Synthesis of Fully Functionalized 3-Bromoazaspiro[4.5]trienones through Ugi Four-Component Reaction (Ugi-4CR) followed by ipso-Bromocyclization

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Received: 03.05.2018  
Accepted after revision: 15.06.2018  
Published online: 19.07.2018  
License terms: 

Abstract  
Biologically attractive azaspiro[4,5]trienones have been prepared via Ugi four-component reaction (Ugi-4CR) followed by bromine-mediated ipso-cyclization. This allows a straightforward synthetic route to a diverse collection of fully functionalized 3-bromoazaspiro[4,5]trienones in moderate to good yields that can be used as templates for further modifications.

Key words  
aldehydes, spiro compounds, cyclization, radical reaction, ring closure

Azaspirocycles, which are nitrogen-containing spirocyclic scaffolds, play significant roles in synthetic and medicinal chemistry. Literature searches on azaspiro cyclic scaffolds have shown that these derivatives possess a broad spectrum of biological and pharmacological properties such as antimitotic, cytotoxic, antibacterial, antimicrobial, ant-inflammatory, antioxidative and antidepressant activities. A few examples of natural and synthetic drugs containing an azaspirocyclic skeleton are shown in Figure 1. Consequently, great efforts have been made to synthesize diverse azaspirocyclic libraries to facilitate the incorporation of these moieties into more biologically and pharmacaceutically active molecules.

Among the recently synthesized azaspirocyclic-containing compounds, azaspiro[4,5]trienones have attracted a great deal of attention due to their chemistry and their biological activities. Very recently, and in the light of the intense interest to develop constrained tamoxifen mimics, Srivastava et al. reported azaspiro[4,5]trienones as novel scaffolds for anticancer drug development (Figure 2, top structure). Furthermore, these compounds serve as valuable intermediates for the construction of azaspiro-fused tricyclic cores with promising anticancer activity by inducing DNA damage (Figure 2). Therefore, more attention has been drawn to the synthesis of functionalized azaspiro[4,5]trienones suitable for further derivatization processes.
Brominated substrates are excellent synthons for further functionalization because they can be further used in well-established cross-coupling reactions, whereas other approaches to such transformations are complex and often result in significant by-product formation. In this respect, especially in light of the fact that brominated triene-diones are ideal scaffolds for further elaboration in the diversity-oriented synthesis, Qiu et al. have recently described the synthesis of 3-bromo-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione through a novel ZnBr$_2$-promoted oxidative ipso-anellation of N-arylpropiolamide.

In light of these findings and as a result of our interest in combination of the Ugi four-component reaction (Ugi-4CR) with efficient post-transformations for generating complex and diverse molecular libraries, we wish to report herein, a simple procedure for the synthesis of fully functionalized 3-bromoazaspiro[4.5]trienones via Ugi-4CR followed by ipso-bromocyclization. (Scheme 1).

Ugi 4-CR of 4-methoxybenzaldehyde (1a), aniline (2a), phenylpropiolic acid (3), and tert-butyl isocyanide (4a) in methanol at room temperature furnished the corresponding Ugi adduct 5a in 83% yield. This compound was chosen as the model substrate to investigate the bromine-mediated ipso-cyclization conditions. Application of (NH$_4$)$_2$S$_2$O$_8$/TBHP (3 equiv/5 equiv) as the oxidant in the presence of N-methylmorpholine (NMM, 0.5 equiv) in acetonitrile at 80 °C under argon atmosphere produced the desired product 6a with a yield of 88%. After screening solvents under these conditions, acetonitrile was found to be the best solvent (Table 1, entries 1–7). When N-methyl-2-pyrrolidone (NMP) was used in place of NMM, a marginal decrease in yield was recorded (entry 8). The application of NMM gave 6a with a yield of 88%, while replacement with triethylamine (TEA), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and N,N-diisopropylethylamine (DIEA) resulted in lower yields (entries 9–11). Other radical initiators including di-tert-butyl peroxide (DTBP), benzoyl peroxide (BP), and m-chloroperbenzoic acid (m-CPBA) were then employed, but all failed to give satisfactory yields (entries 12–14).

