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Papers

NOVEL AMINOBENZENESULFONAMIDES AS POTENTIAL INHIBITORS OF CARBONIC ANHYDRASES**

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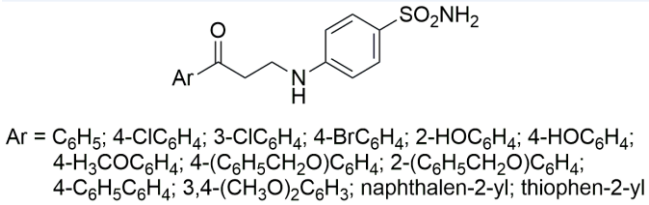
A synthetic approach to *N*-[3-(hetero)aryl-3-oxoprop-1-yl]sulfonamides by *N*-alkylation of sulfanilamide with structurally diverse ketone Mannich base hydrochlorides is being reported. This scarcely explored synthetic strategy that involves aminomethylated ketones as starting materials has afforded novel compounds, potentially useful as inhibitors of carbonic anhydrases, with moderate to good yields.



INTRODUCTION

The rich chemistry of Mannich bases, a structurally heterogeneous class of organic compounds that are produced through the direct aminomethylation of diverse types of substrates that have at least an active hydrogen atom in their structure, has been well-established in the century that has elapsed since the discovery of the Mannich reaction.[1,2] One important feature in the chemistry of Mannich bases is their ability to alkylate a wide range of organic compounds such as alcohols, thiols, amines or heterocyclic compounds. Out of these mechanistically similar kinds of alkylation using Mannich bases, *N*-alkylations allow the replacement in the structure of aminomethylated substrates **1** (which are easily obtained through a direct Mannich reaction) of a common secondary aliphatic amine moiety (such as dimethylamino) with other amines that are less reactive (*e.g.*, arylamines[3,4], Scheme 1) or with *NH*-heterocycles.[5,6]. This synthetic strategy represents a facile and valuable alternative to recently reported direct Mannich reactions using arylamines[7–9] to afford access in a simple manner and in high yields and purity to β-arylamino ketones **2** that have been shown, for example, to possess interesting biological activities,[10–12] or may act as intermediates in the synthesis of other organic compounds.[13,14] While numerous and structurally diverse arylamines have been employed in amine exchange reactions with ketone Mannich bases, no reports dealing with the use of sulfanilamide (4-aminobenzenesulfonamide) in this particular type of reaction are available, to the best of our knowledge. On the other hand, the benzenesulfonamide moiety represents an important

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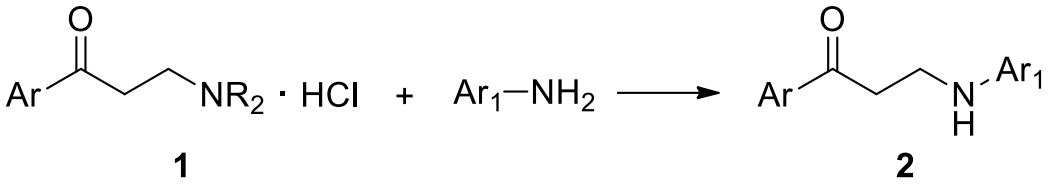
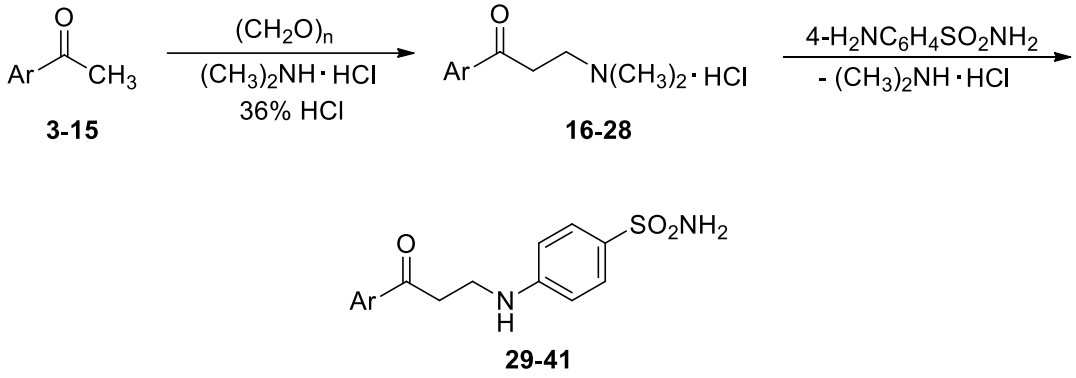
pharmacophore that is present in the structure of many inhibitors of carbonic anhydrases, whose selectivity towards a specific isoform could be tailored through the substitution of the benzenesulfonamide scaffold by specific groups through the "tail approach".[15] Building on our interest in the chemistry and uses of ketone Mannich bases,[5,6,16–19] the present study aims at investigating the *N*-alkylation of sulfanilamide with ketone Mannich bases, a process that is particularly significant as it allows the attachment to the benzenesulfonamide moiety of a 1-arylpropan-1-one "tail" that has the intrinsic potential to be further chemically modified, and leads also to novel derivatives whose activity towards carbonic anhydrases has not been evaluated yet.



