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Radical cyclization of ynamides into six- or eight-membered rings. Application to the synthesis of a protoberberine analog

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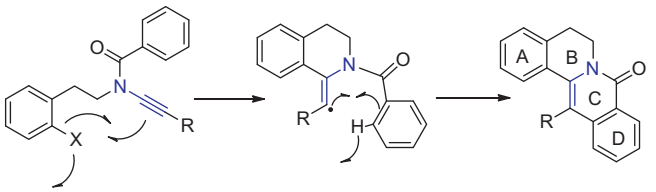
ABSTRACT

A straightforward formation of six- and eight-membered rings via the radical cyclization of specifically designed ynamides is reported. This strategy provides a protoberberine analog in only three steps by a radical cyclization cascade.

The short and efficient synthesis of new heterocyclic compounds remains a challenging task for the synthetic organic chemists with respect to the wealth of applications in medicinal chemistry. Ynamide chemistry has received considerable attention in the last five years and has been developed by exploring many different reactivity profiles. In particular, several radical transformations of ynamides have been recently reported.[1,2] Among them, a radical 5-*exo*-*dig*/6-*endo*-*trig* cascade triggers the cyclization of a fused-ring system with the prior formation of a five-membered ring and therefore figures as a key-step in the preparation of nitrogen containing polycyclic compounds.[1b] Our interest in the radical cyclization of ynamides prompted us to explore the cyclization of compounds with an ynamide moiety in an homobenzylic position or even further from the halogenated aromatic ring. We also disclose here the total synthesis of a protoberberine analog based on the reactivity of such ynamides. This makes a short and original one-pot access to the protoberberine skeleton compared to previous numerous synthesis[3,4] of this family of biologically important alkaloids[5,6] (Scheme 1).

Diverse ynamide radical precursors **7a**–**h** were prepared from the corresponding amides **6a**–**h** following Witulski's procedure[7a] which, among different existing synthetic methods,[7b–f] proved to be the most efficient way to the desired carboxylic amides.[1] These latter amides were obtained by acylation of amines **5a**–**h**. Amine **5a** was obtained from 3-(2-bromophenyl)propanoic acid. The transformation of the acid moiety into the amine **5a** was achieved in a classical two-step pathway described by Ban et al.[8a] In the case of the amine **5b**, the starting material was 2-(bromopyridin-3-yl)methanol. The alcohol function was transformed into sulfonylester **2**. Nucleophilic substitution of the mesylate moiety by NaCN afforded nitrile **3**. Reduction of the cyano group was unfortunately difficult to achieve. Indeed, reaction with $LiAlH_4$ furnished the desired compound **5b** in poor yield (10%)[8b,c] (Scheme 2). After different optimization experiments, activation of lithium aluminium hydride with aluminium chloride increased the yield to 50%.[9]

The iodonium salt **1** was efficiently synthesized in a classical way starting from diacetate iodosobenzene via the intermediary



Scheme 1. Radical cyclization of rings B and C to form a dehydroxoprotoberberine derivative.

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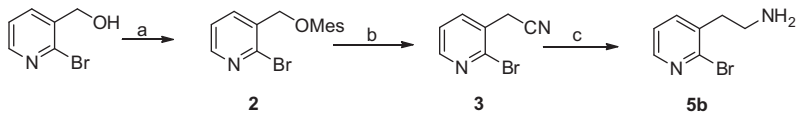
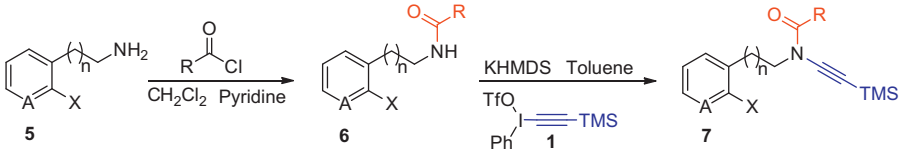


Scheme 2. Reagents and conditions: (a) MesCl, NEt_3, CH_2Cl_2, 0 °C, 74%; (b) NaCN, DMSO, rt, 95%; (c) $LiAlH_4$, $AlCl_3$, THF, rt, 50%.

