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SIMPLE AND EFFICIENT SYNTHESIS OF SOME NOVEL TRIAZOLES SULFONAMIDES

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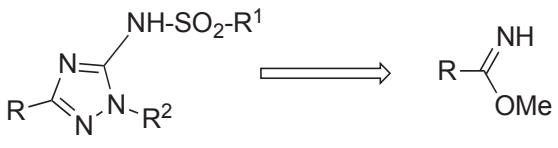
Abstract – Reaction of iminoesters **1** with sulfonyl isocyanates gave the corresponding sulfonamide imidates **2**. The cyclocondensation of the latter with a series of hydrazine in methanol affords new functionalized triazoles in high yields.

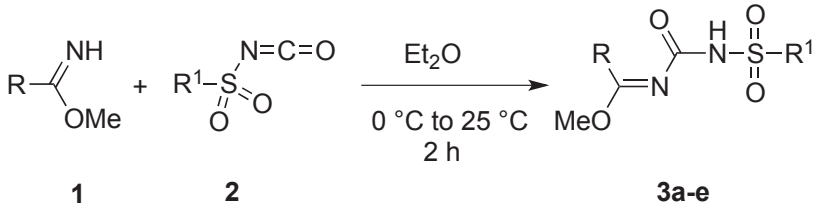
Simple nitrogen-containing heterocycles attached to sulfonamido moieties have received a large amount of attention in the literature, as a consequence of their exciting biological properties and their role as pharmacophores of considerable historical importance. Heterocyclic sulfonamides are used as carbonic anhydrase inhibitors,[1-3] antibacterial agents,[4] anticancer, anti-inflammatory and analgesic agents,[5] β3-adrenergic receptor agonists,[6] PC-1 inhibitors,[7] antifungal agents,[8] and antiviral agents.[9] Triazole derivatives have consistently attracted scientific and practical interest because of their widely varying chemical properties, synthetic versatility, and pharmacological activities, such as antibacterial,[10-12] antifungal,[13-15] antitubercular,[16-18] analgesic,[19,20] anti-inflammatory,[20-22] anticancer,[23,24] anticonvulsant,[25] antiviral,[26] insecticidal,[27] and antidepressant,[28] antiviral properties. Moreover, the triazole compounds carrying sulfone moiety have been reported as antibacterial and antifungal, antihypertensive, analgesic, anti-inflammatory, or antitumoral agents.[29-31] For these vast biological activities and in continuation of our work on the synthesis of novel nitrogen heterocyclic compounds containing a sulfamide group,[32] we



Scheme 1. Retrosynthetic pathway for the preparation of triazole sulfonamides

undertook the synthesis of a new series of compounds incorporating the abovementioned biologically active moieties in one molecule. The scheme **1** depicts the discovery of a practical and high yielding method for the efficient one-pot synthesis of diverse triazole sulfonamides starting from a wide range of imidates.

Some studies reported on the synthesis of 1,3,5-triazoles bearing specific functionalities or substituents using *N*-acylamidrazone as an intermediate.[33] In the same context, we performed the synthesis of *N*-sulfonamide imidates by condensation of iminoesters **1** with sulfonyl isocyanates **2** (Scheme 2) and we next focused our efforts to investigate their behavior towards the synthesis of some novel triazoles.



Scheme 2. Synthesis of *N*-sulfonamide imidates **3a-e**

Table 1. Substrate scope studies

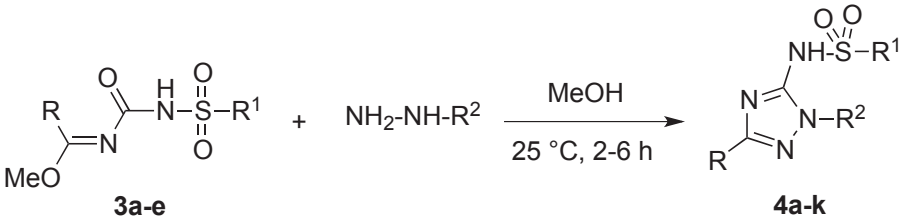
Entry	R	R^1	Yield (%)[a]
a	Ph	PhO	96
b	Ph	tolyl	94
c	Bn	tolyl	96
d	*i*-Pr	tolyl	96
e	*n*-Pr	tolyl	97

[a]Isolated yield.