Scheme 1 – Synthesis of an arylamine-containing ketone Mannich base **2** by replacement of the dialkylamino group in a ketone Mannich base hydrochloride **1** by an arylamino moiety.

RESULTS AND DISCUSSION

With the aim of gleaning information on the influence of the nature of the 2-(aroyl)ethyl moiety on the biological activity of the target *N*-alkylated aminobenzenesulfonamides **29**–**41**, a large number of ketone Mannich bases have been employed in the *N*-alkylation of sulfanilamide (Scheme 2). The intermediate Mannich bases **16**–**28** have been synthesized by the direct aminomethylation of the corresponding appropriately substituted aryl methyl ketones **3**–**14**, or through the direct Mannich reaction of 2-acetylthiophene **15** in the case of Mannich base **28**. The aminomethylation of the starting ketones was performed by heating the ketone substrate with 2 equivalents of paraformaldehyde and 1.1 equivalents of dimethylamine hydrochloride in 2-propanol for 4 hours as described for analogous substrates.[17,18] The resulting ketone Mannich bases separated from the reaction mixture upon dilution with acetone and refrigeration as crystalline solids that were sufficiently pure for the next stage, according to their proton NMR spectra. Most of the intermediate β-amino ketone hydrochlorides in this work are known compounds that have been properly characterized from a structural point of view in the recent literature, while the structural characterization for ketone Mannich bases hydrochlorides **18**, **23**, **24** and **25** that have been described either in the patent literature, or in older or less accessible journals is given herein. The proton spectra of ketone Mannich base hydrochlorides **16**–**28** present in the range from 2.5 ppm to 3.0 ppm a singlet integrating for six protons that is assigned to the magnetically equivalent protons in the dimethylamine moiety, while the protons in the methylene groups linking the dimethylamine moiety and the ketone function in compounds **16**–**28** appear as two triplets in interval between 3.3 ppm and 3.7 ppm in the same spectra. The labile proton attached to the positively charged nitrogen atom generally gives a broad singlet in the off-set of proton spectra that are recorded in deuterated dimethylsulfoxide, but no signal is noticeable in this region when the same spectra are recorded in deuterated water. Introduction of the dimethylaminomethyl moiety in the structure of ketone Mannich bases hydrochlorides **16**–**28** through aminomethylation of substrates **3**–**15** has been confirmed by the presence of three signals in the aliphatic region of their carbon spectra. The most upfield peak of these three characteristic signals can usually be found at approximately 33 ppm in the carbon spectra of these intermediates, and has been associated with the carbon atom in the methylene group adjacent to the carbonyl function. In the case of Mannich bases **20**[17] and **24**, the peak for this particular carbon atom is slightly deshielded (35.0 ppm[17] and 38.1 ppm, respectively), presumably owing to the presence of the substituent in the aromatic ring *ortho* to the carbonyl function. The remaining two signals that have been identified in the aliphatic region of the carbon spectra of ketone Mannich base hydrochlorides **16**–**28** correspond to the carbon atoms adjacent to the positively charged nitrogen atom, the peak that has been assigned to the carbon atom in the dimethylamino group being more shielded than the peak associated with the carbon atom in the methylene group.



3-15 **16-28** **29-41**

3, **16**, **29**: Ar = C_6H_5;
4, **17**, **30**: Ar = 4-ClC_6H_4;
5, **18**, **31**: Ar = 3-ClC_6H_4;
6, **19**, **32**: Ar = 4-BrC_6H_4;
7, **20**, **33**: Ar = 2-HOC_6H_4;
8, **21**, **34**: Ar = 4-HOC_6H_4;
9, **22**, **35**: Ar = 4-$H_3COC_6H_4$;
10, **23**, **36**: Ar = 4-$C_6H_5CH_2OC_6H_4$;
11, **24**, **37**: Ar = 2-$C_6H_5CH_2OC_6H_4$;
12, **25**, **38**: Ar = 3,4-$(CH_3O)_2C_6H_3$;
13, **26**, **39**: Ar = 4-$C_6H_5C_6H_4$;
14, **27**, **40**: Ar = naphthalen-2-yl;
15, **28**, **41**: Ar = thiophen-2-yl

Scheme 2 – Reaction sequence leading to sulfonamides **29**–**41** *N*-substituted with a 3-(hetero)aryl-3-oxoprop-1-yl "tail".

