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One-Pot Deprotonative Synthesis of Biarylazacyclooctynones

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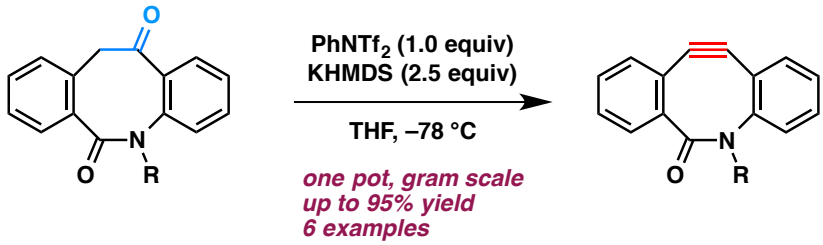

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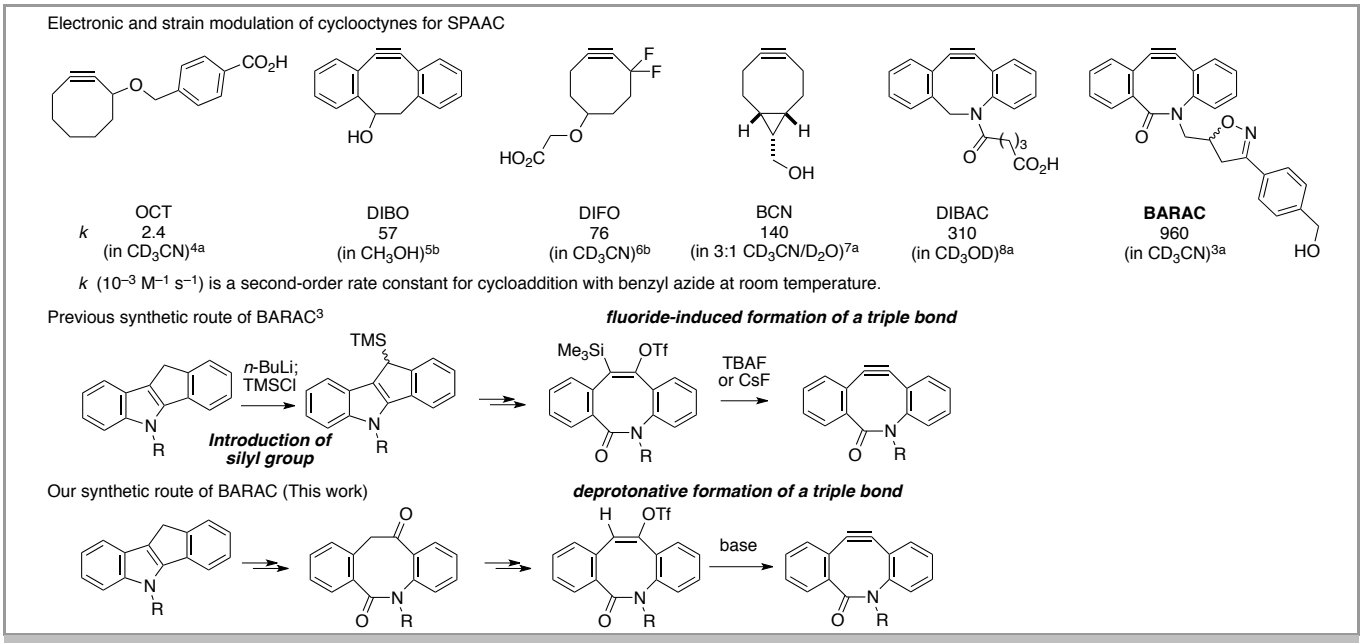
Abstract Deprotonative formation of biarylazacyclooctynone (BARAC) from the corresponding enol triflate is described. The reaction furnished the azacyclooctynone within one hour at −78 °C. This process could be performed in one pot from the starting ketone to provide a range of BARAC derivatives in moderate to excellent yields. The protocol enabled the gram-scale formation of the BARAC skeleton by reducing the number of reaction steps. Furthermore, the established method was applied to the synthesis of the BARAC derivative bearing a coumarin moiety.

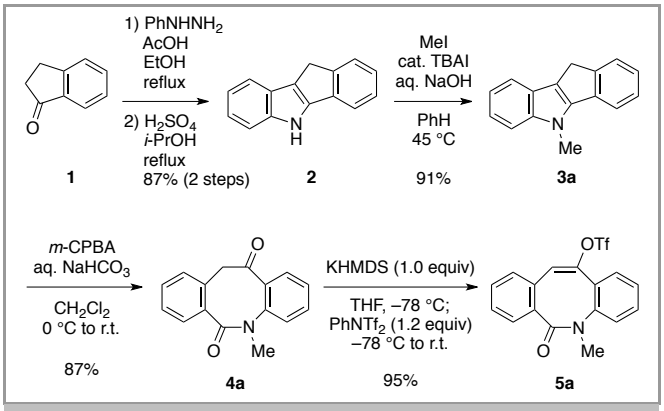
Key words alkynes, bioorganic chemistry, enolate, one-pot reaction, strained molecules

