective aminomethylation of bifunctional substrates: carbonyl versus phenolic hydroxyl, carbonyl versus pyrazole and pyrrole versus phenolic hydroxyl as competing activating groups ☆

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ARTICLE INFO

Article history:
Received 1 October 2013
Revised 27 November 2013
Accepted 2 January 2014
Available online 10 January 2014

This Letter is dedicated with great admiration and affection to Professor Eugenia Comaniţă, teacher and mentor, in recognition of her achievements in Organic Chemistry

Keywords:
Chemoselectivity
Mannich reaction
Ketones
Phenols
Pyrazoles
Pyrroles

ABSTRACT

Chemoselectivity in the Mannich reaction for three different types of bifunctional substrates has been investigated. 1-Hydroxy-2-naphthalenylethanone affords either phenolic Mannich bases at high pH (free amines), or ketonic Mannich bases at low pH (amine hydrochlorides), whereas the use of *N*,*N*-dimethylmethyleneiminium chloride as a preformed dimethylaminomethylation reagent gave the phenolic Mannich base. 1-Aryl-3-(1*H*-pyrazol-1-yl)-1-propanones undergo aminomethylation at position 4 of the pyrazole ring, and not at the methylene group α to the carbonyl function, regardless of the reaction conditions. 4-(2,5-Dimethyl-1*H*-pyrrol-1-yl)phenol is aminomethylated chemoselectively on the pyrrole ring under mild reaction conditions.

Classical aminomethylation reactions (also known as Mannich reactions) are three-component condensations in which the substrate, a compound containing an active hydrogen atom, reacts with formaldehyde and an amine to produce a derivative of the substrate, usually referred to as Mannich base, in which the nitrogen atom of the amine is linked to the substrate through a methylene group. Not only are Mannich bases important to fundamental research, they also have a wide range of practical uses, ranging from detergents, flocculants, chelators and anticorrosion chemicals to radical inhibitors and crosslinking agents.[2] However, the most significant application of aminomethylation can be found in the field of pharmaceutical chemistry, as 30–40% of the papers reporting Mannich reactions are published in medicinal and pharmaceutical chemistry journals. Aminomethylation has played an important role in drug discovery, as shown by the large number of drugs whose synthesis employs the Mannich reaction as a key step, for example, molindone (antipsychotic), dyclonine (anaesthetic), eprazinone (antitussive), oxyfedrine (anti-anginal agent), amodiaquine, amopyroquine, bialamicol and clamoxyquin (antimalarials), pargyline (antihypertensive), morazone (analgesic) and hexetidine (antifungal).[3] Moreover, Mannich bases are precursors of other interesting classes of biologically active compounds such as amino alcohols, or can act as intermediates for the preparation of natural molecules such as alkaloids, hormones, vitamins, flavonoids, porphyrins or terpenoids.[4]

A wide range of substrates have been subjected to aminomethylation, and most of them belong to several classes of organic compounds that possess an activating group. To mention only a few of the most important substrates in aminomethylation and the corresponding activating groups, alkyl ketones feature a carbonyl group in their structure, phenols have at least one hydroxyl group, and aromatic heterocycles are activated by the presence of various heteroatoms.[5] General sets of reaction conditions for each type of substrate are available with the view to optimize the outcome of the Mannich reaction.[5] In the case of polyfunctional substrates that

☆ This communication is Part 24 in the series 'Synthesis and reactivity of Mannich bases'; for Part 23, see Ref. 1.