Replacement of the easily leaving dimethylamino group in ketone Mannich bases hydrochlorides **16**–**28** with sulfanilamide has been conducted in a mixture ethanol–water, which provides a homogeneous reaction medium for both reactants, while allowing the facile separation of the insoluble reaction product by filtration. Most of the resulting sulfonamides come out of solution at some point as the reaction proceeds, but refrigeration of the reaction mixture overnight was required in some cases in order for a solid material to separate. Initially, a reaction time of 1 h was considered to be adequate, as proven by the good results that were previously obtained for *N*-alkylation of other arylamines with ketone Mannich bases hydrochlorides.[20,21] While sulfonamides **29**–**33** were obtained with moderate (albeit satisfactory) yields under these conditions, a reaction time of only 1 h led to dissatisfyingly low yields in the case of compounds **35** and **38** (27% and 17%, respectively). Because it was hypothesized that the presence of alkoxy groups in the structure of the ketone Mannich base hydrochloride is responsible for these low experimental yields, the reaction time was extended to 2 h in the preparation of sulfonamides **36** and **37** (which are also synthesized using alkoxy-substituted Mannich bases), when the yields of isolated reaction products reached approximately 35%. A reaction time of 1 h also resulted in unacceptably low yields of sulfonamide **34** with a *para* hydroxy group in the aromatic ring introduced *via* the Mannich base, which is surprising since the isomeric sulfonamide **33** featuring an *ortho* hydroxy group was obtained with good yields under the same conditions. However, an extension of reaction time to 3 h afforded the desired sulfonamide **34** with improved yields that were close to 40%. The reaction time was extended to 3 h in the case of sulfonamide **39** as well, since the amount of reaction product that separated after the reaction mixture had been heated at reflux temperature for 1 h was deemed to be too slight by visual observation. Several attempts have been made to purify some of the isolated sulfonamides through recrystallization, but this process usually required large volumes of 96% ethanol. An inspection of the proton NMR spectra of the crude sulfonamides **29**, **30**, **35** and **37** showed that the isolated materials were practically devoid of impurities, and a comparison between the proton spectra of the crude and purified samples of each of these sulfonamides also demonstrated that they were identical. Therefore, purification of the rest of the products was instead attempted by briefly heating them at reflux temperature with a little 96% ethanol with a view to facilitate the extraction of any potential unreacted starting materials or reaction by-products (such as aryl vinyl ketones arising from the thermally-promoted deaminomethylation of the ketone Mannich base hydrochlorides). Examination by NMR of the products obtained by following this procedure proved that they were virtually devoid of detectable impurities.

The proton NMR spectra of sulfonamides **29**–**41** present several characteristics signals that have been identified for each of these compounds. First, the

two protons in the methylene group adjacent to the carbonyl give a triplet that could be usually evidenced in the range of 3.2 to 3.4 ppm, with the exception of compound **40** having a naphthalen-2-yl moiety, for which these signals are slightly deshielded and superimpose the signals of the two protons in the methylene group adjacent to the secondary amino function. Second, the protons in the methylene group adjacent to the secondary amino function appear as a multiplet between approximately 3.4 and 3.5 ppm. The third characteristic signal in the proton spectra of compounds **29**–**41** is the triplet at approximately 6.4 ppm and integrating for one proton, which has been associated with the hydrogen atom of the secondary amino function. Finally, the fourth characteristic signal in the proton spectra of the target sulfonamides is the singlet at approximately 6.9 ppm and integrating for two protons, which has been assigned to the hydrogen atoms of the sulfonamido function. The correct number of aromatic protons has been found for all the newly synthesized compounds **29**–**41**, while the aromatic protons in sulfonamide moiety have been ascribed the doublets at approximately 6.6 ppm (for protons *ortho* to the secondary amino function) and 7.5 ppm (for protons *ortho* to the sulfonamido function). The characteristic signals in the carbon NMR spectra of sulfonamides **29**–**41** are the peaks at approximately 37 and 38 ppm given by the two aliphatic carbon atoms of the methylene groups in the oxopropyl linker between the aromatic moieties of these sulfonamides. As an exception, a slight deshielding of approximately 4 ppm of the peak associated with the carbon atom in the methylene group adjacent to the carbonyl was noticed for compound **37**, presumably owing to the close spatial proximity of the bulky benzyloxy substituent.