Table 1
Synthesis of ynamides **7** via amides **6**[a]



Entry	A	*n*	X	R	Yield **6** (%)	Yield **7** (%)
1	CH	1	Br	CF_3	**6a** (60)	**7a** (38)
2	CH	1	Br	CH_3	**6b** (85)	**7b** (59)
3	CH	1	Br	Phenyl	**6c** (95)	**7c** (68)
4	CH	1	Br	3,5-Dimethoxyphenyl	**6d** (75)	**7d** (60)
5	CH	1	I	Phenyl	**6e** (53)	**7e** (53)
6	CH	2	Br	CF_3	**6f** (60)	**7f** (46)
7	N	1	Br	CF_3	**6g** (97)	**7g** (20)
8	N	1	Br	3,5-Dimethoxyphenyl	**6h** (95)	**7h** (—)

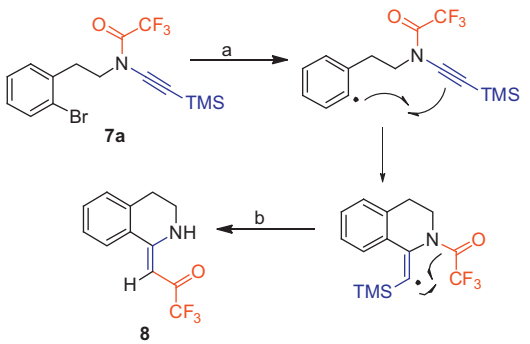
[a] KHMDS = potassium bis(trimethylsilyl)amide.

Zefirov reagent.[10] All of the desired amides **6** were obtained in satisfying yield (Table 1).

Addition of the deprotonated amides **6** in toluene to trimethylsilylethynylphenyliodonium triflate **1** afforded the ynamides **7** in modest to fair yields.[11] Unfortunately, amides **6g** and **6h** containing a 2-bromopyridine moiety did not react with compound **1**. We observed only a moderate conversion (20%) for amide **6g** into ynamide **7g** (Table 1, entry 7), and decomposition for amide **6h** (Table 1, entry 8). The poor reactivity could be explained by the bromine in the *ortho* position to the nitrogen. Indeed, bromine is known to allow a Chichibabin reaction.[12] Moreover, Newkome et al.[13] have shown that nitrile carbanions are subsequently trapped with 2-bromopyridine to afford the SEAr products. However, we were unable to characterize any of the numerous products formed during the reaction.

Radical cyclization was successfully conducted on ynamides **7a**, **7d** and **7f** in benzene in the presence of tin hydride and AIBN to give the cyclized products.[14] Using these same conditions with the other ynamides did not yield significant results. Thus, after complete disappearance of starting ynamides, we observe numerous degradation products and dehalogenated compounds. Surprisingly, in the case of **7a**, we observed a 6-*exo*-dig cyclization and the migration of a trifluoroacetyl moiety to give the product **8** in 49% yield (Scheme 3).

This migration has already been observed but only under ionic conditions via an intramolecular anionic Fries rearrangement.[15] The structure of **8** that we assigned by ^{1}H NMR was confirmed by an X-ray structure analysis (Fig. 1). This shows the delocalized character of the enamine and highlights the hydrogen bond between the amide hydrogen and the oxygen carbonyl. This result in the crystalline state correlates with the important shift observed in ^{1}H NMR for this proton (11.58 ppm).[16]



Scheme 3. Reagents and conditions: (a) AIBN, Bu_3SnH, benzene, 80 °C; (b) (i) NaOH 1 M, (ii) silica gel, 49%.