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0040-4039/$ - see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2014.01.005

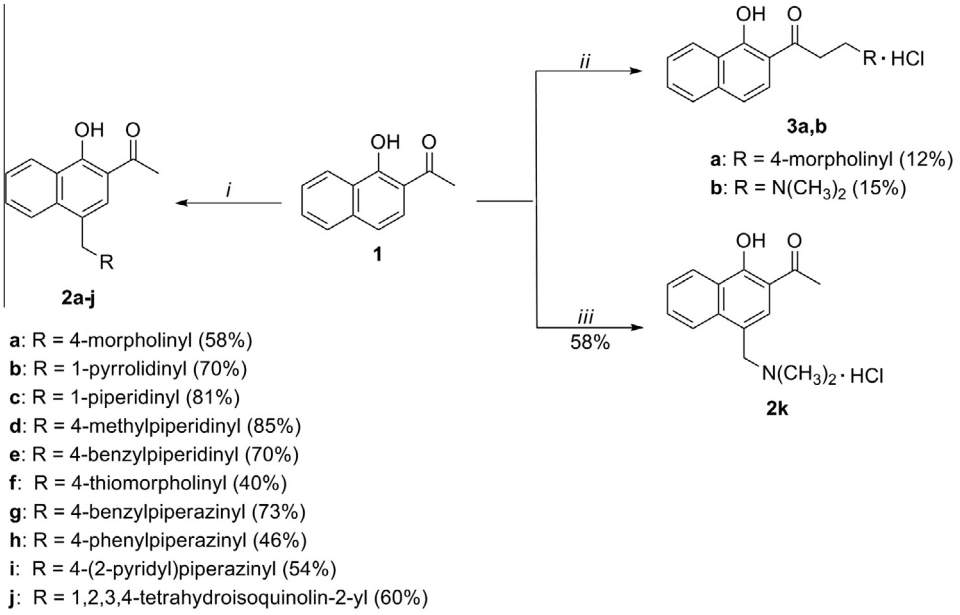
have different reactive sites capable of reacting with an aminomethylating agent, the direction of the Mannich reaction can be rationalized in terms of the relative reactivity of the reactive sites. Also, the aminomethylation may occur at a specific reactive site according to the particular reaction conditions that are employed. In a classical example, hydroxyaryl methyl ketones can be aminomethylated either at the carbon atom α to the carbonyl group or *ortho* to the phenolic hydroxyl, but chemoselective aminomethylation can normally be achieved by using the appropriate reaction conditions.[6] Acetylenic ketones, which have been aminomethylated either α to the carbonyl group in acidic medium, or at the ethynyl function in the presence of copper salts, represent another category of polyfunctional substrates that can undergo the Mannich reaction in a chemoselective manner.[7] In addition, *N*-propargylanilines have been aminomethylated either on the aromatic ring *para* to the amino group or at the propargyl moiety, depending on the reaction conditions.[8] Also, hydroxyindoles generally afford phenolic Mannich bases, but when the position *ortho* to the hydroxyl function is blocked, aminomethylation occurs at C-3 to give an indole Mannich base.[9] To the best of our knowledge, the literature on this topic appears to be limited to the types of substrates mentioned above. In an effort to understand better, and to gain further insight into the aminomethylation of polyfunctional substrates, the present Letter explores the chemoselectivity of the Mannich reaction for three distinct types of substrates, each of them featuring two different activating functional groups in their structure.

