Supplementary Material

Synthesis and antifungal activity of novel oxazolidin-2-one linked-1,2,3-triazole derivatives

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1. Study and development of a novel nanomicelle-catalyzed synthesis of β-ketosulfones in water at room temperature

Despite several protocols describe the synthesis of β-ketosulfones (R_1COCH_2SO_2R_2) by the coupling of α-brominated carbonyls (ArCOCH_2Br) with sulfinate salts through a simple S_N2, a reaction using exclusively water (highly desirable green chemistry conditions) have not been possible at room temperature so far. The surfactant properties of SPGS-550-M (a third generation micellar catalyst now available from Aldrich) enabled the efficient synthesis of β-ketosulfones from α-brominated carbonyls in aqueous medium at room temperature. The mild and environmentally friendly reaction conditions as well as the simplicity of the experimental procedure make this protocol very practical and easy to handle.

In 2004, Prof. Lipshutz reported^1^ the design and synthesis of amphiphile/surfactant ‘Nok’ (i.e., SPGS-550-M; β-sitosterol methoxypolyethyleneglycol succinate). Now available from Sigma-Aldrich^2^ this reagent has fostered an efficient transition in organic synthesis from organic solvents to water.^3^ Water provides the medium and micellar catalysis the crucial ‘solvent’ that affords a reaction.

β-Ketosulfones are very versatile compounds in organic chemistry. Several synthetic methodologies [e.g. from α-bromo aryl ketones (Scheme SI-1, eqn (a)–(h))^4^ alkenes,^5^ enol acetates,^6^ β-dicarboxyles,^7^ alkynes,^8^ and ketones^9^

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^2^Sigma-Aldrich catalog number: 776033.
among others\textsuperscript{10} to afford these compounds have been reported in literature. In this sense, Lipshutz described the aerobic oxosulfonylation of arylacetylenes within nanomicelles in water [eqn (i)].\textsuperscript{11}

During one of our ongoing research projects, focused on the development of novel triazolic antifungal compounds from ketones (e.g. β-Ketosulfones)\textsuperscript{12} as starting materials, we synthetized compounds S1b–S10b from S1a–S10a according to previously described methodologies [Scheme SI-1, eqn (a)–(h)]. The desired products were obtained with high temperatures, but it is of utmost importance to employ a very mild and eco-friendly method for the synthesis of β-ketosulfones. Therefore, we tried to obtain compound S1b from α-bromo ketone S1a in water at room temperature without any co-organic solvent. Unfortunately, no reaction was observed within 120 h. Evidently, the insolubility of the starting material S1a prevents its interaction with the metal sulfinate salt (highly soluble in water). Surprisingly, when the substrates were subjected to a catalytic aqueous solution of SPGS-550-M at room temperature, the corresponding β-Ketosulfone S1b was attained in a very clean reaction in TLC, isolated in high yields (91%).

\textbf{Scheme SI-1.} Lipshutz’s work opened the door to improving the attainment of β-ketosulfones through eco-friendly methods.

These results led us to investigate the alkylation of the α-halo ketone S1a with aryl sulfinate salt in greater detail. Firstly, an excess (1.5 eq) of sodium p-toluenesulfinate (p-TolSO₂Na) was necessary to allow for a complete reaction. Secondly, TLC provided a complete reaction after 12 h. Despite the similar yields obtained when using a hermetic (89%) versus open-flask (91%) system, we decided to adopt the latter as the standard. To evaluate the scope of our protocol, both arylic (S2a–S6a, S11a and S12a) and heteroarylic (S7a–S10a) α-bromo ketone derivatives were subjected to the optimized reaction conditions (Table SI-1). In general, primary bromo alkyl substrates showed excellent yields (71–92%). Unfortunately, both secondary bromo S11a and chloroalkyl S12a derivatives remained intact in the solution.

Table SI-1. Sulfonation of α-bromo ketones with p-tol-SO₂Na and aqueous micellar medium.

<table>
<thead>
<tr>
<th>Entry</th>
<th>α-Bromo ketones</th>
<th>β-Ketosulfone (Yield%)</th>
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<tr>
<td>1</td>
<td>S2a</td>
<td>S2b (71%)</td>
</tr>
<tr>
<td>2</td>
<td>S3a</td>
<td>S3b (84%)</td>
</tr>
<tr>
<td>3</td>
<td>S4a</td>
<td>S4b (81%)</td>
</tr>
<tr>
<td>4</td>
<td>S5a</td>
<td>S5b (87%)</td>
</tr>
<tr>
<td>5</td>
<td>S6a</td>
<td>S6b (87%)</td>
</tr>
<tr>
<td>6</td>
<td>S7a</td>
<td>S7b (85%)</td>
</tr>
<tr>
<td>7</td>
<td>S8a</td>
<td>S8b (92%)</td>
</tr>
</tbody>
</table>

13 α-Bromo ketone compounds (starting materials) were obtained from the corresponding methyl aryl ketones according to synthetic protocols described in literature: Vekariya, R. H.; Patel, H. D. Tetrahedron 2014, 70, 3949–3961.
In conclusion, we have developed a novel organic solvent-free synthesis of β-ketosulfones with aqueous nanomicellar medium. The surfactant nature of SPGS-550-M or ‘NOK’ (a third generation surfactant) allows it to act as an efficient nanoreactor in catalytic amounts. The notable advantages of this methodology over those previously reported include its simplicity of handling, mild conditions, high yields, cheap reagents and great tolerance of functional groups.