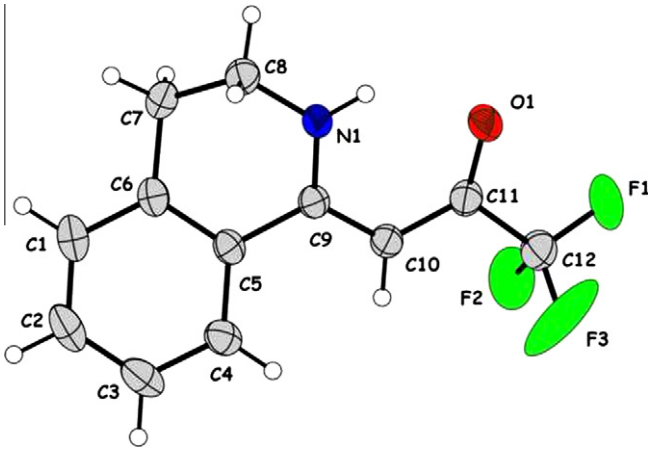
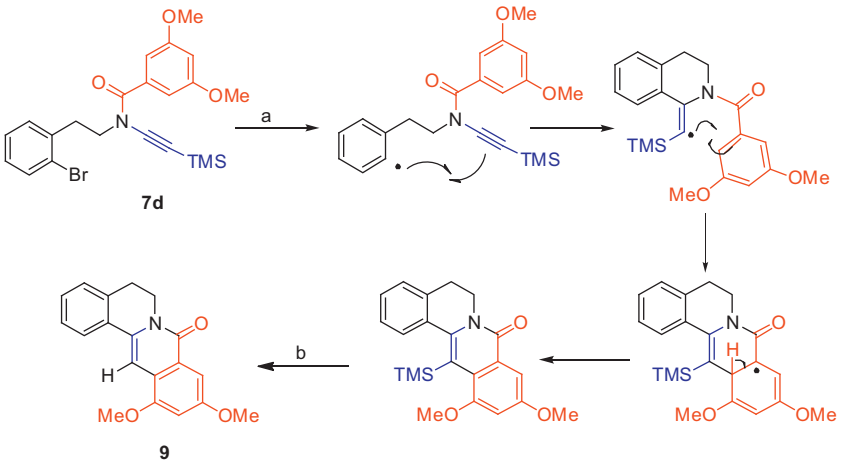


Figure 1. The X-ray crystal structure of **8**.



Scheme 4. Reagents and conditions: (a) AIBN, Bu_3SnH, benzene, 80 °C; (b) (i) NaOH 1 M, (ii) silica gel, 30%.

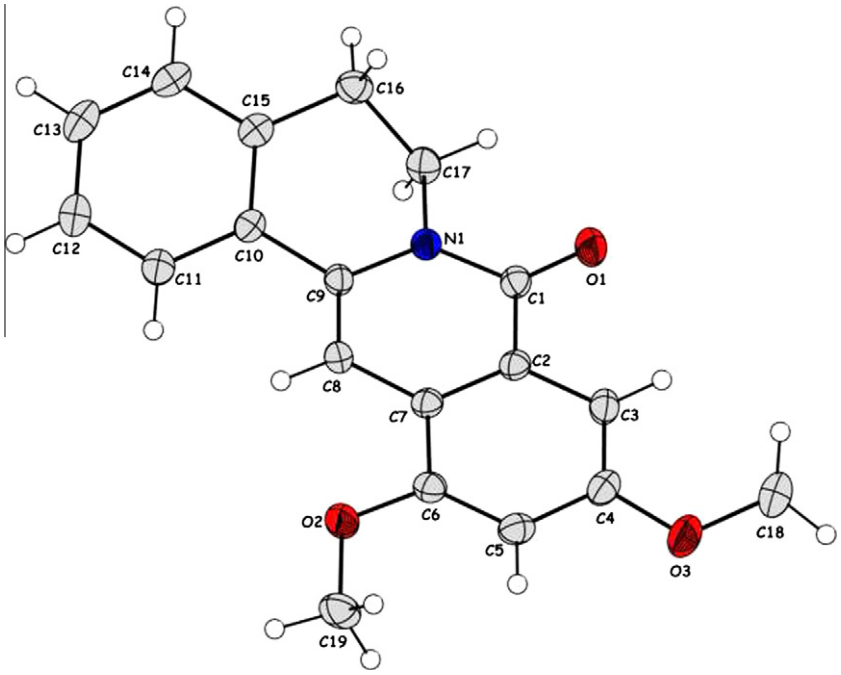


Figure 2. The X-ray crystal structure of **9**.

In the case of ynamide **7d**, the product obtained resulted from a 6-*exo*-dig followed by a 6-*endo*-trig cyclization to afford compound **9** in 30% yield (Scheme 4).[17]

The X-ray structure analysis of **9** was further proof that the synthesis of polycyclic compounds via radical cascade cyclizations is possible (Fig. 2).