The first bifunctional substrate examined in terms of chemoselectivity under the Mannich reaction conditions belongs to the alkyl hydroxyaryl ketones, and features a carbonyl function and a phenolic hydroxyl as activating groups. Simple alkyl hydroxyaryl ketones (such as the isomeric hydroxyacetophenones) have been thoroughly investigated as substrates in aminomethylation reactions, and the formation of ketonic Mannich bases derived from hydroxyaryl methyl ketones has been shown to be favored by the use of amine hydrochlorides in the presence of catalytic amounts of acid,[10] whereas the use of free amines normally affords phenolic Mannich bases.[11,12] However, the application of a set of specific reaction conditions in the Mannich reaction of similar substrates does not always lead to reaction products having similar structures. For example, the aminomethylation of 2,4-dihydroxyacetophenone with morpholine hydrochloride at low pH produces high yields of the 3-substituted phenolic Mannich base instead of the expected ketonic Mannich base.[13] To further complicate the course of the Mannich reaction of this type of substrate, the proximity of the acetyl and hydroxyl groups in *ortho*-hydroxyacetophenones is known to lead to aminomethylated chromanones obtained through a sequence comprising the Mannich reaction of the substrate and ring-closure between the aforementioned groups in the presence of excess paraformaldehyde.[14] In contrast to hydroxyacetophenones, the Mannich reaction of hydroxynaphthalenylethanones appears to have been less investigated. A survey of the literature uncovered a paper by Okuda and Matsumoto[15] that reports the formation of a series of aminomethylated derivatives of 1-hydroxy-2-naphthalenylethanone (**1**) at high pH (free amines as amine reagents), to which they assigned the structure of the corresponding ketonic Mannich bases. Intrigued by the apparently abnormal behaviour of substrate **1** in the Mannich reaction, we decided to replicate the conditions used by the Japanese researchers (Scheme 1). When heated at reflux temperature in the presence of 37% formaldehyde (500 μL, 5.5 mmol), and morpholine (435 μL, 5 mmol) in ethanol (4 mL) for 2 h, substrate **1** (5 mmol) gave a yellow solid which, after one recrystallization from ethanol, melted at 126–127 °C (Osuka and Matsumoto[15] reported 124–126 °C for the compound arising from the same reaction). The NMR analysis of the isolated compound showed that aminomethylation of substrate **1** had occurred on the aromatic ring *para* to the phenolic hydroxyl to afford 1-[1-hydroxy-4-(morpholin-4-ylmethyl)-2-naphthalenyl]ethanone (**2a**), and not at the methylene α to the carbonyl function.[16] The use of a two-fold excess of formaldehyde and morpholine under the same reaction conditions raised the yield of **2a** to 85%; no other by-products could be detected in the crude reaction mixture by ^{1}H NMR. The same compound could be obtained, albeit in a lower yield (42%), when one equivalent of substrate **1** was reacted with one equivalent of morpholine and two equivalents of 37% aq formaldehyde in benzene at reflux temperature for 3 h.[17] The latter synthetic methodology was subsequently used to obtain a series of phenolic Mannich bases **2b**–**j** from other secondary aliphatic amines. It should be noted that diallylamine, *N*-methylbenzylamine and *N*-ethylbenzylamine did not react with substrate **1** under these conditions.

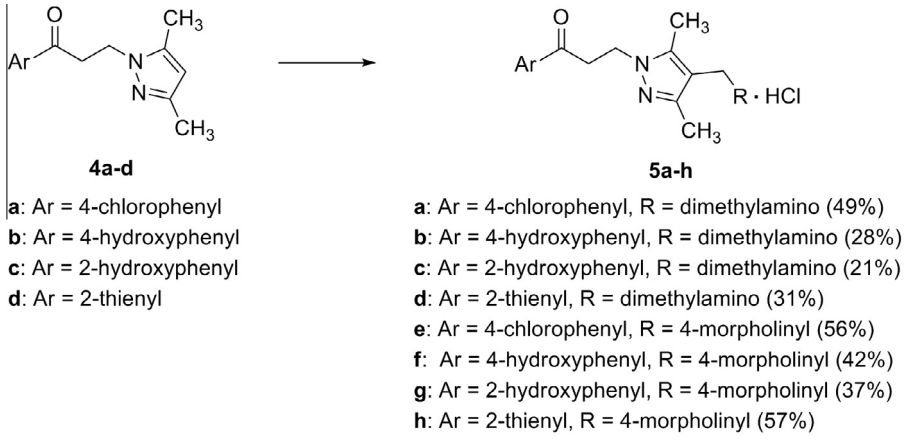
In order to obtain the ketonic Mannich base from **1**, the substrate was subjected to aminomethylation at low pH under the same conditions (1:2:1 molar ratio of substrate **1**, paraformaldehyde and morpholine hydrochloride, a catalytic amount of concd HCl, 2-propanol, reflux, 4 h)[12] that were successfully used for hydroxyacetophenones (Scheme 1). As the work-up afforded only a low yield (12%) of the desired 3-(morpholin-4-yl)-1-(1-hydroxy-2-naphthalenyl)-1-propanone hydrochloride (**3a**),[18] the reaction time was increased to 24 h, but the yield was improved only marginally. In addition, 1-(1-hydroxynaphthalen-2-yl)prop-2-en-1-one, a by-product formed from ketonic Mannich base **3a** through a deamination process due to prolonged heating, was detected by ^{1}H NMR in the solid isolated after work-up. No trace of the phenolic Mannich base **2a** (as a hydrochloride salt) could be identified in the proton NMR spectrum of crude **3a**, and the TLC analysis of the extract in ethyl acetate of the aqueous solution of crude **3a** after treatment with excess Na_2CO_3 [R_f 0.23 (EtOAc–hexanes, 1:1 v/v) for the free base of compound **3a**] showed no trace of compound **2a** (R_f 0.44, EtOAc–hexanes, 1:1 v/v). Replacement of morpholine hydrochloride with dimethylamine hydrochloride afforded **3b** in a yield comparable to that of Mannich base **3a**. Hence, the rule according to which alkyl hydroxyaryl ketones can be chemoselectively aminomethylated either at the carbon atom α to the carbonyl group or *ortho*/*para* to the phenolic hydroxyl, depending on the pH of the medium, applies to 1-hydroxy-2-naphthalenylethanone (**1**) as well.