General experimental procedure for the direct conversion of α-bromo ketones to β-ketosulfones: To a 10-mL round-bottom flask equipped with a magnetic stir bar was added 1 mmol of α-bromo ketone. Then 3.0 mL of SPGS-550-M aq. (2% w/w) and 1.5 mmol of sodium p-toluenesulfinate were added, stirring such reaction mixture at room temperature for 12 h in an open-flask system. After adding brine (ca. 15.0 mL) to the reaction, the mixture was washed with ethyl acetate (3×8 mL). The organic layer was dried (Na$_2$SO$_4$) and the solvent evaporated under reduced pressure. The crude extract was purified by flash column chromatography to afford the corresponding sulfonyl derivative.
2. Experimental section

2.1. Chemistry

General

Flash column chromatography was carried out with SiO$_2$ 60 (230–400 mesh). For TLC, silica-gel plates (SiO$_2$; 0.20-mm thickness) were employed and visualized with UV light at 254 nm. Melting point (uncorrected) was determined on a Fischer-Johns scientific melting point apparatus. $^1$H and $^{13}$C NMR spectra were recorded on Bruker Avance and Varian apparatuses at 300 and 500 MHz, respectively: $\delta$ in ppm relative to Me$_4$Si as internal standard, and $J$ in Hz. MS was conducted on a Shimadzu GCMS-QP2010 Plus apparatus in m/z (rel. %).

Experimental procedures

3-(2-chloroethyl)-4,5-diphenyloxazol-2(3H)-one 7

In a sealed tube 2-chloroethyl isocyanate $^6$ (0.422 g, 4 mmol) and benzoin $^5$ (0.387 g, 4.4 mmol) were stirred for 24 hours at 180 °C under nitrogen atmosphere and anhydrous conditions. Afterwards, TLC indicated the disappearance of the starting materials, and then the solution was brought to room temperature under continuous stirring for 10 min. The mixture was diluted with CH$_2$Cl$_2$ (10 mL), stirred for 20 min and filtered. The solvent was evaporated under reduced pressure to give the yellow solid. The residue was purified by flash chromatography over silica, eluting with ethyl acetate/hexane 1/9 to afford the white solid 7 (0.428 g, 61%). $R_f$: 0.50 (EtOAc/Hex 3/7). m.p. 104-105 °C. $^1$H NMR: (300 MHz, CDCl$_3$): $\delta$ = 7.59–7.57 (m, 3 H$_{ar}$), 7.50–7.47 (m, 2H$_{ar}$), 7.29–7.22 (m, 5H$_{ar}$), 3.68 (t, $J$ = 6.1 Hz, 2H, CH$_2$), 3.53 (t, $J$ = 6.1 Hz, 2H, CH$_2$) ppm. $^{13}$C NMR: (75.4 MHz, CDCl$_3$) $\delta$= 154.3 (C=O), 134.8 (C$_{ar}$), 130.5 (C$_{ar}$), 130.2 (C$_{ar}$), 129.6 (C$_{ar}$), 128.4 (C$_{ar}$), 127.8 (C$_{ar}$), 127.5 (C$_{ar}$), 126.7 (C), 124.4 (C$_{ar}$), 123.1 (C), 48.6 (CH$_2$), 41.1 (CH$_2$) ppm.

3-(2-azidoethyl)-4,5-diphenyloxazol-2(3H)-one 8

To a mixture of the 3-(2-chloroethyl)-4,5-diphenyloxazol-2(3H)-one 7 (0.105 g, 0.6 mmol) in 3 mL of DMF was added sodium azide (0.043 g, 0.66 mmol). It was stirred for 12 hours at 60 °C under nitrogen atmosphere. Afterwards, TLC indicated the disappearance of the starting materials, and then the solution was brought to room temperature under continuous stirring for 20 min. DMF was removed with extractions by using a brine solution and AcOEt, dried over anhydrous Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude was purified by flash chromatography over silica, eluting with AcOEt /hexane 1/9 to furnish the white solid 8 (0.062 g, 58%). $R_f$:...
0.32 (AcOEt /Hex 2/8). m.p. 77-78 °C. 

\(^1\)H NMR: (300 MHz, CDCl\(_3\)) \(\delta = 7.57-7.54\) (m, 3H\(\text{ar}\)), 7.49-7.44 (m, 2H), 7.27-7.19 (m, 5H), 3.66 (t, \(J = 6.0\), 2H, CH\(_2\)), 3.50 (t, \(J = 6.0\), 2H, CH\(_2\)) ppm. 

\(^1\)C NMR: (75 MHz, CDCl\(_3\)) \(\delta = 154.36\) (C=O), 134.90 (C\(\text{ar}\)), 130.64 (C\(\text{ar}\)), 130.34 (C\(\text{ar}\)), 129.70 (C\(\text{ar}\)), 128.50 (C\(\text{ar}\)), 127.85 (C\(\text{ar}\)), 126.79 (C\(\text{ar}\)), 124.45 (C\(\text{ar}\)), 123.15 (C), 48.68 (CH\(_2\)), 41.17(CH\(_3\)) ppm.

4,5-diphenyl-3-(2-(5-phenyl-4-tosyl-1H-1,2,3-triazol-1-yl)ethyl)oxazol-2(3H)-one 4a

To a solution of the azide 8 (0.045 g, 0.15 mmol) and ketone 11a (0.043 g, 0.15 mmol) dissolved in anhydrous DMF (3 mL) was added DBU (0.044 mL, 0.3 mmol) under nitrogen atmosphere. The solution was stirred for 24 h at 50-60°C, at which time TLC indicated the disappearance of the starting materials. Brine (~40 mL) was added and then the reaction mixture was washed with EtOAc (3x10 mL). The organic layer was dried (Na\(_2\)SO\(_4\)) and the solvent evaporated under reduced pressure. The crude extract was purified by flash column chromatography, eluting with hexane/AcOEt 3/7 to provide the white solid 4a (0.062 g, 58%). Rf: 0.11 (hexane/AcOEt 7/3). m.p. 150-152 °C. 