The reaction is thought to proceed via nucleophilic attack of the NH group of iminoesters on the carbonyl group of sulfonyl isocyanates giving rise to an imidate. The structures of the title compounds were established on the basis of their spectral data. It was shown that no peak duplication is observed suggesting that these compounds were obtained as *E* isomer. Moreover, a study conducted using RX in our laboratory[34] on the *N*-functionalized iminoesters confirm this finding. In ^{1}H-NMR spectra, we observed essentially the total disappearance of the signal of the NH group and the appearance of a new signal around 11 ppm characteristic of the protons of the amide group. ^{13}C-NMR chemical shifts of

different types of atoms are consistent with the structure of the synthesized compounds. Analysis of the ^{13}C-NMR spectra shows the appearance of a new signal around 160 ppm attributed to the carbonyl of the amide group.

The imidates **3** possess several reagent sites in particular in position 1,3. The bis electrophilic character of imidates **3** would allow to postulate that their reaction with the hydrazine derivatives could constitute an easy access to new series of triazole **4**. Effectively, good yields of triazole sulfonamides **4** have been obtained by the reaction of *N*-sulfonamide imidates **3** with a series of hydrazine in methanol at room temperature (Scheme 3). In order to demonstrate the efficiency and generality of this protocol, we examined the reactions of various imidates and substituted hydrazine (Table 2). All substrates react to give the corresponding triazole sulfonamides in good to excellent yields.



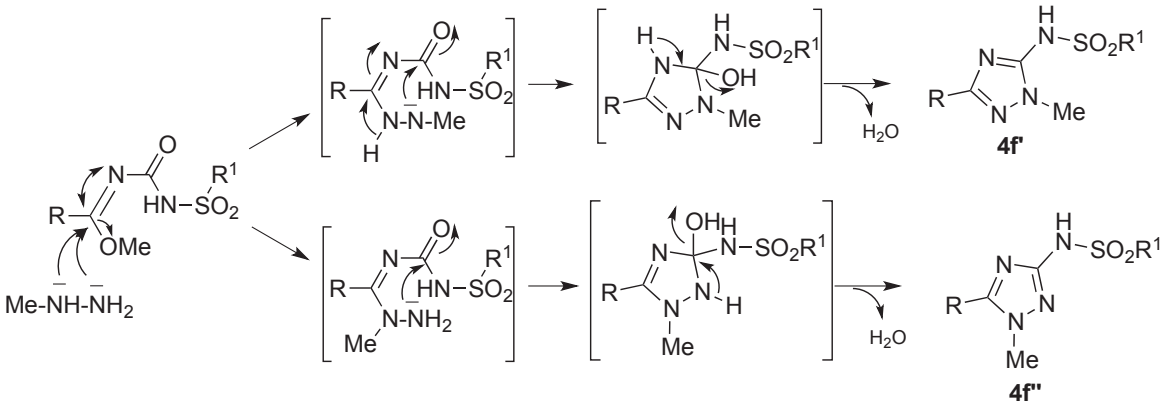
Scheme 3. Synthesis of triazole sulfonamides from imidates **3a-e**

Table 2. Substrate scope studies

Entry	R	R^1	R^2	Yield (%)[a]
a	Ph	PhO	H	90
b	Ph	tolyl	H	88
c	Bn	tolyl	H	89
d	Ph	tolyl	Ph	88
e	Bn	tolyl	Ph	88
f	Ph	tolyl	Me	96 (75/25 ratio)
g	Ph	tolyl	NC-CH_2-CH_2-	85
h	Ph	tolyl	$(EtO)_2P(O)$-	82
i	Ph	tolyl	$(EtO)_2P(S)$-	85
j	*n*-Pr	tolyl	H	90
k	*i*-Pr	tolyl	H	90

[a]Isolated yield.

