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

DOI: 10.1055/s-0037-1610205; Art ID: so-2018-d0033-I

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 alkynes, 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 azaspirocyclic scaffolds have shown that these derivatives possess a broad spectrum of biological and pharmacological properties such as antimitotic, cytotoxic, antibacterial, antimicrobial, anti-inflammatory, antioxidative and antidepressant activities.¹ A few examples of natural and synthetic drugs containing an azaspirocyclic skeleton are shown in Figure 1.² Consequently, great efforts have been made to synthesize diverse azaspirocycles libraries to facilitate the incorporation of these moieties into more biologically and pharmaceutically active molecules.^{3–7}

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.⁸ Very recently, and in the light of the intense interest to develop constrained tamoxifen mimics,

Figure 1 Structures of some natural and synthetic drugs containing an azaspirocyclic skeleton

Srivastava et al. reported azaspiro[4.5]trienones as novel scaffolds for anticancer drug development (Figure 2, top structure).⁹ 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).^{10–12} Therefore, more attention has been drawn to the synthesis of functionalized azaspiro[4.5]trienones suitable for further derivatization processes.^{13–15}

Figure 2 Recently reported cytotoxic azaspiro[4.5]trienones and cytotoxic alkaloids with azaspiro-fused tricyclic cores

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.¹⁶ 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*-annulation of *N*-arylpropiolamide.⁵

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,¹⁷ 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**), phenylpropionic 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 $(\text{NH}_4)_2\text{S}_2\text{O}_8$ /TBHP (3 equiv/5 equiv) as the oxidant in the presence of *N*-methylmorpholine (NMM, 0.5 equiv) in acetonitrile at 80 °C un-

der 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*-chloroperoxybenzoic 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).¹⁸

The structures of the products were confirmed based on NMR spectroscopy and HRMS (ESI) analysis. The characteristic resonances in the ^1H 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. The ^{13}C NMR spec-

Scheme 1 Synthesis of 3-bromoazaspiro[4.5]trienones **6a–n** via Ugi-4CR followed by *ipso*-bromocyclization

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

Entry	Oxidant (3 equiv/ 5 equiv)	Base (0.5 equiv)	Solvent	Yield 6a (%) ^b
1	(NH ₄) ₂ S ₂ O ₈ /TBHP	NMM	DMF	trace
2	(NH ₄) ₂ S ₂ O ₈ /TBHP	NMM	EtOH	20
3	(NH ₄) ₂ S ₂ O ₈ /TBHP	NMM	DCE	20
4	(NH ₄) ₂ S ₂ O ₈ /TBHP	NMM	toluene	15
5	(NH ₄) ₂ S ₂ O ₈ /TBHP	NMM	H ₂ O	trace
6	(NH ₄) ₂ S ₂ O ₈ /TBHP	NMM	H ₂ O/MeCN	25
7	(NH₄)₂S₂O₈/TBHP	NMM	MeCN	88
8	(NH ₄) ₂ S ₂ O ₈ /TBHP	NMP	MeCN	75
9	(NH ₄) ₂ S ₂ O ₈ /TBHP	TEA	MeCN	40
10	(NH ₄) ₂ S ₂ O ₈ /TBHP	DBU	MeCN	59
11	(NH ₄) ₂ S ₂ O ₈ /TBHP	DIEA	MeCN	63
12	(NH ₄) ₂ S ₂ O ₈ /DTBP	NMM	MeCN	23
13	(NH ₄) ₂ S ₂ O ₈ /BPO	NMM	MeCN	20
14	(NH ₄) ₂ S ₂ O ₈ / <i>m</i> -CPBA	NMM	MeCN	57
15	(NH ₄) ₂ S ₂ O ₈ /TBHP	NMM	MeCN	41 ^c

^a Optimal reaction condition: **5a** (1 equiv), NBS (1.5 equiv), (NH₄)₂S₂O₈ (3 equiv), TBHP (5 equiv), and NMM (0.5 equiv) in MeCN (2 mL) at 80 °C under argon atmosphere for 12 h.

^b Isolated yield.

^c This reaction was performed at room temperature.

tra of compounds exhibited characteristic signals at δ = 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 pat-

terns 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.