After carrying out the Ugi 4-CR, the solvent was evaporated under reduced pressure, and the conditions were switched for the bromine-mediated ipso-cyclization, which gave compound 6a in 67% overall yield, comparable with the 73% total yield obtained in the two-step procedure.

Subsequently, the scope of the reaction was investigated by using different aromatic aldehydes, anilines, and isocyanides (Scheme 2).

The structures of the products were confirmed based on NMR spectroscopy and HRMS (ESI) analysis. The characteristic resonances in the $^1$H NMR spectra of all synthesized compounds appeared as four double doublets with coupling constants 9.9 and 1.8 Hz for the sp$^2$ C–H under argon atmosphere produced the desired product 6a with a yield of 88%. After screening solvents under these conditions, acetonitrile was found to be the best solvent (Table 1, entries 1–7). When N-methyl-2-pyrrolidone (NMP) was used in place of NMM, a marginal decrease in yield was recorded (entry 8). The application of NMM gave 6a with a yield of 88%, while replacement with triethylamine (TEA), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and N,N-disopropylethylamine (DIEA) resulted in lower yields (entries 9–11). Other radical initiators including di-tert-butyl peroxide (DTBP), benzoyl peroxide (BP), and m-chloroperbenzoic acid (m-CPBA) were then employed, but all failed to give satisfactory yields (entries 12–14).

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The spectra of compounds exhibited characteristic signals at $\delta = 165.6, 166.9, 184.0$ ppm associated with the carbonyls of the amidic moieties and unsaturated ketone.

Initially, the effect of ring substituents on the aromatic aldehydes $6a–f$ was examined. Both electron-donating and electron-withdrawing substituents on the phenyl ring were tolerated as outlined (Scheme 2). With regard to the isocyanide component, tert-butyl isocyanide furnished the desired products in better yields than cyclohexyl isocyanide. A survey of aniline derivatives with differing substitution patterns revealed that aniline derivatives bearing substituents at the ortho-position were consistent with the optimal conditions, providing $6m$ and $6n$ in moderate to good yields.

Treatment of para-halogen-substituted anilines with 4-chlorobenzaldehyde ($1b$), phenylpropionic acid ($3$), and tert-butyl isocyanide ($4a$) delivered product $6b$, but the reaction did not proceed at all when the aniline ring contained a para-nitro group (Scheme 3). It is noteworthy that, in all cases where yields were lower than average, the reaction was inefficient at the ipso-bromocyclization step, with a complex mixture of products being obtained.