The reaction was assumed to proceed by the substitution of the methoxy group of imidates **3** by the NH_2 group of hydrazine giving an intermediate which then immediately yielded via a heterocyclization the correspondent triazole sulfonamides. It has been shown that in the case of methylhydrazine, reaction lead to the formation of two triazole isomers (**4f'** and **4f''** in 75/25 ratio). Methoxy group of imidates **3** can be substituted indifferently by the two nitrogen atoms of methylhydrazine. One of these nitrogen atoms is less sterically hindered (Me-NH-$\underline{NH_2}$) so we have obtained **4f'** as major regioisomer in accordance with the literature.[35-38]



Scheme 4. Proposed mechanism for the formation of triazoleisomers **4f'** and **4f''**

Triazole sulfonamides **4a-k** were characterized by their spectroscopic data of IR, NMR and by satisfactory HRMS. Examination of the ^{13}C-NMR spectra of the products **4a-k** shows the disappearance of the signal at 50 ppm relative to methoxy carbon and the appearance of new signal around 157 ppm attributable to the endocyclic imine carbon. The ^{1}H-NMR spectra are consistent with the literature data for closely related compounds.

In conclusion, we have developed a convenient method for the synthesis of some new triazole sulfonamide derivatives in high yields from corresponding substituted hydrazine and *N*-sulfonamide imidates. This procedure offers significant advantages over prior reports, such as efficiency, and mild reaction conditions.

EXPERIMENTAL

Melting points were measured with a Kofler hot-staged apparatus and are uncorrected. ^{1}H, ^{31}P and ^{13}C NMR spectra were recorded with $CDCl_3$ as the solvent, on a Bruker-300 spectrometer. The chemical shifts are reported in ppm relative to TMS (internal reference) for ^{1}H and ^{13}C-NMR and relative to 85% H_3PO_4 (external reference) for ^{31}P-NMR. The coupling constants are reported in Hz. For the ^{1}H-NMR, the multiplicities of signals are indicated by the following abbreviations: s: singlet, m: multiplet. Mass

spectra were determined on a VOYAGER DE STR spectrometer under MALDI ionization conditions. IR spectra were recorded on a Nicolet IR200 spectrometer. The progress of the reactions was monitored by TLC. The starting materials (iminoesters **1** and phosphorylated hydrazine) were prepared according to reported procedures.[39,40]

General procedure for the preparation of imidates (3a-e).

To a well-stirred solution of iminoester **1** (1 mmol) in dry Et_2O (20 mL) was added aroxysulfonyl isocyanate **2** dropwise over 2 min at 0 °C. The reaction mixture was stirred for 2 h. Resulting precipitate was filtered of in satisfactory purity.

3a: White solid; mp 180 °C, Yield: 96%. IR (KBr, cm^{-1}): 3257 (NH), 3087 (CH_{arom}), 1680 (C=O), 1346, 1154 (SO_2). ^{1}H-NMR ($CDCl_3$): 3.9 (s, OCH_3), 11.5 (br s, NH), 7.1-7.95 (m, 10H, Ar-H). ^{13}C-NMR (75 MHz, $CDCl_3$): 52.13, 122.04-149.60 (C_{arom}), 153.60, 161.56.

3b: White solid; mp 183 °C, Yield: 94%. IR (KBr, cm^{-1}): 3274 (NH), 3053 (CH_{arom}), 1688 (C=O), 1370, 1156 (SO_2). ^{1}H-NMR ($CDCl_3$): 2.35 (s, CH_3), 3.5 (s, OCH_3), 11.09 (s, NH), 7.01-7.96 (m, 9H, Ar-H). ^{13}C-NMR (75 MHz, $CDCl_3$): 21.50, 52.13, 123.55-138.77 (C_{arom}), 152.50, 161.41.