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, ^1H 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).

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

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 partake 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.

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

Supporting Information

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

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- (18) **Sequential U4-CR/*ipso*-Bromocyclization to Synthesize Compounds 6a–o; General Procedure**
To a solution of aldehyde **1a** (1 mmol) in methanol (5 mL) was added aniline **2a** (1 mmol), and the reaction mixture was stirred at room temperature for 2 h. Then, phenylpropionic acid **3a** (1 mmol) was added and stirring was continued for 15 min, followed by addition of isocyanide **4a** (1 mmol); the solution was then stirred for 24 h at room temperature. The solvent was removed under reduced pressure and MeCN (10 mL) was added to the residue. *N*-Bromosuccinimide (1.5 mmol), (NH₄)₂S₂O₈ (3 mmol), TBHP (5 mmol) and NMM (0.5 mmol) were added and the reaction mixture was stirred at 80 °C for 12 h under an argon atmosphere. The progress of the reaction was monitored using TLC (*n*-hexane–EtOAc, 5:1). The resulting reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography (silica gel, appropriate mixture of *n*-hexane/ethyl acetate) to afford **6a**.
2-(3-Bromo-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-3,6,9-trien-1-yl)-*N*-(*tert*-butyl)-2-(4-methoxyphenyl)acetamide (6a)
Yield: 357 mg (67%); colorless solid; m.p. 240–242 °C; ¹H NMR (CDCl₃, 300 MHz): δ = 1.30 (s, 9 H, 3 Me), 3.79 (s, 3 H, -OCH₃), 4.77 (s, 1 H, C(sp³)-H), 5.50 (s, 1 H, N-H), 6.21 (dd, *J* = 9.9, 1.8 Hz, 1 H, =CH), 6.24 (dd, *J* = 9.9, 1.8 Hz, 1 H, =CH), 6.53 (dd, *J* = 9.9, 3.1 Hz, 1 H, =CH), 6.70 (dd, *J* = 9.9, 3.1 Hz, 1 H, =CH), 6.83 (d, *J* = 8.7 Hz, 2 H, H-Ar), 7.20–7.28 (m, 2 H, H-Ar), 7.30–7.34 (m, 3 H, H-Ar), 7.36 (d, *J* = 8.7 Hz, 2 H, H-Ar). ¹³C NMR (75 MHz CDCl₃): δ = 28.5, 51.9, 55.3, 62.1, 69.5, 114.3, 120.1, 127.1, 127.8, 128.5, 130.0, 130.1, 131.0, 132.1, 132.2, 144.4, 152.3, 160.2, 165.6, 166.9, 184.0. HRMS (ESI): *m/z* [M+H]⁺ calcd. for C₂₈H₂₈⁷⁹BrN₂O₄: 535.1227; found: 535.1232; *m/z* [M+Na]⁺ calcd. for C₂₈H₂₇⁷⁹BrN₂NaO₄: 557.1046; found: 557.1050; *m/z* [M+K]⁺ calcd. for C₂₈H₂₇⁷⁹BrKN₂O₄: 573.0786; found: 573.0791; *m/z* [2 M+H]⁺ calcd. for C₅₆H₅₅⁷⁹Br₂N₄O₈: 1069.2381; found: 1069.2394; *m/z* [2 M+Na]⁺ calcd. for C₅₆H₅₄⁷⁹Br₂N₄NaO₈: 1091.2201; found: 1091.2213; *m/z* [2 M+K]⁺ calcd. for C₅₆H₅₄⁷⁹Br₂KN₄O₈: 1107.1940; found: 1107.1952. IR: 1663, 1708, 3316 cm⁻¹. Crystal used for X-ray crystallographic analysis: colorless needle, dimensions 0.64 × 0.05 × 0.04 mm. Crystal system: trigonal; space group: R3c; *Z* = 18; *a* = 36.587(8) Å, *b* = 36.587(8) Å, *c* = 9.942(2) Å, α = 90 deg, β = 90 deg, γ = 120 deg; *V* = 11525(6) Å³; ρ = 1.389 g/cm³; *T* = 200(2) K; Theta_{max} = 17.402 deg; Radiation Mo Kα; λ = 0.71073 Å; 0.5 deg omega-scans with CCD area detector, covering the asymmetric unit in reciprocal space with a mean redundancy of 23.1 and a completeness of 99.8% to a resolution of 1.19 Å. 19242 Reflections measured, 1586 unique (*R*(int) = 0.1093), 1419 observed (*I* > 2σ(*I*)). Intensities were corrected for Lorentz and polarization effects, an empirical scaling and absorption correction was applied using SADABS based on the Laue symmetry of the reciprocal space, μ = 1.64 mm⁻¹, *T*_{min} = 0.67, *T*_{max} = 0.95, structure refined against *F*² with a full-matrix least-squares algorithm using the SHELXL-2016/6 (Sheldrick, 2016) software.¹⁹ 316 Parameters were refined, hydrogen atoms were treated using appropriate riding models. Flack absolute structure parameter 0.077(16), goodness of fit 1.15 for observed reflections, final residual values *R*(*F*) = 0.071, *wR*(*F*²) = 0.145 for observed reflections, residual electron density –0.30 to 0.38 eÅ⁻³. CCDC 1587337 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data-request/cif.
2-(3-Bromo-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-3,6,9-trien-1-yl)-2-(4-bromophenyl)-*N*-(*tert*-butyl)acetamide (6c)
Yield: 355 mg (61%); colorless solid; m.p. 250–252 °C; ¹H NMR (CDCl₃, 300 MHz): δ = 1.29 (s, 9 H, 3 Me), 4.60 (s, 1 H, C(sp³)-H), 5.51 (s, 1 H, N-H), 6.25 (dd, *J* = 9.9, 1.8 Hz, 1 H, =CH), 6.37 (dd, *J* = 9.9, 1.8 Hz, 1 H, =CH), 6.44 (dd, *J* = 10.0, 3.0 Hz, 1 H, =CH), 6.81 (dd, *J* = 10.0, 3.0 Hz, 1 H, =CH), 7.24–7.28 (m, 2 H, H-Ar), 7.31–7.36 (m, 5 H, H-Ar), 7.49 (d, *J* = 8.4 Hz, 2 H, H-Ar). ¹³C NMR (75 MHz, CDCl₃): δ = 28.5, 52.2, 62.3, 69.6, 119.9, 123.5, 127.8, 128.7, 130.0, 130.2, 130.9, 132.4, 132.6, 133.0, 134.4, 143.8, 144.1, 152.5, 165.8, 166.0, 183.7. HRMS (ESI): *m/z* [M+H]⁺ calcd. for C₂₇H₂₅⁷⁹Br₂N₂O₃: 583.0226; found 583.0233; *m/z* [M+Na]⁺