\(^1\)H NMR: (300 MHz, CDCl\(_3\)) \(\delta = 7.68-7.63\) (m, 2H), 7.57-7.49 (m, 2H), 7.47-7.41 (m, 4H), 7.22-7.14 (m, 7H), 7.02-6.98 (m, 2H), 6.93-6.89 (m, 2H), 4.44 (t, \(J = 5.1\), 2H, CH\(_2\)), 3.77 (t, \(J = 5.1\), 2H, CH\(_2\)), 2.35 (s, 3H, CH\(_3\)) ppm.

\(^1\)C NMR: (75.4 MHz, CDCl\(_3\)) \(\delta = 153.39\) (C=O), 145.57 (C), 144.49 (C\(\text{ar}\)), 138.99 (C\(\text{ar}\)), 134.44 (C\(\text{ar}\)), 130.60 (C\(\text{ar}\)), 130.19 (C\(\text{ar}\)), 129.72 (C\(\text{ar}\)), 129.63 (C\(\text{ar}\)), 129.38 (C\(\text{ar}\)), 129.21 (C\(\text{ar}\)), 128.70 (C\(\text{ar}\)), 128.22 (C\(\text{ar}\)), 127.70 (C\(\text{ar}\)), 127.66 (C\(\text{ar}\)), 126.94 (C\(\text{ar}\)), 125.39 (C\(\text{ar}\)), 124.02 (C\(\text{ar}\)), 123.25 (C), 45.44 (CH\(_2\)), 41.32 (CH\(_2\)), 21.29 (CH\(_3\)) ppm. MS [EI+] m/z (%): 562.1674 (M+).

4,5-diphenyl-3-(2-(5-(p-tolyl)-4-tosyl-1H-1,2,3-triazol-1-yl)ethyl)oxazol-2(3H)-one 4b

Following the synthetic procedure for 4a, compound 8 (0.045 g, 0.15 mmol) and 11b (0.042 g, 0.15 mmol) were coupled in the presence of DBU (0.044 mL, 0.3 mmol). The crude extract was purified by flash column chromatography, eluting with hexane/AcOEt 3/7 to provide the white solid 4b (0.0523 g, 61%). Rf: 0.11 (hexane/AcOEt 7/3). m.p. 150-152 °C. 

\(^1\)H NMR: (300 MHz, CDCl\(_3\)) \(\delta = 7.68-7.63\) (m, 2H), 7.57-7.49 (m, 2H), 7.47-7.41 (m, 4H), 7.22-7.14 (m, 7H), 7.02-6.98 (m, 2H), 6.93-6.89 (m, 2H), 4.44 (t, \(J = 5.1\), 2H, CH\(_2\)), 3.77 (t, \(J = 5.1\), 2H, CH\(_2\)), 2.35 (s, 3H, CH\(_3\)) ppm. 

\(^1\)C NMR: (75.4 MHz, CDCl\(_3\)) \(\delta = 153.30\) (C=O), 145.57 (C), 144.49 (C\(\text{ar}\)), 138.99 (C\(\text{ar}\)), 137.33 (C), 134.44 (C\(\text{ar}\)), 130.60 (C\(\text{ar}\)), 130.19 (C\(\text{ar}\)), 129.72 (C\(\text{ar}\)), 129.63 (C\(\text{ar}\)), 129.38 (C\(\text{ar}\)), 129.21 (C\(\text{ar}\)), 128.70 (C\(\text{ar}\)), 128.22 (C\(\text{ar}\)), 127.70 (C\(\text{ar}\)), 127.66 (C\(\text{ar}\)), 126.94 (C\(\text{ar}\)), 125.39 (C\(\text{ar}\)), 124.02 (C\(\text{ar}\)), 123.25 (C), 45.44 (CH\(_2\)), 41.32 (CH\(_2\)), 21.29 (CH\(_3\)) ppm. MS [EI+] m/z (%): 562.1674 (M+).
3-(2-(5-(4-nitrophenyl)-4-tosyl-1H-1,2,3-triazol-1-yl)ethyl)-4,5-diphenyloxazol-2(3H)-one 4c

Following the synthetic procedure for 4a, compound 8 (0.045 g, 0.15 mmol) and 11c (0.047 g, 0.15 mmol) were coupled in the presence of DBU (0.044 mL, 0.3 mmol). The crude extract was purified by flash column chromatography, eluting with hexane/AcOEt 3/7 to give the yellow solid 4c (0.0661 g, 74%). Rf: 0.04 (hexane/AcOEt 7/3). m.p. 219-221 °C. \(^1\)H NMR: (300 MHz, CDCl\(_3\)): \(\delta = 8.30–8.25 (m, 2H), 7.69 (d, J = 8.3, 2H), 7.54–7.40 (m, 3H), 7.24 – 7.17 (m, 7H), 7.14-7.10 (m, 2H), 6.95–6.91 (m, 2H), 4.44 (t, J = 5.4, 2H), 3.71 (t, J = 5.4, 2H), 2.35 (s, 3H) ppm. \(^13\)C NMR: (75.4 MHz, CDCl\(_3\)) \(\delta = 153.66 (C=O), 149.24 (C), 146.66 (C\_ar), 145.37 (C\_ar), 137.08 (C\_ar), 136.98 (C), 135.00 (C\_ar), 131.03 (C\_ar), 130.66 (C\_ar), 130.12 (C\_ar), 130.08 (C\_ar), 129.94 (C\_ar), 128.65 (C\_ar), 128.27 (C\_ar), 128.05 (C\_ar), 126.96 (C\_ar), 125.67 (C), 124.33 (C\_ar), 124.07 (C\_ar), 122.39 (C), 45.98 (CH\_2), 41.48 (CH\_2), 21.66 (CH\_3) ppm. MS [EI\(^+\)] m/z (%): 607.1533 (M\(^+\)).