3c: Yellow solid; mp 175 °C, Yield: 96%. IR (KBr, cm^{-1}): 3273 (NH), 3067 (CH_{arom}), 1693 (C=O), 1347, 1130 (SO_2). ^{1}H-NMR ($CDCl_3$): 2.5 (s, CH_3), 3.49 (s, CH_2), 3.8 (s, OCH_3), 11.23 (br s, NH), 6.96-7.93 (m, 9H, Ar-H). ^{13}C-NMR (75 MHz, $CDCl_3$): 21.65, 43.70, 52.13, 124.11-136.87 (C_{arom}), 154.20, 162.36.

3d: White solid; mp 178 °C, Yield: 96%. IR (KBr, cm^{-1}): 3267 (NH), 3051 (CH_{arom}), 1710 (C=O), 1339, 1158 (SO_2). ^{1}H-NMR ($CDCl_3$): 1.1 (m, 6H), 2.4 (s, CH_3), 2.6 (m, 1H), 3.5 (s, OCH_3), 11.15 (br s, NH), 7.11-7.86 (m, 4H, Ar-H). ^{13}C-NMR (75 MHz, $CDCl_3$): 18.66, 21.54, 32.48, 52.82, 128.3-137.60 (C_{arom}), 151.30, 162.7.

3e: White solid; mp 185°C, Yield: 97%. IR (KBr, cm^{-1}): 3227 (NH), 3023 (CH_{arom}), 1697 (C=O), 1351, 1155 (SO_2). ^{1}H-NMR ($CDCl_3$): 0.92 (m, CH_3), 1.44 (m, CH_2), 1.61 (m, CH_2), 2.36 (CH_3), 3.5 (s, OCH_3), 11.29 (br s, NH), 7.40-7.80 (m, 4H, Ar-H). ^{13}C-NMR (75 MHz, $CDCl_3$): 13.16, 14.87, 19.03, 37.25, 52.79, 128.19-140.60 (C_{arom}), 154.10, 161.71.

General synthetic procedure for triazole sulfonamides (4a-k).

To a solution of sulfonamide imidates **3** (1 mmol) in MeOH (10 mL) were added hydrazine derivatives (1 mmol). The mixture was stirred for 2-6 h at room temperature. The precipitate thus formed was collected by filtration, washed with MeOH (10 mL), dried and recrystallized from petroleum ether. The crude product **4f** was purified using flash chromatography (silica gel:EtOAc/hexane) to give pure compounds **4f'** and **4f''**.

4a: Pink solid; mp 230 °C, Yield: 90%. IR (KBr, cm^{-1}): 3273, 3178 (NH), 3053 (CH_{arom}), 1604 (C=N), 1345, 1154 (SO_2). ^{1}H-NMR (DMSO-d_6): 7.01-8.06 (m, 10H, Ar-H), 7.95 (br s, NH). ^{13}C-NMR (DMSO-d_6): 121.5-145.17 (C_{arom}), 156.6, 161.68. HRMS (EI): *m/z* calculated for $C_{14}H_{12}N_4O_3S$ $(M+H)^+$: 317.07; found 317.18.

4b: White solid; mp 250 °C, Yield: 88%. IR (KBr, cm^{-1}): 3278, 3130 (NH), 3097 (CH_{arom}), 1588 (C=N), 1394, 1186 (SO_2). ^{1}H-NMR (DMSO-d_6): 2.36 (s, CH_3), 7.29 (br s, NH), 6.96-7.93 (m, 9H, Ar-H). ^{13}C-NMR (DMSO-d_6): 20.84, 124.71-136.81 (C_{arom}), 157.33, 161.32. HRMS (EI): *m/z* calculated for $C_{15}H_{14}N_4O_2S$ $(M+H)^+$: 315.09; found 315.13.