Dissatisfied with the low yields of ketonic Mannich base **3a**, we decided to attempt to improve them and shorten the reaction time by employing a microwave-assisted variant of the reaction. An attempt to conduct a typical experiment as described previously[19] (2 mmol of substrate **1**, 2 mmol of paraformaldehyde, 2 mmol of morpholine hydrochloride in 4 mL of 1,4-dioxane at 180 °C for 500 s) using a CEM Discover reactor resulted in significant charring of the insoluble part of the reaction mixture (presumably the amine hydrochloride, which is also known to readily absorb microwaves). A second run under milder conditions (90 °C for 500 s) was accompanied by reduced charring of the insoluble part of the reaction mixture, but the work-up led only to the recovery of substrate **1**. Both the extensive charring and the failure to obtain any reaction products may be due to the limited solubility of morpholine hydrochloride in 1,4-dioxane.

Preformed aminomethylation reagents have become powerful tools in the Mannich reaction of various types of substrates.[20] Iminium salts (Eschenmoser's salt and the corresponding chloride salt, in particular) have been mostly employed for the preparation of ketonic Mannich bases,[21] although reports on the aminomethylation of phenols[22] as well as indoles[23] with these preformed Mannich reagents are also available. Even though both activating groups present in substrate **1** could potentially direct the Mannich reaction to either reactive site when iminium salts are employed as aminomethylating reagents, only the hydrochloride of the phenolic



Scheme 1. Chemoselective aminomethylation of 1-hydroxy-2-naphthalenylethanone (**1**). Reagents and conditions: (i) 37% aq formaldehyde, secondary aliphatic amine, benzene, reflux 3 h; (ii) paraformaldehyde, secondary aliphatic amine hydrochloride, 36% HCl, 2-propanol, reflux, 4 h; (iii) *N*,*N*-dimethylmethyleneiminium chloride, anhyd MeCN, reflux, 3 h.



Scheme 2. Chemoselective aminomethylation of 1-aryl-3-(1*H*-pyrazol-1-yl)-1-propanones **4**. Reagents and conditions: paraformaldehyde, secondary aliphatic amine hydrochloride, 36% HCl, 2-propanol, reflux, 4 h.

Mannich base **2k** was obtained in good yield (58%) by heating 1-hydroxy-2-naphthalenylethanone **1** and *N*,*N*-dimethylmethyleneiminium chloride at reflux temperature in anhydrous acetonitrile for 3 h (Scheme 1).[24] Under these conditions, **1** was chemoselectively aminomethylated *para* to the hydroxyl function, thus providing an indication that the phenolic hydroxyl is a stronger activating group in the Mannich reaction of substrate **1** than the carbonyl function.