EXPERIMENTAL

Materials and methods

All reagents and solvents were purchased from commercial suppliers (Sigma–Aldrich, TCI Europe N.V., Merck KGaA) and were used without further purification. Melting points were taken on a Mel Temp II apparatus and are uncorrected. NMR spectra were recorded on a Bruker Avance NEO spectrometer at 400 MHz, with a 5 mm probe for direct detection of H, C, F, Si. The residual signals of the deuterated solvents were used as internal standard (DMSO-d_6: δ = 2.51 ppm for ^{1}H and δ = = 39.47 ppm for ^{13}C).

4-(Benzyloxy)acetophenone **10** was prepared through the reaction of 4-hydroxyacetophenone and benzyl chloride in the presence of KOH in 96% ethanol as previously described.[22] 2-(Benzyloxy)acetophenone **11** was obtained by *O*-alkylation of 2′-hydroxyacetophenone with benzyl chloride in the presence of KOH in 96% ethanol.[23] The following known ketone Mannich base hydrochlorides were synthesized through the general procedure given in Experimental, and their structure and purity was checked through ^{1}H NMR experiments and determination of their melting points: 3-(dimethylamino)-1-phenyl-1-propanone hydrochloride **16** (mp 153–154 °C; lit.[24] mp 153.6–153.7 °C); 1-(4-chlorophenyl)-3-(dimethylamino)-1-propanone hydrochloride **17** (mp 173–174 °C; lit.[25] mp 172.5–173.5 °C); 1-(4-bromophenyl)-3-(dimethylamino)-1-propanone hydrochloride **19** (mp 194–195 °C; lit.[26] mp 193 °C); 3-(dimethylamino)-1-(2-hydroxyphenyl)-1-propanone hydrochloride **20** (mp 174–175 °C; lit.[17] mp 175–176 °C); 3-(dimethylamino)-1-(4-hydroxyphenyl)-1-propanone hydrochloride **21** (mp 199–200 °C; lit.[27] mp 192 °C); 3-(dimethylamino)-1-(4-methoxyphenyl)-1-propanone hydrochloride **22** (mp 183–184 °C; lit.[28] mp 184–186 °C); 1-(4-biphenyl-1-yl)-3-(dimethylamino)-1-propanone hydrochloride **26** (mp 187–188 °C; lit.[29] mp 191–192 °C); 3-(dimethylamino)-1-(naphthalen-2-yl)-1-propanone hydrochloride **27** (mp 174–175 °C; lit.[30] mp 168 °C), and 3-(dimethylamino)-1-(thiophen-2-yl)-1-propanone hydrochloride **28** (mp 184–185 °C; lit.[31] mp 184 °C).

Synthesis of ketone Mannich bases hydrochlorides – General procedure

A mixture of substituted (hetero)aryl methyl ketone (10 mmole), paraformaldehyde (600 mg, 20 mmole), dimethylamine hydrochloride (892 mg, 11 mmole) and 37% HCl (3 drops) in 2-propanol (5 mL) was heated at reflux temperature for 4 h. The mixture was allowed to cool to 50–60 °C, then acetone (45 mL) was gradually added under efficient stirring. Refrigeration overnight afforded a precipitate, which was filtered, washed with acetone, air-dried and recrystallized to give the desired ketone Mannich base hydrochlorides, which were sufficiently pure for the next stage. Analytical samples of the new compounds (**18** and **23**–**25**) were recrystallized from 96% ethanol prior to NMR analysis.

1-(3-Chlorophenyl)-3-(dimethylamino)-1-propanone hydrochloride (**18**)

This compound was obtained from 3-chloroacetophenone **5** as colorless crystals (1.96 g, 79%), mp 200–201 °C (lit.[32] mp 193–195 °C); ^{1}H NMR (DMSO-d_6): δ 2.81 (s, 6H), 3.39 (t, *J* = 7.2 Hz, 2H), 3.63 (t, *J* = 7.2 Hz, 2H), 7.61 (dd, *J* = 8.0 and 8.4 Hz, 1H), 7.77 (dd, *J* = 1.2 and 8.0 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 8.04 (t, *J* = 1.6 Hz, 1H), 10.40 (br s, 1H, exchangeable with D); ^{13}C NMR (DMSO-d_6): δ 33.3, 42.2, 51.5, 126.6, 127.8, 130.8, 133.3, 133.7, 137.7, 195.7.