4c: White solid; mp 230 °C, Yield: 89%. IR (KBr, cm^{-1}): 3301, 3125 (NH), 3105 (CH_{arom}), 1591 (C=N), 1371, 1174 (SO_2). ^{1}H-NMR (DMSO-d_6): 2.34 (s, CH_3), 3.56 (s, CH_2), 7.16-7.73 (m, 9H, Ar-H) 7.52 (br s, NH). ^{13}C-NMR (DMSO-d_6): 21.15, 33.2, 125.3-138.1 (C_{arom}), 157.2, 161.2. HRMS (EI): *m/z* calculated for $C_{16}H_{16}N_4O_2S$ $(M+H)^+$: 329.10; found 329.16.

4d: White solid; mp 251 °C, Yield: 88%. IR (KBr, cm^{-1}): 3337, 3143 (NH), 3022 (CH_{arom}), 1604 (C=N), 1357, 1176 (SO_2). ^{1}H-NMR (DMSO-d_6): 2.38 (s, CH_3), 7.99 (br s, NH), 7.41-8.05 (m, 14H, Ar-H). ^{13}C-NMR (DMSO-d_6): 19.94, 127.62-137.4 (C_{arom}), 154.3, 160.98. HRMS (EI): *m/z* calculated for $C_{21}H_{18}N_4O_2S$ $(M+H)^+$: 391.12; found 391.16.

4e: White solid; mp 245 °C, Yield: 88%. IR (KBr, cm^{-1}): 3276, 3123 (NH), 3066 (CH_{arom}), 1583 (C=N), 1363, 1188 (SO_2). ^{1}H-NMR (DMSO-d_6): 2.33 (s, CH_3), 3.64 (s, CH_2), 7.22-8.12 (m, 14H, Ar-H), 7.40 (br s, NH). ^{13}C-NMR (DMSO-d_6): 19.39, 32.90, 123.62-139.14 (C_{arom}), 155.31, 161.87. HRMS (EI): *m/z* calculated for $C_{22}H_{20}N_4O_2S$ $(M+H)^+$: 405.13; found 405.19.

4f': White solid; mp 255 °C, Yield: 72%. IR (KBr, cm^{-1}): 3224, 3157 (NH), 3056 (CH_{arom}), 1612 (C=N), 1384, 1159 (SO_2). ^{1}H-NMR (DMSO-d_6): 2.34 (s, CH_3), 3.89 (s, CH_3), 7.13-7.95 (m, 9H, Ar-H), 7.83 (br s, NH). ^{13}C-NMR (DMSO-d_6): 20.3, 31.21, 122.12-137.31 (C_{arom}), 158.3, 162.4. HRMS (EI): *m/z* calculated for $C_{16}H_{16}N_4O_2S$ $(M+H)^+$: 329.10; found 329.12.

4f'': White solid; mp 255 °C, Yield: 24%. IR (KBr, cm^{-1}): 3228, 3152 (NH), 3076 (CH_{arom}), 1608 (C=N), 1392, 1189 (SO_2). ^{1}H-NMR (DMSO-d_6): 2.35 (s, CH_3), 3.87 (s, CH_3), 7.13-7.95 (m, 9H, Ar-H), 7.8 (br s, NH). ^{13}C-NMR (DMSO-d_6): 20.55, 29.87, 12.12-138.09 (C_{arom}), 158.43, 162.49. HRMS (EI): *m/z* calculated for $C_{16}H_{16}N_4O_3S$ $(M+H)^+$: 329.10; found 329.13.