The chemoselectivity in the Mannich reaction was also investigated for a bifunctional substrate that has a carbonyl function and a pyrazole ring as activating groups. Given our previous experience on the synthesis of 1-aryl-3-(1*H*-pyrazol-1-yl)-1-propanones,[1,25] we decided that these compounds, in which the activating groups are separated by two methylene groups, would serve adequately as models for this type of substrate. It is well known that acetophenones (a type of substrate among alkyl aryl ketones which has been heavily employed in the Mannich reaction) aminomethylate smoothly. Furthermore, substitution of the carbon atom α to the carbonyl function with alkyl,[26] aryl[27] or aryloxy[28] moieties does not appear to affect significantly the reactivity of these substrates in the Mannich reaction. Although the literature contains a wealth of information on the Mannich reaction of alkyl aryl ketones, reports on aminomethylation of pyrazoles are scarce.[29,30] According to these reports, 3,5-dimethylpyrazole and its analogues substituted at N-1 can be aminomethylated at C-4 either with free amines[29] at high pH, or with amine hydrochlorides at low pH.[30] As the latter reaction conditions are usually employed for the aminomethylation of ketones as well, the Mannich reaction of 1-(4-chlorophenyl)-3-(3,5-dimethyl-1*H*-pyrazol-1-yl)propan-1-one (**4a**) with dimethylamine hydrochloride was examined under these conditions, which lead chemoselectively to aminomethylated pyrazole derivative **5a**.[31] The limitation of the Mannich reaction with this type of substrate under identical conditions was also examined briefly. Substrates **4b–d** featuring 4-hydroxyphenyl, 2-hydroxyphenyl and 2-thienyl moieties instead of a 4-chlorophenyl residue afforded the corresponding 4-dimethylaminomethylated pyrazoles **5b–d** in fair to good yields (Scheme 2). The replacement of dimethylamine hydrochloride with morpholine hydrochloride

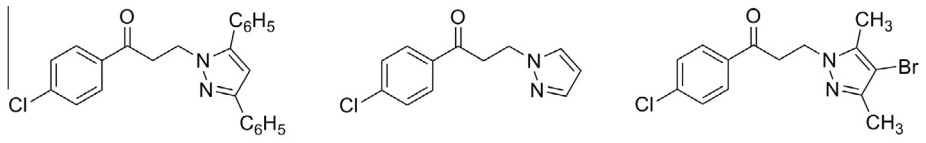
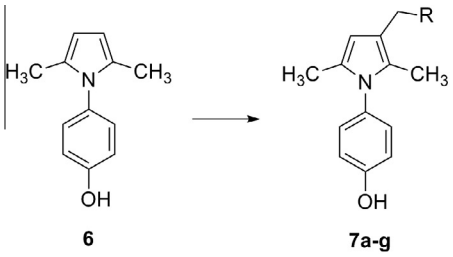


Figure 1. 1-(4-Chlorophenyl)-3-(1*H*-pyrazol-1-yl)-1-propanones **4e**–**g** as examples of unreactive substrates in the Mannich reaction.



a: R = piperidinyl (49%)
b: R = 4-morpholinyl (52%)
c: R = 4-thiomorpholinyl (46%)
d: R = pyrrolidinyl (52%)
e: R = 4-phenylpiperazinyl (44%)
f: R = 4-(2-pyridyl)piperazinyl (42%)
g: R = diethylamino (43%)

Scheme 3. Chemoselective aminomethylation of 4-(2,5-dimethyl-1*H*-pyrrol-1-yl)phenol (**6**). Reagents and conditions: 37% aq formaldehyde, secondary aliphatic amine, EtOH, rt, 5 d.