1-[4-(Benzyloxy)phenyl]-3-(dimethylamino)-1-propanone hydrochloride (**23**)

This compound was obtained from 4-(benzyloxy)acetophenone **10** as colorless crystals (1.76 g, 55%), mp 154–156 °C (lit.[33] mp 167–169 °C); ^{1}H NMR (DMSO-d_6): δ 2.78 (s, 6H), 3.37 (t, *J* = 7.2 Hz, 2H), 3.57 (t, *J* = 7.2 Hz, 2H), 5.23 (s, 2H), 7.16 (d, *J* = 8.8 Hz, 2H), 7.31–7.37 (m, 1H), 7.37–7.44 (m, 2H), 7.47 (d, *J* = 7.2 Hz, 2H), 7.99 (d, *J* = 8.8 Hz, 2H), 10.79 (br s, 1H, exchangeable with D); ^{13}C NMR (DMSO-d_6): δ 32.7, 42.2, 51.9, 69.6, 114.8, 127.8, 128.1, 128.5, 129.0, 130.4, 136.4, 162.6, 195.1

1-[2-(Benzyloxy)phenyl]-3-(dimethylamino)-1-propanone hydrochloride (**24**)

This compound was obtained from 2-(benzyloxy)acetophenone **11** as colorless crystals (1.5 g, 47%), mp 149–150 °C; ^{1}H NMR (DMSO-d_6): δ 2.62 (s, 6H), 3.31 (t,

J = 7.2 Hz, 2H), 3.49 (t, *J* = 7.2 Hz, 2H), 7.07 (t, *J* = 7.2 Hz, 1H), 7.30 (d, *J* = 8.8 Hz, 1H), 7.32–7.39 (m, 1H), 7.39–7.47 (m, 2H), 7.54–7.62 (m, 3H), 7.69 (d, *J* = 7.6 Hz, 1H), 10.89 (br s, 1H, exchangeable with D); ^{13}C NMR (DMSO-d_6): δ 38.1, 41.9, 51.7, 70.2, 113.8, 120.7, 126.7, 128.1, 128.2, 128.6, 129.9, 134.4, 136.3, 157.7, 197.3.

3-(Dimethylamino)-1-[3,4-(dimethoxy)phenyl]propan-1-one hydrochloride (**25**)

This compound was obtained from 3,4-dimethoxyacetophenone **12** as colorless crystals (2.24 g, 82%), mp 179–180 °C (lit.[34] mp 181–182 °C); ^{1}H NMR (DMSO-d_6): δ 2.80 (s, 6H), 3.38 (t, *J* = 7.6 Hz, 2H), 3.60 (t, *J* = 7.6 Hz, 2H), 3.84 (s, 3H), 3.87 (s, 3H), 7.12 (d, *J* = 8.8 Hz, 1H), 7.49 (d, *J* = 2.0 Hz, 1H), 7.71 (dd, *J* = 1.6 and 8.4 Hz, 1H), 10.95 (br s, 1H, exchangeable with D); ^{13}C NMR (DMSO-d_6): δ 32.7, 42.1, 51.9, 55.6, 55.8, 110.2, 110.9, 123.0, 128.9, 148.6, 153.5, 195.1.

Synthesis of *N*-alkylated aminobenzenesulfonamides – General procedure

A mixture of ketone Mannich base hydrochloride (4 mmole) and sulfanilamide (688 mg, 4 mmole) in a mixture of 96% ethanol (10 mL) and water (5 mL) was heated at reflux temperature for the amount of time specified in each case. The reaction mixture was refrigerated overnight, the resulting solid material was filtered, washed twice with a mixture of 96% ethanol–water (9 mL, 2:1, *v*/*v*), and air-dried. Analytical samples of compounds **29**, **30**, **35** and **37** were obtained by recrystallization of the isolated material from 96% ethanol, while the remaining sulfonamides have been stirred with boiling 96% ethanol (15 mL) for 5 min, the suspension was then allowed to reach room temperature, and then the solid was filtered, washed with fresh 96% ethanol (10 mL), and air-dried prior to analysis.