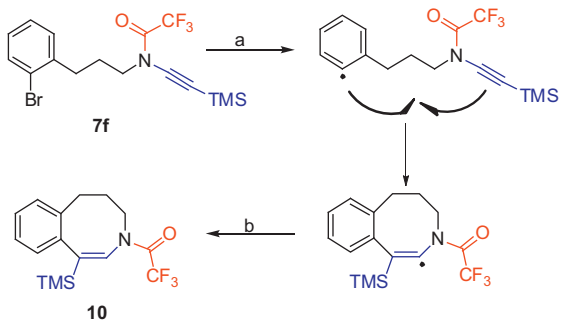
In only three steps, our synthetic path has allowed to isolate a new protoberberin analog **9**. These results support the observation that in the case of an aromatic ring with a two carbon side chain, the cyclization of ynamides is 6-*exo*-dig. This selectivity is in agreement with other 6-*exo*-dig cyclizations reported in the literature that show 6-*exo*-dig cyclizations are more favored over their competitive endo-*dig* ones.[18] We observed the loss of the trimethylsilyl moiety in both cases. This is probably due to the acidic nature of the silica gel, which weakens the carbon silicon bond in the *exo* position.

Radical cyclization also occurred with ynamide **7f** possessing a three carbon side chain (Scheme 5).

The major product of the reaction resulted from an 8-*endo*-dig cyclization and was confirmed by an X-ray structure analysis of **10** in 29% yield (Fig. 3).[19]

Thus, this reaction also provides access to unsaturated eight-membered rings contributing to the few already reported examples of 8-*endo*-dig cyclization in the literature. In 1999, Reissig et al. described the first use of SmI_2 in radical cyclization.[20a] The authors then used the ketyl radical anion to synthesize benzannulated cyclooctene.[20b] More recently, Rosas and co-workers described the synthesis of oxocin-4-one by an 8-*endo*-dig cyclization under ionic conditions.[20c] Finally, Echavarren and co-workers obtained Indoloazocine through a gold catalysis complex.[20d,e]

These results show the reactivity of homobenzylic ynamides under radical conditions leading to the closure of a six-membered ring. Lengthening the carbon chain between the brominated aromatic ring and the nitrogen atom by one supplementary carbon atom allowed us to isolate an eight-membered ring via a rarely reported 8-*endo*-dig cyclization process. Moreover, we have



Scheme 5. Reagents and conditions: (a) AIBN, Bu_3SnH, benzene, 80 °C; (b) (i) NaOH 1 M, (ii) silica gel, 29%.

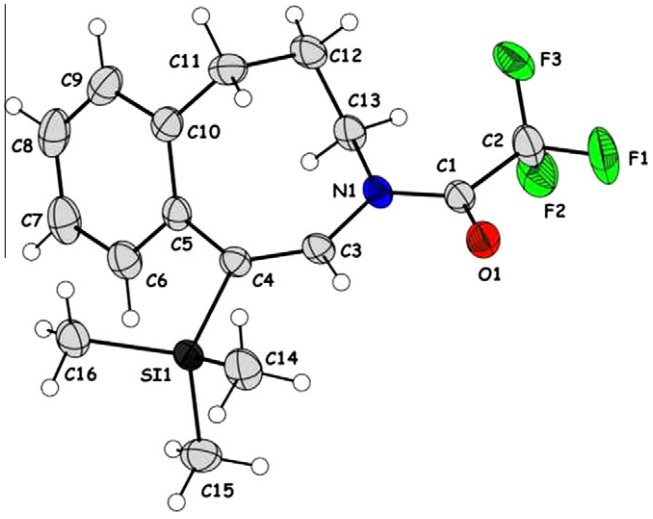


Figure 3. The X-ray crystal structure of **10**.

extended our methodology to a radical cyclization cascade to efficiently access a new protoberberine analog.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.03.118.