as the amine reagent afforded consistently better yields of Mannich bases **5**. Substitution of the 3,5-dimethyl-1*H*-pyrazol-1-yl with a 3,5-diphenyl-1*H*-pyrazol-1-yl moiety as in substrate **4e**, or with a 1*H*-pyrazol-1-yl moiety as in substrate **4f** (Fig. 1) rendered the pyrazole residue unreactive towards aminomethylation under the same conditions. While steric hindrance at the reactive site could be deemed responsible for the lack of reactivity of the phenyl-substituted pyrazole, it could however not be the reason for the lack of reactivity of the unsubstituted pyrazole derivative. These results suggest that the aminomethylation of the pyrazole ring is governed by electronic effects rather than by steric factors. Interestingly, no trace of a ketonic Mannich base was detected in the experiments using substrates with phenyl-substituted or unsubstituted pyrazole, even when aminomethylation did not occur on the pyrazole ring. In addition, 1-(4-chlorophenyl)-3-(4-bromo-3,5-dimethyl-1*H*-pyrazol-1-yl)propan-1-one (**4g**), a substrate having a structure similar to compounds **4a**–**d**, but presenting the methylene α to the carbonyl function as the sole reactive site, was completely unreactive in the Mannich reaction under the conditions normally employed for **4a**–**d**. Also, no Mannich base could be isolated even when *N*,*N*-dimethylmethyleneiminium chloride was used as the aminomethylating reagent with substrate **4g**. On the other hand, substrate **4a** reacted easily with the same preformed aminomethylating reagent in acetonitrile at reflux temperature to afford Mannich base **5a** in excellent yield (95%). Thus, not only is 3,5-dimethylpyrazole highly reactive at position 4 in the Mannich reaction, but it seems to also deactivate the carbon atom α to the carbonyl function in the 3-aryl-3-oxopropyl appendage in substrates **4** towards aminomethylating species.

The third type of bifunctional substrate whose reactivity in the Mannich reaction has been under scrutiny in this study has a phenolic hydroxyl and a pyrrole ring as activating functions. An inspection of the literature provides numerous examples of the Mannich reaction with commonly substituted phenols, naphthols or phenols fused with various heterocyclic ring systems, and the usual experimental procedure involves the use of aqueous formaldehyde as the aldehyde component and a free amine as the amine reagent. As mentioned in a previous review,[32] the Mannich reaction of pyrroles is best performed either with free amines, usually in the presence of acetic acid, or with amine hydrochlorides. 4-(2,5-Dimethyl-1*H*-pyrrol-1-yl)phenol (**6**) was chosen as a model compound for the exploration of the Mannich reaction of this type of bifunctional substrate, especially as compound **6** has already been reported to lead to the corresponding phenolic Mannich bases upon treatment with formaldehyde and diethylamine.[33] In the initial experiment, we decided to replace diethylamine with a more reactive secondary aliphatic amine, and to simplify and adapt the general experimental procedure to our particular substrate. Under very mild reaction conditions, aminomethylation with piperidine as the amine reagent occurred at one of the free β positions of the pyrrole ring to produce Mannich base **7a**,[34] and not *ortho* to the phenolic hydroxyl (Scheme 3). The replacement of piperidine with other secondary aliphatic amines led to the same type of Mannich bases. Although the attack of the aminomethylating species normally takes place at the more reactive α position in pyrroles, examples of the Mannich reaction of 2,5-disubstituted pyrroles at the free β positions are well known.[35] The results obtained for this particular type of substrate indicate that the phenolic hydroxyl is a weaker activating group than the nitrogen in pyrrole, even under the appropriate reaction conditions for the aminomethylation of phenols, and that the Mannich reaction of **6** proceeds chemoselectively on the pyrrole ring even in the absence of acetic acid, the catalyst normally employed in the synthesis of aminomethylated pyrroles. For the sake of comparison, the aminomethylation of 4-(1*H*-pyrrol-1-yl)phenol under the same reaction conditions employed for **6** was briefly explored, and the unreacted starting material was determined by TLC to be the major component of the reaction mixture after five days. Several reaction products were also present as minor components of the mixture, but the investigation of the identity of these products was not pursued any further owing to their insignificant contribution to the mixture. The dissimilar reactivity of **6** and 4-(1*H*-pyrrol-1-yl)phenol under these mild aminomethylation conditions parallels the difference noted in the reactivity of 2,5-dimethyl-1-phenyl-1*H*-pyrrole and 1-phenyl-1*H*-pyrrole in the Mannich reaction under slightly more enforcing conditions.[36]