4g: White solid; mp 261 °C, Yield: 85%. IR (KBr, cm^{-1}): 3297, 3144 (NH), 3036 (CH_{arom}), 1579 (C=N), 1391, 1184 (SO_2). ^{1}H-NMR (DMSO-d_6): 2.34 (s, CH_3), 3.21 (m, CH_2), 5.19 (m, CH_2), 7.34-8.08 (m, 9H, Ar-H), 7.94 (br s, NH). ^{13}C-NMR (DMSO-d_6): 15.65, 20.3, 41.1, 118.9, 125.62-136.32 (C_{arom}), 157.12,

161.73. HRMS (EI): *m/z* calculated for $C_{18}H_{17}N_5O_2S$ $(M+H)^+$: 368.11; found 368.14.

4h: Hygroscopic yellow solid; mp 279 °C, Yield: 82%. IR (KBr, cm^{-1}): 3283, 3171 (NH), 3010 (CH_{arom}), 1622 (C=N), 1363, 1147 (SO_2), 1253 (P=O). ^{1}H-NMR (DMSO-*d*$_6$): 1.29 (m, CH_3), 2.34 (s, CH_3), 4.01 (m, CH_2), 7.13-8.02 (m, 9H, Ar-H), 7.2 (br s, NH). ^{13}C-NMR (DMSO-*d*$_6$): 16.55, 21.3, 59.1, 124.76-137.23 (C_{arom}), 158.3, 160.22. ^{31}P NMR (DMSO-*d*$_6$): 1.43. HRMS (EI): *m/z* calculated for $C_{19}H_{23}N_4O_5PS$ $(M+H)^+$: 451.12; found 451.19.

4i: Hygroscopic yellow solid; mp 281 °C, Yield: 85%. IR (KBr, cm^{-1}): 33337, 3181 (NH), 3050 (CH_{arom}), 1587 (C=N), 1361, 1167 (SO_2), 1270 (P=S). ^{1}H-NMR (DMSO-*d*$_6$): 1.17 (m, CH_3), 2.39 (s, CH_3), 3.87 (m, CH_2), 7.23-7.78 (m, 9H, Ar-H), 7.42 (s, NH). ^{13}C-NMR (DMSO-*d*$_6$): 17.12, 23.11, 57.32, 123.57-135.96 (C_{arom}), 156.44, 163.08. ^{31}P NMR (DMSO-*d*$_6$): 23.16.HRMS (EI): *m/z* calculated for $C_{19}H_{23}N_4O_4PS_2$ $(M+H)^+$: 467.09; found 467.17.

4j: White solid; mp 251 °C, Yield: 90%. IR (KBr, cm^{-1}): 3265, 3154 (NH), 3020 (CH_{arom}), 1624 (C=N), 1377, 1123 (SO_2). ^{1}H-NMR: (DMSO-*d*$_6$): 1.15 (m, CH_3), 1.69 (m, CH_2) 2.36 (s, CH_3), 2.89 (m, CH_2), 7.39 (br s, NH), 7.12-7.85 (m, 4H, Ar-H). ^{13}C-NMR (DMSO-*d*$_6$): 16.31, 20.37, 22.09, 30.1, 127.19-139.43 (C_{arom}), 157.43, 163.71. HRMS (EI): *m/z* calculated for $C_{12}H_{16}N_4O_2S$ $(M+H)^+$: 281.10; found 281.18.

4k: White solid; mp 251 °C, Yield: 90%. IR (KBr, cm^{-1}): 3312, 3123 (NH), 3072 (CH_{arom}), 1593 (C=N), 1352, 1145 (SO_2). ^{1}H-NMR: (DMSO-*d*$_6$): 1.23 (m, 6H), 2.36 (s, CH_3), 3.17 (m, 1H), 7.93 (br s, NH), 7.11-7.97 (m, 4H, Ar-H). ^{13}C-NMR (DMSO-*d*$_6$): 21.1, 21.4, 30.1, 128.9-138.2 (C_{arom}), 154.5, 162.12. HRMS (EI): *m/z* calculated for $C_{12}H_{16}N_4O_2S$ $(M+H)^+$: 281.10; found 281.23.

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