4-(3-Oxo-3-phenylpropyl)aminobenzenesulfonamide (**29**)

This compound was obtained from 3-(dimethylamino)-1-phenyl-1-propanone hydrochloride **16** as colorless crystals (535 mg, 44% after a reaction time of 1 h), mp 196–197 °C (lit.[35] mp 201–205 °C; lit.[14] mp 220 °C); ^{1}H NMR (DMSO-d_6): δ 3.33 (t, *J* = 6.4 Hz, 2H), 3.42–3.50 (m, 2H), 6.41 (t, *J* = 5.6 Hz, 1H), 6.65 (d, *J* = 8.8 Hz, 2H), 6.92 (s, 2H), 7.49–7.58 (m, 4H), 7.61–7.68 (m, 1H), 7.98 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 37.3, 37.6, 110.7, 127.4, 127.9, 128.8, 130.1, 133.3, 136.6, 151.2, 198.5.

4-[3-(4-Chlorophenyl)-3-oxopropyl]aminobenzenesulfonamide (**30**)

This compound was obtained from 1-(4-chlorophenyl)-3-(dimethylamino)-1-propanone hydrochloride **17** as colorless crystals (850 mg, 64% after a reaction time of 1 h), mp 181–182 °C (ethanol); ^{1}H NMR (DMSO-d_6): δ 3.32 (t, *J* = 6.4 Hz, 2H), 3.40–3.49 (m, 2H), 6.40 (t, *J* = 6.4 Hz, 1H), 6.64 (d, *J* = 8.8 Hz, 2H), 6.93 (s, 2H), 7.52 (d, *J* = 8.8 Hz, 2H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.98 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 37.4, 37.5, 110.7, 127.4, 128.9, 129.9, 130.1, 135.3, 138.2, 151.2, 197.6.

4-[3-(3-Chlorophenyl)-3-oxopropyl]aminobenzenesulfonamide (**31**)

This compound was obtained from 1-(3-chlorophenyl)-3-(dimethylamino)-1-propanone hydrochloride **18** as colorless crystals (935 mg, 69% after a reaction time of 1 h), mp 194–195 °C; ^{1}H NMR (DMSO-d_6): δ 3.34 (t, *J* = 6.4 Hz, 2H), 3.40–3.48 (m, 2H), 6.40 (t, *J* = 5.6 Hz, 1H), 6.64 (d, *J* = 8.8 Hz, 2H), 6.92 (s, 2H), 7.52 (d, *J* = 8.8 Hz, 2H), 7.57 (dd, *J* = 8.0 and 8.4 Hz, 1H), 7.72 (dd, *J* = 1.2 and 8.0 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.96 (d, *J* = 1.6 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 37.5, 37.6, 110.7, 126.6, 127.4, 127.6, 130.1, 130.8, 132.9, 133.7, 138.5, 151.2, 197.6.

4-[3-(4-Bromophenyl)-3-oxopropyl]aminobenzenesulfonamide (**32**)

This compound was obtained from 1-(4-bromophenyl)-3-(dimethylamino)-1-propanone hydrochloride **19** as colorless crystals (935 mg, 61% after a reaction time of 1 h), mp 201–203 °C; ^{1}H NMR (DMSO-d_6): δ 3.31 (t, *J* = 6.4 Hz, 2H), 3.40–3.49 (m, 2H), 6.40 (t, *J* = 5.6 Hz, 1H), 6.64 (d, *J* = 8.8 Hz, 2H), 6.92 (s, 2H), 7.52 (d, *J* = 8.8 Hz, 2H), 7.75 (d, *J* = 8.8 Hz, 2H), 7.90 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 37.4, 37.5, 110.7, 127.3, 127.4, 130.0, 130.1, 131.8, 135.6, 151.2, 197.8.

4-[3-(2-Hydroxyphenyl)-3-oxopropyl]aminobenzenesulfonamide (**33**)

This compound was obtained from 3-(dimethylamino)-1-(2-hydroxyphenyl)-1-propanone hydrochloride **20** as colorless crystals (885 mg, 69% after a reaction time of 1 h), mp 170–171 °C; ^{1}H NMR (DMSO-d_6): δ 3.38 (t, *J* = 6.4 Hz, 2H), 3.41–3.50 (m, 2H), 6.43 (t, *J* = 5.6 Hz, 1H), 6.65 (d, *J* = 8.8 Hz, 2H), 6.89–7.01 (m, 4H), 7.49–7.57 (m, 3H), 7.87 (dd, *J* = 1.2 and 8.0 Hz, 1H), 11.82 (br s, 1H); ^{13}C NMR (DMSO-d_6): δ 37.5, 38.4, 110.8, 117.7, 119.2, 120.7, 127.4, 130.2, 130.6, 136.0, 151.2, 160.5, 204.2.