3-(2-(5-(3-nitrophenyl)-4-tosyl-1H-1,2,3-triazol-1-yl)ethyl)-4,5-diphenyloxazol-2(3H)-one 4d

Following the synthetic procedure for 4a, compound 8 (0.045 g, 0.15 mmol) and 11d (0.047 g, 0.15 mmol) were coupled in the presence of DBU (0.044 mL, 0.3 mmol). The crude extract was purified by flash column chromatography, eluting with hexane/AcOEt 3/7 to afford the yellow solid 4d (0.0625 g, 70%). Rf: 0.06 (hexane/AcOEt 7/3). m.p. 146-149 °C. \(^1\)H NMR: (300 MHz, CDCl\(_3\)): \(\delta = 8.82–8.80 (m, 1H), 8.44 (ddd, J = 8.4, 2.3, 1.1 Hz, 1H), 7.85 (t, J = 2.0 Hz, 1H), 7.74–7.70 (m, 4H), 7.49-7.44 (m, 3H), 7.36 (d, J = 8.3 Hz, 1H), 7.23-7.19 (m, 3H), 7.17–7.12 (m, 2H), 6.93–6.89 (m, 2H), 4.49 (t, J = 5.4 Hz, 2H), 3.77 (t, J = 5.4 Hz, 2H), 2.38 (s, 3H) ppm. \(^13\)C NMR: (75.4 MHz, CDCl\(_3\)) \(\delta = 153.54 (C=O), 150.80 (C), 148.02 (C), 146.52 (C\_ar), 145.28 (C\_ar), 136.64 (C), 135.58 (C\_ar), 134.81 (C\_ar), 131.06 (C\_ar), 130.57 (C\_ar), 130.25 (C\_ar), 129.91 (C\_ar), 129.86 (C\_ar), 128.43 (C\_ar), 128.05 (C\_ar), 127.89 (C\_ar), 126.83 (C\_ar), 125.64 (C\_ar), 124.43 (C\_ar), 124.17 (C\_ar), 122.32 (C), 121.10 (C), 45.77 (CH\_2), 41.39 (CH\_2), 21.52 (CH\_3) ppm. MS [EI\(^+\)] m/z (%): 607.1533 (M\(^+\)).

3-(2-(5-(4-chlorophenyl)-4-tosyl-1H-1,2,3-triazol-1-yl)ethyl)-4,5-diphenyloxazol-2(3H)-one 4e

Following the synthetic procedure for 4a, compound 8 (0.045 g, 0.15 mmol) and 11e (0.046 g, 0.15 mmol) were coupled in the presence of DBU (0.044 mL, 0.3 mmol). The crude extract was purified by flash column chromatography, eluting with hexane/AcOEt 3/7 to furnish the yellow solid 4e (0.0621 g, 72%). Rf: 0.06 (hexane/AcOEt 7/3). m.p. 146-149 °C. \(^1\)H NMR: (300 MHz, CDCl\(_3\)): \(\delta = 8.82–8.80 (m, 1H), 8.44 (ddd, J = 8.4, 2.3, 1.1 Hz, 1H), 7.85 (t, J = 2.0 Hz, 1H), 7.74–7.70 (m, 4H), 7.49-7.44 (m, 3H), 7.36 (d, J = 8.3 Hz, 1H), 7.23-7.19 (m, 3H), 7.17–7.12 (m, 2H), 6.93–6.89 (m, 2H), 4.49 (t, J = 5.4 Hz, 2H), 3.77 (t, J = 5.4 Hz, 2H), 2.38 (s, 3H) ppm. \(^13\)C NMR: (75.4 MHz, CDCl\(_3\)) \(\delta = 153.54 (C=O), 150.80 (C), 148.02 (C), 146.52 (C\_ar), 145.28 (C\_ar), 136.64 (C), 135.58 (C\_ar), 134.81 (C\_ar), 131.06 (C\_ar), 130.57 (C\_ar), 130.25 (C\_ar), 129.91 (C\_ar), 129.86 (C\_ar), 128.43 (C\_ar), 128.05 (C\_ar), 127.89 (C\_ar), 126.83 (C\_ar), 125.64 (C\_ar), 124.43 (C\_ar), 124.17 (C\_ar), 122.32 (C), 121.10 (C), 45.77 (CH\_2), 41.39 (CH\_2), 21.52 (CH\_3) ppm. MS [EI\(^+\)] m/z (%): 607.1533 (M\(^+\)).
5H), 7.23-7.13 (m, 7H), 6.96 (d, J = 8.3, 2H, H$_2$), 4.42 (t, J = 5.2, 2H, CH$_2$), 3.76 (t, J = 5.2, 2H, CH$_2$), 2.36 (s, 3H, CH$_3$) ppm. $^{13}$C NMR: (75.4 MHz, CDCl$_3$) $\delta$ = 153.45 (C=O), 145.88 (C), 144.71 (C$_{ar}$), 137.79 (C$_{ar}$), 137.21 (C), 130.62 (C$_{ar}$), 130.25 (C$_{ar}$), 129.77 (C$_{ar}$), 129.49 (C$_{ar}$), 129.13 (C$_{ar}$), 128.27 (C$_{ar}$), 127.81 (C$_{ar}$), 127.71 (C$_{ar}$), 126.84 (C$_{ar}$), 125.44 (C$_{ar}$), 124.05 (C$_{ar}$), 122.18 (C), 121.65 (C), 45.52 (CH$_2$), 41.19 (CH$_2$), 21.33 (CH$_3$) ppm.