### Table 1 Optimization of the Reaction Conditions for the Synthesis of 3-Bromoazaspiro[4.5]trienone $6a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant (3 equiv)</th>
<th>Base (0.5 equiv)</th>
<th>Solvent</th>
<th>Yield $6a$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$(\text{NH}_4)_2\text{S}_2\text{O}_8$/TBHP</td>
<td>NMM</td>
<td>DMF</td>
<td>trace</td>
</tr>
<tr>
<td>2</td>
<td>$(\text{NH}_4)_2\text{S}_2\text{O}_8$/TBHP</td>
<td>NMM</td>
<td>EtOH</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>$(\text{NH}_4)_2\text{S}_2\text{O}_8$/TBHP</td>
<td>NMM</td>
<td>DCE</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>$(\text{NH}_4)_2\text{S}_2\text{O}_8$/TBHP</td>
<td>NMM</td>
<td>toluene</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>$(\text{NH}_4)_2\text{S}_2\text{O}_8$/TBHP</td>
<td>NMM</td>
<td>$\text{H}_2\text{O}$</td>
<td>trace</td>
</tr>
<tr>
<td>6</td>
<td>$(\text{NH}_4)_2\text{S}_2\text{O}_8$/TBHP</td>
<td>NMM</td>
<td>$\text{H}_2\text{O}$/MeCN</td>
<td>25</td>
</tr>
<tr>
<td>7</td>
<td>$(\text{NH}_4)_2\text{S}_2\text{O}_8$/TBHP</td>
<td>NMM</td>
<td>MeCN</td>
<td>88</td>
</tr>
<tr>
<td>8</td>
<td>$(\text{NH}_4)_2\text{S}_2\text{O}_8$/TBHP</td>
<td>NMP</td>
<td>MeCN</td>
<td>75</td>
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<tr>
<td>9</td>
<td>$(\text{NH}_4)_2\text{S}_2\text{O}_8$/TBHP</td>
<td>TEA</td>
<td>MeCN</td>
<td>40</td>
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<tr>
<td>10</td>
<td>$(\text{NH}_4)_2\text{S}_2\text{O}_8$/TBHP</td>
<td>DBU</td>
<td>MeCN</td>
<td>59</td>
</tr>
<tr>
<td>11</td>
<td>$(\text{NH}_4)_2\text{S}_2\text{O}_8$/TBHP</td>
<td>DIEA</td>
<td>MeCN</td>
<td>63</td>
</tr>
<tr>
<td>12</td>
<td>$(\text{NH}_4)_2\text{S}_2\text{O}_8$/TBHP</td>
<td>NMM</td>
<td>MeCN</td>
<td>23</td>
</tr>
<tr>
<td>13</td>
<td>$(\text{NH}_4)_2\text{S}_2\text{O}_8$/TBHP</td>
<td>NMM</td>
<td>MeCN</td>
<td>20</td>
</tr>
<tr>
<td>14</td>
<td>$(\text{NH}_4)_2\text{S}_2\text{O}_8$/m-CPBA</td>
<td>NMM</td>
<td>MeCN</td>
<td>57</td>
</tr>
<tr>
<td>15</td>
<td>$(\text{NH}_4)_2\text{S}_2\text{O}_8$/TBHP</td>
<td>NMM</td>
<td>MeCN</td>
<td>41</td>
</tr>
</tbody>
</table>

*Optimal reaction condition: $5a$ (1 equiv), NBS (1.5 equiv), $(\text{NH}_4)_2\text{S}_2\text{O}_8$ (3 equiv), TBHP (5 equiv), and NMM (0.5 equiv) in MeCN (2 mL) at 80 °C under argon atmosphere for 12 h.

*Isolated yield.

*This reaction was performed at room temperature.
Scheme 2 Substrate scope for the synthesis of fully functionalized 3-bromoazaspiro[4.5]trienones 6a–n

Scheme 3 The effect of halogen substituents on the aniline ring at the para-position
Crude products were purified on a silica gel column (EtOAc/n-hexane, 1:5) and the purified compounds were fully characterized by IR, $^1$H NMR, $^{13}$C NMR spectroscopy and HRMS analysis. In addition, in the case 6a, the structure was confirmed by single-crystal X-ray diffraction analysis (Figure 3).

The proposed reaction mechanism involves the formation of vinyl radical I through the addition of a bromo radical generated from NBS and $(\text{NH}_4)_2\text{S}_2\text{O}_8$ to the alkyne group of the Ugi product. Subsequent intramolecular radical cyclization yields the intermediate II. Trapping of the radical intermediate II by the tert-butylperoxy radical generated from TBHP, and then elimination of tert-butyl alcohol provides the desired product (Scheme 4).

In conclusion, we have prepared a diverse array of fully functionalized 3-bromoazaspiro[4.5]trienones through Ugi-4CR followed by ipso-bromocyclization. Considering the biological importance of azaspiro[4.5]trienones and the potential utility of the bromo organic compounds to participate in further modifications, these compounds can be further exploited in the synthesis of lead compounds in medicinal chemistry.

**Funding Information**

We would like to thank the Iran National Science Foundation (INSF, Grant No. 96003234) and the National Institute for Medical Research Development (NIMAD, Grant No. 963388) for their financial support.