In conclusion, the influence of the activating groups on the direction of the Mannich reaction was investigated in three types of bifunctional substrates. In the case of 1-hydroxy-2-naphthalenylethanone, aminomethylation takes place either on the aromatic ring *para* to the phenolic hydroxyl when free amines are used (high pH), or at the methylene group α to the carbonyl function at low pH (with amine hydrochlorides as amine reagents). On the other hand, the use of *N*,*N*-dimethylmethyleneiminium chloride, a

preformed Mannich reagent capable of aminomethylating both phenols and ketones, gave the hydrochloride of the phenolic Mannich base of 1-hydroxy-2-naphthalenylethanone, which suggests that, in this particular case, the phenolic hydroxyl is a stronger activating group than the carbonyl function. The direct Mannich reaction of a series of 1-aryl-3-(1*H*-3,5-dimethylpyrazol-1-yl)-1-propanones proceeded in a chemoselective manner to afford the corresponding pyrazoles aminomethylated at position 4 in fair yields, which could be improved significantly by the use of *N*,*N*-dimethylmethyleneiminium chloride as the aminomethylating reagent. However, this type of substrate failed to react either on the pyrazole ring or at the methylene group α to the carbonyl function when the 3,5-dimethylpyrazole moiety was replaced with pyrazole, 3,5-diphenylpyrazole or 4-bromo-3,5-dimethylpyrazole. Finally, the aminomethylation of 4-(2,5-dimethyl-1*H*-pyrrol-1-yl)phenol occurred at one of the free β positions on the pyrrole ring under mild reaction conditions, indicating that the nitrogen atom in the pyrrole is a stronger activating group than the phenolic hydroxyl in this type of bifunctional substrate.

Acknowledgments

This work was supported by the European Union's Seventh Framework Programme (FP7/2007–2013) under grant agreement No. 264115—STREAM.