4,5-diphenyl-3-(2-(5-(thiophen-2-yl)-4-tosyl-1H-1,2,3-triazol-1-yl)ethyl)oxazol-2(3H)-one 4f

Following the synthetic procedure for 4a, compound 8 (0.045 g, 0.15 mmol) and 11f (0.043 g, 0.15 mmol) were coupled in the presence of DBU (0.044 mL, 0.3 mmol). The crude extract was purified by flash column chromatography, eluting with hexane/AcOEt 3/7 to provide the yellow oil 4f (0.0593 g, 68%). Rf: 0.11 (hexane/AcOEt 7/3).

$^1$H NMR: (300 MHz, CDCl$_3$): $\delta$ = 7.80-7.68 (m, 4H), 755-752 (m, 2H), 7.48-7.41 (m, 3H), 7.33 (s, 1H), 7.23-7.14 (m, 6H), 6.94-6.90 (m, 1H), 4.53-4.49 (t, J = 5.2, 2H), 3.83-3.80 (t, J = 5.2, 2H), 2.42 (s, 3H, CH$_3$) ppm.

$^{13}$C NMR: (75.4 MHz, CDCl$_3$) $\delta$ = 153.72 (C=O), 146.76 (C), 145.33 (C$_{ar}$), 144.85 (C$_{ar}$), 144.45 (C$_{ar}$), 137.22 (C$_{ar}$), 135.39 (C$_{ar}$), 132.41 (C), 130.69 (C$_{ar}$), 130.57 (C$_{ar}$), 130.51 (C$_{ar}$), 130.40 (C$_{ar}$), 130.22 (C$_{ar}$), 130.17 (C$_{ar}$), 129.86 (C$_{ar}$), 129.74 (C$_{ar}$), 129.63 (C$_{ar}$), 129.58 (C$_{ar}$), 129.49 (C$_{ar}$), 128.56 (C$_{ar}$), 128.50 (C$_{ar}$), 128.40 (C$_{ar}$), 128.37 (C$_{ar}$), 127.93 (C$_{ar}$), 127.89 (C$_{ar}$), 127.72 (C), 124.57 (C$_{ar}$), 124.32 (C), 41.49 (CH$_2$), 41.04 (CH$_2$), 21.59 (CH$_3$) ppm.

3-(2-(5-chlorothiophen-2-yl)-4-tosyl-1H-1,2,3-triazol-1-yl)ethyl)-4,5-diphenyloxazol-2(3H)-one 4g

Following the synthetic procedure for 4a, compound 8 (0.045 g, 0.15 mmol) and 11g (0.047 g, 0.15 mmol) were coupled in the presence of DBU (0.044 mL, 0.3 mmol). The crude extract was purified by flash column chromatography, eluting with hexane/AcOEt 3/7 to yield the brown solid 4g (0.0575 g, 64%). Rf: 0.18 (hexane/AcOEt 7/3). m.p. 82-84 °C.

$^1$H NMR: (300 MHz, CDCl$_3$): $\delta$ = 7.98-7.73 (m, 3H), 7.52-7.44 (m, 3H), 7.28-7.19 (m, 7H), 6.98-6.94 (m, 2H), 6.78-6.75 (m, 1H), 4.52 (t, J = 5.2 Hz, 2H), 3.85 (t, J = 5.2 Hz, 2H), 2.39 (s, 3H, CH$_3$) ppm.

$^{13}$C NMR: (75.4 MHz, CDCl$_3$) $\delta$ = 153.60 (C=O), 146.98 (C), 144.93 (C$_{ar}$), 136.83 (C$_{ar}$), 135.51 (C), 132.15 (C$_{ar}$), 131.71 (C$_{ar}$), 131.49 (C$_{ar}$), 130.30 (C$_{ar}$), 129.73 (C$_{ar}$), 129.62 (C$_{ar}$), 129.58 (C$_{ar}$), 129.51 (C$_{ar}$), 129.26 (C$_{ar}$), 128.79 (C$_{ar}$), 128.74 (C$_{ar}$), 128.44 (C$_{ar}$), 128.26 (C$_{ar}$), 127.85 (C$_{ar}$), 127.81 (C$_{ar}$), 127.20 (C$_{ar}$), 126.91 (C$_{ar}$), 126.87 (C$_{ar}$), 125.43 (C$_{ar}$), 124.15 (C), 122.22 (C$_{ar}$), 119.50 (C), 46.02 (CH$_2$), 41.25 (CH$_2$), 21.38 (CH$_3$) ppm.