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**Scheme 4** The proposed reaction mechanism for the synthesis of 3-bromoazaspiro[4.5]trienones 6a–l

**Figure 3** ORTEP view of compound 6a
Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610205.

References

calcd. for $\text{C}_{27}\text{H}_{24}\text{Br}_{2}\text{N}_2\text{NaO}_3$: 605.0046; found: 605.0051; $m/z$ [M+K]$^+$ calcd. for $\text{C}_{27}\text{H}_{24}\text{Br}_{2}\text{KN}_2\text{O}_3$: 620.9785; found: 620.9794. IR: 1621, 1692, 1709, 3417 cm$^{-1}$.

2-(3-Bromo-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-3,6,9-trien-1-yl)-$N$-cyclohexyl-2-(4-fluorophenyl)acetamide (6h)

Yield: 263 mg (48%); colorless solid; m.p. 268–269 °C; $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ = 1.015–1.14 (m, 3 H, H-cyc), 1.22–1.32 (m, 2 H, H-cyc), 1.57 (s, 3 H, H-cyc), 1.76–1.93 (m, 2 H, H-cyc), 3.76–3.78 (m, 1 H, H-cyc), 4.83 (s, 1 H, C(sp$^3$)-H), 5.65 (d, $J$ = 7.8 Hz, 1 H, N-H), 6.27 (d, $J$ = 9.9 Hz, 1 H, =CH), 6.32 (d, $J$ = 9.9 Hz, 1 H, =CH), 5.50 (dd, $J$ = 9.9, 2.4 Hz, 1 H, =CH), 6.78 (dd, $J$ = 9.9, 2.4 Hz, 1 H, =CH), 7.04 (t, $J$ = 8.7 Hz, 2 H, H-Ar), 7.27 (d, $J$ = 7.2 Hz, 2 H, H-Ar), 7.35 (d, $J$ = 7.2 Hz, 2 H, H-Ar), 7.40–7.65 (m, 3 H, H-Ar). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 24.5, 24.6, 25.3, 32.5, 32.7, 49.1, 61.1, 69.6, 116.2 (d, $J_{C,F}$ = 21.0 Hz), 119.8, 127.8, 128.4, 128.6, 130.2 (d, $J_{C,F}$ = 7.8 Hz), 131.0, 131.4, 131.5, 132.6, 132.7, 143.9, 144.2, 152.6, 161.4, 165.9, 166.4, 183.8. HRMS (ESI): $m/z$ [M+H]$^+$ calcd. for $\text{C}_{29}\text{H}_{27}\text{BrF}\text{N}_2\text{O}_3$: 549.1184; found: 549.1187; $m/z$ [M+K]$^+$ calcd. for $\text{C}_{29}\text{H}_{30}\text{BrFK}\text{N}_2\text{O}_3$: 587.0742; found: 587.0746. IR: 1659, 1713, 3254 cm$^{-1}$.

$N$-(tert-butyl)-2-(3,6-dibromo-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-3,6,9-trien-1-yl)-2-phenylacetamide (6m)

Yield: 222 mg (38%); yellow solid; m.p. 238–239 °C; $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ = 1.36 (s, 9 H, 3 Me), 5.38 (s, 1 H, C(sp$^3$)-H), 5.97 (br, s, 1 H, N-H), 6.26 (dd, $J$ = 9.9, 1.6 Hz, 1 H, =CH), 6.28 (d, $J$ = 1.6 Hz, 1 H, =CH), 7.20–7.42 (m, 11 H, H-Ar, =CH). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 28.6, 52.0, 63.3, 72.7, 121.0, 128.0, 128.2, 128.6, 129.1, 129.7, 130.2, 130.6, 130.9, 131.7, 135.9, 142.8, 144.0, 152.5, 166.6, 167.2, 181.9. MS (ESI): $m/z$ [M+H]$^+$ found for $\text{C}_{27}\text{H}_{24}\text{Br}_2\text{N}_2\text{O}_3$: 582.6; $m/z$ [M+H]$^+$ found for $\text{C}_{27}\text{H}_{26}\text{Br}_2\text{N}_2\text{O}_3$: 584.6; IR: 1713, 3322 cm$^{-1}$.