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16. *Compound* ***2a***: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.50 (br s, 4H), 2.70 (s, 3H), 3.69 (t, J = 4.4 Hz, 4H), 3.79 (br s, 2H), 7.49–7.61 (m, 2H), 7.63–7.72 (m, 1H), 8.23 (d, J = 8.4 Hz, 1H), 8.48 (d, J = 8.4 Hz, 1H), 13.98 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.7, 27.0, 54.5, 58.5, 112.6, 124.6, 124.8, 125.1, 125.6, 125.8, 126.0, 130.2, 136.6, 162.2, 204.4. Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.79; H, 6.98; N, 4.66.
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18. *Compound* ***3a***: Mp 218–219 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.17 (br s, 2H), 3.53 (t, J = 6.8 Hz, 4H), 3.81 (t, J = 6.8 Hz, 4H), 4.00 (br s, 2H), 7.50 (d, J = 8.8 Hz, 1H), 7.62 (t, J = 7.6 Hz, 1H), 7.75 (t, J = 7.2 Hz, 1H), 7.93 (m, 2H), 8.35 (d, J = 8.0 Hz, 1H), 10.73 (br s, 1H), 13.57 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 32.8, 42.7, 51.4, 63.3, 112.7, 118.7, 123.7, 124.2, 124.8, 126.5, 127.8, 130.5, 137.0, 160.9, 203.0. Anal. Calcd for $C_{17}H_{20}ClNO_3$: C, 63.45; H, 6.26; N, 4.35. Found: C, 63.74; H, 6.02; N, 4.11.
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24. *Compound* ***2k***: Mp 210–211 °C (EtOH); ^{1}H NMR (CD_3OD, 400 MHz): δ 2.77 (s, 3H), 2.94 (s, 6H), 4.77 (s, 2H), 7.63–7.70 (m, 1H), 7.82–7.89 (m, 1H), 8.14–8.20 (m, 2H), 8.52 (dd, J = 0.8 and 8.4 Hz, 1H); ^{13}C NMR (CD_3OD, 100 MHz): δ 27.2, 43.2, 58.4, 113.9, 117.7, 124.3, 126.1, 126.8, 127.7, 132.6, 132.7, 136.8, 164.3, 206.2. Anal. Calcd for $C_{15}H_{18}ClNO_2$: C, 64.40; H, 6.49; N, 5.01. Found: C, 64.62; H, 6.17; N, 4.75.
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31. *Representative procedure for* ***5***: A mixture of 1-(4-chlorophenyl)-3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-1-propanone (**4a**) (1050 mg, 4 mmol), paraformaldehyde (240 mg, 8 mmol), dimethylamine hydrochloride (360 mg, 4.4 mmol) and 36% aq HCl (4 drops) in 2-propanol (10 mL) was heated at reflux temperature for 4 h. The solvent was removed under reduced pressure, and the residue was diluted with EtOAc (25 mL) with vigorous stirring. The resulting solid was filtered and recrystallized from EtOH to give 1-(4-chlorophenyl)-3-(4-dimethylaminomethyl-3,5-dimethyl-1*H*-pyrazol-1-yl)-1-propanone hydrochloride (**5a**) as colorless crystals (625 mg, 49%), mp 198–199 °C; ^{1}H NMR (D_2O, 400 MHz): δ 2.21 (s, 3H), 2.33 (s, 3H), 2.74 (s, 6H), 3.56 (t, J = 6.0 Hz, 2H), 4.12 (s, 2H), 4.49 (t, J = 6.0 Hz, 2H), 7.45 (d, J = 8.8 Hz, 2H), 7.79 (d, J = 8.8 Hz, 2H); ^{13}C NMR (D_2O, 100 MHz): δ 9.3, 10.4, 37.7, 41.6, 44.4, 49.9, 106.3, 129.0, 129.8, 134.2, 140.1, 143.6, 148.5, 200.7. Anal. Calcd for $C_{17}H_{23}Cl_2N_3O$: C, 57.31; H, 6.51; N, 11.79. Found: C, 57.56; H, 6.23; N, 11.55.
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34. *Representative procedure for* ***7***: A mixture of 4-(2,5-dimethyl-1*H*-pyrrol-1-yl)phenol (**6**) (935 mg, 5 mmol), 37% formaldehyde (0.7 mL) and piperidine (425 mg, 5 mmol) in EtOH (3 mL) was kept at room temperature for 5 d. The solid that gradually separated was filtered, washed with cold EtOH and recrystallized to give 4-(2,5-dimethyl-3-(piperidin-1-ylmethyl)-1*H*-pyrrol-1-yl)phenol (**7a**) as tan crystals (695 mg, 49%), mp 208–209 °C (EtOH); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.30–1.51 (m, 6H), 1.86 (s, 3H), 1.90 (s, 3H), 2.30 (br s, 4H), 3.16 (s, 2H), 5.70 (s, 1H), 6.83 (d, J = 8.8 Hz, 2H), 6.99 (d, J = 8.8 Hz, 2H), 9.69 (br s, 1H, exchangeable with D); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 10.6, 12.6, 24.2, 25.6, 53.7, 55.0, 107.7, 114.5, 115.6, 125.7, 126.5, 129.1, 129.6, 156.7. Anal. Calcd for $C_{18}H_{24}N_2O$: C, 76.02; H, 8.51; N, 9.85. Found: C, 75.71; H, 8.33; N, 9.94.
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