3-(2-(5-pentyl-4-tosyl-1H-1,2,3-triazol-1-yl)ethyl)-4,5-diphenyloxazol-2(3H)-one 4h

Following the synthetic procedure for 4a, compound 8 (0.045 g, 0.15 mmol) and 11g (0.047 g, 0.15 mmol) were coupled in the presence of DBU (0.044 mL, 0.3 mmol). The crude extract was purified by flash column chromatography, eluting with hexane/AcOEt 3/7 to yield the brown solid 4h (0.0575 g, 64%). Rf: 0.18 (hexane/AcOEt 7/3). m.p. 82-84 °C.
Following the synthetic procedure for 4a, compound 8 (0.045 g, 0.15 mmol) and 11h (0.038 g, 0.15 mmol) were coupled in the presence of DBU (0.044 mL, 0.3 mmol). The crude extract was purified by flash column chromatography, eluting with hexane/AcOEt 3/7 to give the yellow solid 4h (0.0590 g, 71%). Rf: 0.11 (hexane/AcOEt 7/3). m.p. XX. 1H NMR: (300 MHz, CDCl₃): δ = 8.06 (d, J = 7.1, 1H), 7.58-7.54 (m, 3H), 7.50-7.39 (m, 3H), 7.27-7.18 (m, 6H), 6.95-6.92 (m, 1H), 4.54 (t, J = 5.9, 2H, CH₂), 3.66 (t, J = 6.1, 2H, CH₂), 3.50 (t, J = 5.9, 2H, CH₂), 2.88 (s, 3H, CH₃), 1.61 (q, J = 7.1, 2H, CH₂), 1.34-1.24 (m, 4H), 0.88 (t, J = 6.6 Hz, 3H) ppm. 

13C NMR: (75.4 MHz, CDCl₃) δ= 153.38 (C=O), 148.97(C), 146.39 (Car), 145.10 (C), 136.80 (Car), 136.70(C), 134.73 (Car), 130.75 (Car), 130.39 (Car), 129.85 (Car), 129.81 (Car), 129.77 (Car), 129.66 (Car), 128.38 (Car), 127.99 (Car), 127.77 (Car), 126.69 (Car), 125.39 (C), 124.05 (Car), 123.80 (Car), 122.11 (C), 45.70 (CH₂), 41.21 (CH₂), 21.39 (CH₃) ppm.

3-(2-(4-acetyl-5-methyl-1H-1,2,3-triazol-1-yl)ethyl)-4,5-diphenyloxazol-2(3H)-one 4i

Following the synthetic procedure for 4a, compound 8 (0.045 g, 0.15 mmol) and 11i (0.0147 g, 0.15 mmol) were coupled in the presence of DBU (0.044 mL, 0.3 mmol). The crude extract was purified by flash column chromatography, eluting with hexane/AcOEt 3/7 to afford the brown solid 4i (0.0415 g, 73%). Rf: 0.11 (hexane/AcOEt 7/3). m.p. 151-154 °C. 1H NMR: (300 MHz, CDCl₃): δ = 7.64 – 7.47 (m, 6H), 7.20–7.12 (m, 4H), 4.59 (t, J = 6.0 Hz, 2H, CH₂), 4.01 (t, J = 6.0 Hz, 2H, CH₂), 2.72 (s, 3H, CH₃), 2.42 (s, 3H, CH₂) ppm. 

13C NMR: (75.4 MHz, CDCl₃) δ= 193.89 (C=O), 154.05 (C=O), 143.41 (C), 141.78 (C), 137.00 (Car), 136.94 (Car), 130.37 (C), 130.02 (Car), 129.53 (Car), 128.35 (Car), 129.81 (Car), 129.77 (Car), 129.66 (Car), 128.38 (Car), 127.99 (Car), 127.77 (Car), 125.39 (C), 124.05 (Car), 123.80 (Car), 122.11 (C), 45.70 (CH₂), 41.21 (CH₂), 27.56 (CH₃), 8.44 (CH₃) ppm. MS [EI⁺] m/z (%): 388.1536 (M⁺).

3-(2-(4-benzoyl-5-phenyl-1H-1,2,3-triazol-1-yl)ethyl)-4,5-diphenyloxazol-2(3H)-one 4j

Following the synthetic procedure for 4a, compound 8 (0.045 g, 0.15 mmol) and 11j (0.0336 g, 0.15 mmol) were coupled in the presence of DBU (0.044 mL, 0.3 mmol). The crude extract was purified by flash column chromatography, eluting with hexane/AcOEt 3/7 to furnish the yellow solid 4j (0.0545 g, 71%). Rf: 0.11 (hexane/AcOEt 7/3). m.p. 151-154 °C. 1H NMR: (300 MHz, CDCl₃): δ = 8.29–8.25 (m, 2H), 7.61–7.39 (m, 11H), 7.22–7.13 (m, 5H), 7.04 – 7.00 (m, 2H), 4.55–4.50 (t, J = 5.4 Hz, 2H, CH₂), 3.86 – 3.82 (t, J = 5.4 Hz, 2H, CH₂) ppm. 

13C NMR: (75.4 MHz, CDCl₃) δ= 185.83 (C=O), 153.59 (C=O), 143.49 (C), 141.78 (C), 136.66 (Car), 134.56 (Car), 132.83 (Car), 130.38 (Car), 130.16 (Car), 129.92 (Car), 129.46 (Car), 129.05 (Car), 128.69 (Car), 128.21 (Car),
127.99 (C\textsubscript{ar}), 127.66 (C\textsubscript{ar}), 127.06 (C\textsubscript{ar}), 125.85 (C\textsubscript{ar}), 125.41 (C), 124.09 (C\textsubscript{ar}), 122.24 (C), 45.35 (CH\textsubscript{3}), 41.56 (CH\textsubscript{2}) ppm. MS [EI\textsuperscript{+}] m/z (%): 512.1845 (M\textsuperscript{+}).