4-[3-(4-Hydroxyphenyl)-3-oxopropyl]aminobenzenesulfonamide (**34**)

This compound was obtained from 3-(dimethylamino)-1-(4-hydroxyphenyl)-1-propanone hydrochloride **21** as colorless crystals (485 mg, 38% after a reaction time of 3 h), mp 245–247 °C; ^{1}H NMR (DMSO-d_6): δ 3.21 (t, *J* = 6.4 Hz, 2H), 3.36–3.48 (m, 2H), 6.37 (t, *J* = 5.6 Hz, 1H), 6.63 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.91 (d, 2H), 7.51 (d, *J* = 8.8 Hz, 2H), 7.85 (d, *J* = 8.8 Hz, 2H), 10.36 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 36.8, 37.8, 110.7, 115.3, 127.4, 128.3, 130.0, 130.5, 151.3, 162.1, 196.6.

4-[3-(4-Methoxyphenyl)-3-oxopropyl]aminobenzenesulfonamide (**35**)

This compound was obtained from 3-(dimethylamino)-1-(4-methoxyphenyl)-1-propanone hydrochloride **22** as colorless crystals (360 mg, 27% after a reaction time of 1 h), mp 188–189 °C (ethanol); ^{1}H NMR (DMSO-d_6): δ 3.26 (t, *J* = 6.4 Hz, 2H), 3.39–3.48 (m, 2H), 3.84 (s, 3H), 6.40 (t, *J* = 5.6 Hz, 1H), 6.64 (d, *J* = 8.8 Hz, 2H), 6.92 (s, 2H), 7.05 (d, *J* = 8.8 Hz, 2H), 7.52 (d, *J* = 8.8 Hz, 2H), 7.95 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 36.9, 37.7, 55.6, 110.7, 113.9, 127.4, 129.6, 130.1, 130.3, 151.3, 163.2, 196.9.

4-{3-[4-(Benzyloxy)phenyl]-3-oxopropyl}aminobenzenesulfonamide (**36**)

This compound was obtained from 1-[4-(benzyloxy)phenyl]-3-(dimethylamino)-1-propanone hydrochloride **23** as colorless crystals (575 mg, 35% after a reaction time of 2 h), mp 207–209 °C; ^{1}H NMR (DMSO-d_6): δ 3.25 (t, *J* = 6.4 Hz, 2H), 3.39–3.48 (m, 2H), 5.21 (s, 2H), 6.39 (t, *J* = 5.6 Hz, 1H), 6.64 (d, *J* = 8.8 Hz, 2H), 6.92 (s, 2H), 7.13 (d, *J* = 8.8 Hz, 2H), 7.30–7.37 (m, 1H), 7.37–7.43 (m, 2H), 7.46 (d, *J* = 7.2 Hz, 2H), 7.52 (d, *J* = 8.8 Hz, 2H), 7.95 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 36.9, 37.7, 69.5, 110.7, 114.7,

127.4, 127.8, 128.0, 128.5, 129.8, 130.1, 130.2, 136.5, 151.3, 162.2, 196.9.

4-(3-[2-(Benzyloxy)phenyl]-3-oxopropyl}aminobenzenesulfonamide (**37**)

This compound was obtained from 1-[2-(benzyloxy)phenyl]-3-(dimethylamino)-1-propanone hydrochloride **24** as colorless crystals (575 mg, 35% after a reaction time of 2 h), mp 140–141 °C (ethanol); ^{1}H NMR (DMSO-d_6): δ 3.24 (t, J = 6.4 Hz, 2H), 3.32–3.40 (m, 2H), 5.24 (s, 2H), 6.32 (t, J = 5.6 Hz, 1H), 6.57 (d, J = 8.8 Hz, 2H), 6.92 (s, 2H), 7.01–7.08 (m, 1H), 7.24 (d, J = 8.4 Hz, 1H), 7.29–7.40 (m, 3H), 7.42–7.57 (m, 5H), 7.61 (d, J = 7.6 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 37.7, 42.7, 70.0, 110.7, 113.7, 120.7, 127.4, 127.8, 128.0, 128.1, 128.5, 129.7, 130.1, 133.7, 136.4, 151.2, 157.3, 200.1.