calcd. for $C_{27}H_{24}^{79}Br_2N_2NaO_3$: 605.0046; found: 605.0051; m/z $[M+K]^+$ calcd. for $C_{27}H_{24}^{79}Br_2KN_2O_3$: 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; 1H NMR ($CDCl_3$, 300 MHz): δ = 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(sp³)-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), 6.50 (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, $CDCl_3$): δ = 24.5, 24.6, 25.3, 32.5, 32.7, 49.1, 61.1, 69.6, 116.2 (d, $^2J_{C-F}$ = 21.0 Hz), 119.8, 127.8, 128.4, 128.6, 130.2 (d, $^3J_{C-F}$ = 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 $C_{29}H_{27}^{79}BrFN_2O_3$: 549.1184; found: 549.1187; m/z $[M+K]^+$ calcd. for $C_{29}H_{26}^{79}BrFKN_2O_3$: 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; 1H NMR ($CDCl_3$, 300 MHz): δ = 1.36 (s, 9 H, 3 Me), 5.38 (s, 1 H, C(sp³)-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, $CDCl_3$): δ = 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 $C_{27}H_{24}^{79}Br_2N_2O_3$: 582.6; m/z $[M+H]^+$ found for $C_{27}H_{24}^{81}Br_2N_2O_3$: 584.6; IR: 1713, 3322 cm^{-1} .

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