1-(2-(2-oxo-4,5-diphenyloxazol-3(2H)-yl)ethyl)-5-phenyl-1H-1,2,3-triazole-4-carbonitrile 4k

Following the synthetic procedure for 4a, compound 8 (0.045 g, 0.15 mmol) and 11k (0.0213 g, 0.15 mmol) were coupled in the presence of DBU (0.044 mL, 0.3 mmol). The crude extract was purified by flash column chromatography, eluting with hexane/AcOEt 3/7 to provide the yellow solid 4k (0.0636 g, 67%). Rf: 0.09 (hexane/AcOEt 3/7). m.p. 134-136 °C. \textsuperscript{1}H NMR: (300 MHz, CDCl\textsubscript{3}): \(\delta = 7.59-7.46 \text{ (m, } 6\text{H}), 7.25-7.14 \text{ (m, } 7\text{H}), 7.07-7.03 \text{ (m, } 2\text{H}), 4.62 \text{ (t, } J = 5.5 \text{ Hz, } 2\text{H, CH}_2\text{), 3.88 \text{ (t, } J = 5.5 \text{ Hz, } 2\text{H, CH}_2\text{) ppm.} \textsuperscript{13}C NMR: (75.4 MHz, CDCl\textsubscript{3}) \(\delta = 153.51 \text{ (C=O), 143.79 (C), 134.72 (C\textsubscript{ar}), 131.13 \text{ (C\textsubscript{ar}), 130.28 (C\textsubscript{ar}), 129.78 (C\textsubscript{ar}), 129.74 (C\textsubscript{ar}), 129.54 (C\textsubscript{ar}), 129.47 (C\textsubscript{ar}), 128.31 (C\textsubscript{ar}), 128.24 (C\textsubscript{ar}), 127.82 (C\textsubscript{ar}), 124.12 (C\textsubscript{ar}), 124.02 (C\textsubscript{ar}), 122.30 (C\textsubscript{ar}), 121.97 (C), 120.32 (C), 111.38 (C), 46.04 (CH\textsubscript{3}), 41.19 (CH\textsubscript{2}) ppm. MS [EI\textsuperscript{+}] m/z (%): 433.1538 (M\textsuperscript{+}).

2.2. Microbiology

The culture medium used is synthetic medium RPMI 1640 with glutamine and without sodium bicarbonate, buffered with morpholino propane sulfonic acid (MOPS) 0.164 M adjusted to pH 7 ± 0.1 and with 0.2% glucose. The standard compound is Itraconazole.

Method M27-A3 Yeast.

A) Antifungals insoluble in water (itraconazole)

1. Prepare a solution with a concentration of 1600 \(\mu\text{g} / \text{ml} \) (100 times the highest concentration of antifungal to be tested) and dissolve it in dimethyl sulfoxide (DMSO). (FigureSI- 1).

![Figure SI-1. Dilutions of water-insoluble antifungals.](image-url)
The second step of the preparation is to make a 1:50 dilution to obtain a final concentration of 16-0.03 μg/mL. This process is shown in Figure SI-2.

Figure SI-2. Filling the plates.

**B) Preparation of the inoculum.**

It is prepared by touching with the culture loop 5 colonies ≥1 mm and 24 h growth on SDA plaques that are resuspended in a saline tube (0.85% NaCl). Stir well and, with the aid of a spectrophotometer (wavelength: 530 nm), adjust to a 0.5 McFarland optical density, adding the required amount of saline. This solution has an approximate concentration of 1x10⁶ - 5x10⁶ CFU/ml. Subsequently a 1:1000 dilution is performed with RPMI medium. This last dilution is the one used to inoculate the antifungal plaques.

**C) Inoculation of plaques**

They are inoculated with 100 μl of the yeast suspension from well 2 to 12. Column No.1 containing 200 μl of RPMI is used for the control of sterility of the medium. Column No.12 does not contain antifungal but must have the same solvent concentration as the antifungal wells. It is growth control.

**D) Incubation of plates**

The plates are incubated at 35 °C. Those inoculated with *Candida* species for 48 h.

**E) Visual Reading.**

The visual reading should be done with the help of an inverted mirror. Azoles and 5-fluorocytosine: MIC is the lowest concentration of antifungal that produces an apparent reduction in yeast growth (≥50%), compared to control growth after 48 h of incubation.

**Method M38-A. Filamentous fungi.**

The characteristics of the culture medium, pH, preparation of the antifungal stock solution and dilutions are the same as those of the M27-A3 method. So far by this method the species of the genus *Aspergillus, Fusarium, Rhizopus*, as well as in *Pseudallescheria boydii* and in the micellar forms of *Sporothrix schenckii* have been evaluated.

In the genus *Aspergillus* and *P. boydii* species, *R. arrhizus* and *S. schenckii* the inoculum is prepared from a 7 day growth culture at 35 °C on potato glucose agar (PDA), a medium that induces formation of conidia or
sporangiospores. The inoculums of the evaluated strains of *Trichosporon cutaneum*, *Rhizopus oryzae* and *Mucor hiemalis*, were prepared as described by Method M38-A for *Aspergillus fumigatus*.

A) Preparation of the inoculum.

1. To facilitate the collection of conidia, introduce the culture handle in Tween 20 and pass it over the conidia; then resuspend in saline.

2. Allow the particles to settle for 3-5 min, transfer the supernatant to another tube and shake vigorously for 15 seconds.

3. Because the size of the conidia is different for each species, the optical density (OD) to obtain a concentration of $1-5 \times 10^6$ will vary with the species. For *Aspergillus spp.* is adjusted to an OD of 0.09-0.17 (80-82% transmittance): 0.41-0.56 McFarland.

4. Dilute 1/50 in RPMI 1640.

B) Visual Reading.

The visual reading should be done with the help of an inverted mirror. MIC of azoles is the lowest concentration that results in total inhibition of growth (100%).