4-[3-(3,4-Dimethoxyphenyl)-3-oxopropyl]aminobenzenesulfonamide (**38**)

This compound was obtained from 3-(dimethylamino)-1-[3,4-(dimethoxy)phenyl]propan-1-one hydrochloride **25** as colorless crystals (245 mg, 17% after a reaction time of 1 h), mp 184–185 °C; ^{1}H NMR (DMSO-d_6): δ 3.27 (t, J = 6.4 Hz, 2H), 3.40–3.49 (m, 2H), 3.80 (s, 3H), 3.84 (s, 3H), 6.39 (t, J = 5.6 Hz, 1H), 6.64 (d, J = 8.8 Hz, 2H), 6.92 (s, 2H), 7.07 (d, J = 8.4 Hz, 1H), 7.46 (d, J = 1.6 Hz, 1H), 7.52 (d, J = 8.8 Hz, 1H), 7.64 (dd, J = 1.6 and 8.4 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 36.9, 37.9, 55.5, 55.8, 110.2, 110.7, 110.9, 122.7, 127.4, 129.6, 130.1, 148.6, 151.2, 153.1, 197.0.

4-[3-(Biphenyl-4-yl)-3-oxopropyl]aminobenzenesulfonamide (**39**)

This compound was obtained from 1-(4-biphenyl-1-yl)-3-(dimethylamino)-1-propanone hydrochloride **26** as colorless crystals (625 mg, 41% after a reaction time of 3 h), mp 242–244 °C; ^{1}H NMR (DMSO-d_6): δ 3.36 (t, J = 6.0 Hz, 2H), 3.44–3.53 (m, 2H), 6.44 (t, J = 5.6 Hz, 1H), 6.67 (d, J = 8.8 Hz, 2H), 6.94 (s, 2H), 7.40–7.47 (m, 1H), 7.47–7.58 (m, 4H), 7.76 (d, J = 7.2 Hz, 2H), 7.84 (d, J = 8.0 Hz, 2H), 8.06 (d, J = 8.0 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 37.4, 37.7, 110.8, 126.9, 127.0, 127.4, 128.4, 128.7, 129.1, 130.1, 135.4, 138.9, 144.6, 151.3, 198.1.

4-[3-(Naphthalen-2-yl)-3-oxopropyl]aminobenzenesulfonamide (**40**)

This compound was obtained from 3-(dimethylamino)-1-(naphthalen-2-yl)-1-propanone hydrochloride **27** as colorless crystals (720 mg, 51% after a reaction time of 1 h), mp 211–212 °C; ^{1}H NMR (DMSO-d_6): δ 3.44–3.57 (m, 4H), 6.47 (t, J = 5.2 Hz, 1H), 6.68 (d, J = 8.8 Hz, 2H), 6.94 (s, 2H), 7.54 (d, J = 8.8 Hz, 2H), 7.59–7.72 (m, 2H), 7.95–8.07 (m, 3H), 8.13 (d, J = 8.0 Hz, 1H), 8.68 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 37.4, 37.7, 110.8, 123.5, 127.0, 127.4, 127.7, 128.3, 128.7, 129.6, 130.0, 130.1, 132.2, 133.9, 135.1, 151.3, 198.5.

4-[3-Oxo-3-(thiophen-2-yl)propyl]aminobenzenesulfonamide (**41**)

This compound was obtained from 3-(dimethylamino)-1-(thiophen-2-yl)-1-propanone hydrochloride **28** as colorless crystals (655 mg, 53% after a reaction time of 1 h), mp 207–208 °C; ^{1}H NMR (DMSO-d_6): δ 3.26 (t, J = 6.4 Hz, 2H), 3.40–3.50 (m, 2H), 6.44 (t, J = 5.6 Hz, 1H), 6.65 (d, J = 8.8 Hz, 2H), 6.93 (s, 2H), 7.24 (d, J = 4.0 and 4.8 Hz, 1H), 7.52 (d, J = 8.8 Hz, 2H), 7.95 (d, J = 4.0 Hz, 1H), 8.01 (d, J = 4.8 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 37.7, 37.8, 110.8, 127.4, 128.8, 130.2, 133.4, 134.9, 143.8, 151.2, 191.6.

CONCLUSIONS

N-Alkylation of sulfanilamide with ketone Mannich base hydrochlorides derived from various (hetero)aryl methyl ketones was successfully conducted by heating at reflux equimolar quantities of the corresponding reagents in a mixture of ethanol–water. Depending on the reactivity of the alkylating agent, the target sulfonamides were obtained with modest to moderate yields, which could be improved by extending the reaction time. The structure and purity of the resulting sulfonamides, which could potentially be useful as inhibitors of carbonic anhydrases, was examined and proved through NMR analysis.

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