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11. *General procedure for the formation of ynamides*: KHMDS (5.36 mL, 2.68 mmol, 0.5 M solution in toluene) was added to a solution of amide (2.42 mmol) in anhydrous toluene (90 mL) at room temperature. The reaction mixture was heated to 80 °C for 2 h. Phenyl-trimethylsilyl ethynyl iodonium triflate (3.03 mmol) was then added. After 30 min the resulting mixture was cooled to room temperature, quenched with 12 g of silica, then concentrated and the residue was purified by flash chromatography (petroleum ether/diethylether 90:10).
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14. *General procedure for radical cyclization*: Tributyltin hydride (0.88 mmol) and AIBN (0.22 mmol) were added to a degassed solution of ynamide (0.44 mmol) in benzene (30 mL). The reaction mixture was refluxed until TLC indicated that the starting material had completely reacted, then cooled to room temperature. 1 M aq NaOH (30 mL) was added and the resulting mixture was stirred for 30 min then extracted with ethyl acetate (2 × 40 mL), dried over MgSO4 and concentrated. The residue was purified by flash chromatography (petroleum ether/ethyl acetate: 97:3) to afford the cyclized products.
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16. *3-(3,4-Dihydroisoquinolin-1(2H)-ylidene)-1,1,1-trifluoro-3-(trimethylsilyl) propan-2-one* **8**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.58 (br s, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.51 (t, J = 7.2 Hz, 1H), 7.39 (t, J = 8.4 Hz, 1H), 5.98 (s, 1H), 3.61 (qt, J = 7.6 Hz, 2H), 3.00 (t, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.10 (q, J = 33 Hz, CO), 162.38, 136.62, 132.65, 128.43, 127.63, 127.56, 126.18, 115.55 (q, J = 287 Hz, CF_3), 83.83, 38.90, 27.57; ^{19}F NMR (376 MHz, $CDCl_3$) δ −76.79; IR (KBr) ν (cm^{-1}): 3052, 2984, 1619, 1582, 1564, 1264, 737; HRMS (ESI) for $C_{12}H_{10}NONaF_3$: calcd 264.0612; found 264.0616, CCDC 772462 contains the supplementary crystallographic data for this molecule.
17. *10,12-Dimethoxy-5H-isoquinolino[3,2-a]isoquinolin-8(6H)-one* **9**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, J = 7.2 Hz, J = 1.4 Hz, 1H), 7.45 (d, J = 1.4 Hz, 1H), 7.37 (s, 1H), 7.36-7.23 (m, 3H), 6.70 (d, J = 1.4 Hz, 1H), 4.43 (t, J = 8.0 Hz, 2H), 3.98 (s, 3H), 3.97 (s, 3H), 3.05 (t, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.43, 159.27, 155.97, 134.76, 134.51, 130.68, 128.62, 124.84, 122.61, 102.86, 99.05, 97.39, 55.81, 55.73, 39.87, 28.57; HRMS (ESI) for $C_{19}H_7NO_3Na$: calcd 330.1106; found 330.1103. CCDC 772463 contains the supplementary crystallographic data for this molecule.
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19. *2,2,2-Trifluoro-1-(1-(trimethylsilyl)-5,6-dihydrobenzo[d]azocin-3(4H)-yl)ethanone* **10**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.12 (m, 4H), 6.86 (d, J = 1.6 Hz, 1H), 3.73 (td, J = 13.6 Hz, J = 4.4 Hz, 1H), 3.47 (td, J = 10.4 Hz, J = 2.8 Hz, 1H), 2.80 (t, J = 2.0 Hz,

1H), 2.78 (t, J = 4.0 Hz, 1H), 2.63 (td, J = 12.8 Hz, J = 4.0 Hz, 1H), 2.05 (m, 1H), 1.43 (m, 1H), 0.16 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.78 (q, J = 36 Hz), 137.88, 137.57, 129.90, 129.86, 129.16, 128.63, 127.73, 127.45, 125.82, 115.45 (q, J = 286 Hz, CF_3), 42.28, 30.99, 26.95, −0.58; ^{19}F NMR (376 MHz, $CDCl_3$) δ −68.69; HRMS (ESI) for $C_{16}H_{20}NOF_3NaSi$: calcd 350.1164; found 350.1167. CCDC 772464 contains the supplementary crystallographic data for this molecule.

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