### 2.2.1. Reproducibility

The following tables show the results obtained in triplicate using the inverted mirror observation method indicated in the CLSI documents M27-A3 and M48-A

<table>
<thead>
<tr>
<th>Compound</th>
<th>C. albicans</th>
<th>C. tropicalis</th>
<th>C. utilis</th>
<th>C. krusei</th>
<th>C. glabrata</th>
<th>C. parapsilosis</th>
</tr>
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<td>3</td>
<td>1</td>
<td>2</td>
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</tr>
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<td>8</td>
<td>8</td>
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</tbody>
</table>

**Standard**

| 0.03 | 0.03 | 0.03 | 0.06 | 0.06 | 0.06 | 0.25 | 0.25 | 0.25 | 0.25 | 0.25 | 0.25 | 1 | 1 | 1 | 0.06 | 0.06 | 0.06 |

**Abbreviations:** C., Candida, *Itraconazole*.

Determination of the sensitivity of yeast (according to document M27-A3): Susceptible (S), dose-dependent sensitive (SDD) and resistant (R).

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<th>Compound</th>
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<th>C. gla</th>
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<td>R</td>
<td>R</td>
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<td>R</td>
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<td>SDD</td>
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<tr>
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<td>R</td>
<td>R</td>
<td>R</td>
<td>S</td>
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### Abbreviations:
- C. alb.: Candida albicans
- C. trop.: Candida tropicalis
- C. uti.: Candida utilis
- C. kru.: Candida krusei
- C. gla.: Candida glabrata
- C. par.: Candida parapsilosis

**Itraconazole. Interpretive criteria:** Breakpoints (MIC, μg/mL) = 0.12 [S], 0.25–0.5 [SDD], 1 [R].

**In vitro antifungal activities of synthesized compounds in filamentous fungi (MIC, mg/mL)**

<table>
<thead>
<tr>
<th>Compound</th>
<th>M. hiemalis</th>
<th>A. fumigatus</th>
<th>T. cutaneum</th>
<th>R. oryzae</th>
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**Abbreviations:** M. hiem.: Mucor hiemalis; A. fum.: Aspergillus fumigatus; T. cut.: Trichosporon cutaneum; R. ory.: Rhizopus oryzae

*Itraconazole.*
3. Copies of $^1$H-NMR, $^{13}$C-NMR and Mass spectra of all compounds
Compound 8
**Instrument:** JEOL GCmate  
**Inlet:** My Inlet  
**Ionization mode:** EI+  

Scan: 355-357  
Base: m/z 562; 6.1% FS  
TIC: 245287  
R.T.: 4.76  
#Ions: 150  

Selected Isotopes: $\text{H}_2\text{O}$, $\text{C}_{12}$, $\text{N}_{14}$, $\text{O}_{16}$, $\text{S}_{32}$  
Error Limit: 5 ppm  

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<tr>
<th>Measured Mass</th>
<th>% Base</th>
<th>Formula</th>
<th>Calculated Mass</th>
<th>Error</th>
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Compound 4b
Instrument: JEOL GC mate
Inlet: My Inlet
Ionization mode: EI+

Scan: 173
Base: m/z 607; 1.2% FS TIC: 156256
R.T.: 2.31
Ions: 114

Selected Isotopes: H₂₃C₂₃N₄O₅S₂
Error Limit: 5 ppm

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<th>Formula</th>
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<td>C₂₃H₂₃N₄O₅S₂</td>
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Compound 4d
Instrument: JEOL GCmate
Inlet: My Inlet
Ionization mode: EI+

Scan: 177-179
Base: m/z 555; 7% FS TIC: 140287
R.T.: 2.27
#Ions: 135

Selected Isotopes: \( \text{H}_{0.25} \text{C}_{0.32} \text{N}_{0.5} \text{O}_{0.6} \text{S}_{1.1} \)
Error Limit: 5 ppm

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Compound 4e
Instrument: JEOL GCmate
Inlet: My Inlet
Ionization mode: EI+

Scan: 135
Base: m/z 596; 3.3% FS TIC: 209040

R.T.: 1.8
Ions: 114

Selected Isotopes: H\textsubscript{0.25}C\textsubscript{6.32}N\textsubscript{0.4}O\textsubscript{8.6}S\textsubscript{0.1}Cl\textsubscript{0.1}

<table>
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Error Limit: 5 ppm
Compound 4g
Compound 4h
Compound 4i
Instrument: JEOL GCmate
Inlet: My Inlet
Ionization mode: EI+

Scan: 352
Base: m/z 381; 2.7% FS TIC: 217536
R.T.: 4.68
#Ions: 134

Selected Isotopes: \( \text{H}\text{H}^{26}\text{C}\text{C}^{12}\text{N}^{14}\text{O}^{16}\text{O}^{16}\)
Error Limit: 5 ppm

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Compound 4j
Instrument: JEOL GCmate
Inlet: My Inlet
Ionization mode: EI+

Scan: 393  R.T.: 5.2
Base: m/z 512; 3.9% FS  TIC: 210064  #Ions: 135

Selected Isotopes: $\text{H}_0\text{.C}_0\text{.N}_0\text{.D}_0\text{.H}_0\text{.D}_0\text{.H}_0\text{.D}_0$
Error Limit: 5 ppm

<table>
<thead>
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<th>Measured Mass</th>
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<th>Formula</th>
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</table>
Compound 4k
Instrument: JEOL GCmate
Inlet: My Inlet  Ionization mode: EI+

Scan: 168  R.T.: 2.24
Base: m/z 433; 5% FS TIC: 229424  #Ions: 129

Selected isotopes: H2062C18O2N205O2
Error Limit: 5 ppm

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<tr>
<th>Measured Mass</th>
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