Direct imaging of living cells has recently been one of the key research topics in organic chemistry.[1] A molecule covalently linked to a fluorescent tag is often utilized to visualize a target protein within a cell. Strain-promoted azide-alkyne cycloaddition (SPAAC)[2] reaction has been utilized for this purpose, because the reaction proceeds smoothly at ambient temperature and in the absence of toxic copper salts, owing to the high reactivity of the strained cyclooctyne. Bertozzi and coworkers reported that biarylazacyclooctynone (BARAC)[3] was the most reactive toward SPAAC compared to the related cyclooctynes[4–9] (Scheme 1). The high reaction rate has attracted considerable attention for performing SPAAC in a living cell, where the molecules of this type are maintained at low concentrations. Despite its importance, the synthesis of BARAC requires multiple reaction steps including incorporation of silyl groups, thus a more practical synthetic method is undoubtedly required. Herein we report the formation of the BARAC skeleton using deprotonation of the corresponding enol triflate. The described method allows the gram-scale preparation of BARAC derivatives in less number of steps and was applied to the synthesis of a coumarin-tethered BARAC derivative.



Scheme 1 Reactivity of cyclooctynes for SPAAC and comparison of the synthetic routes to BARAC

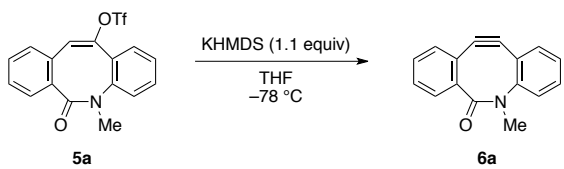
We initially prepared the eight-membered ketolactam **4a** bearing a methyl group on the nitrogen atom for the synthesis of N-methylated BARAC, based on Bertozzi's method (Scheme 2).[3] The synthesis commenced with a Fischer indole synthesis of 1-indanone (**1**) and phenylhydrazine to produce indane-fuzed indole **2** in 87% yield over two steps. N-methylation of the indole nitrogen followed by oxidative cleavage of indole **3a** furnished the desired eight-membered ketolactam **4a**. This compound was converted to the corresponding enol triflate **5a** using a combination of KHMDS and $PhNTf_2$ in 95% yield.



Scheme 2 Preparation of N-methylated eight-membered enol triflate **5a**

We then investigated the formation of the BARAC skeleton through deprotonation of the enol triflate and subsequent elimination of the triflate moiety. Among the various amide bases tested, KHMDS proved the most effective for the smooth reaction within 1 h, even at −78 °C.[10] Further optimization process revealed that the yield of N-Me BARAC **6a** was significantly affected by the reaction time. Formation of N-Me BARAC **6a** was observed in 50% ^{1}H NMR yield with recovery of 37% of the starting triflate **5a**, after the reaction mixture was allowed to react for 5 min at −78 °C (Table 1, entry 1). Prolonged reaction time resulted in improvement of the product yields (entries 2 and 3). However, the yield was slightly reduced to 71% when the reaction time was 150 min, probably due to the instability of BARAC (entry 4).[11] Under the optimal reaction conditions (−78 °C, 40 min), N-Me BARAC **6a** was successfully isolated in 83% yield after purification using flash column chromatography on silica gel.

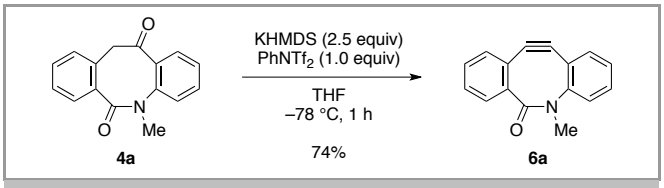
Table 1 Effects of reaction time on the yield of N-Me BARAC **6a**



Entry	Reaction time (min)	Recovered **5a** (%)[a]	N-Me BARAC **6a** (%)
1	5	37[a]	50[a]
2	20	24[a]	75[a]
3	40	–[c]	83[b]
4	150	–[d]	71[a]

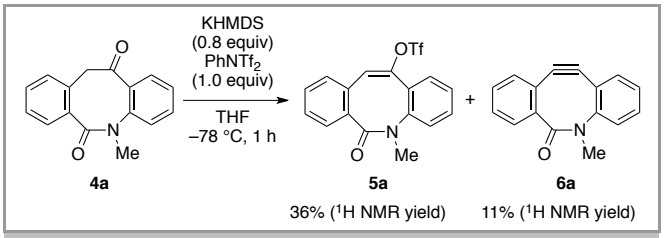
[a] The yield was determined from the ^{1}H NMR spectrum of the crude material using 1,1,2,2-tetrachloro-ethane as the internal standard. [b] Isolated yield. [c] Not determined. [d] Not detected in the ^{1}H NMR spectrum of the crude material.

Having found that KHMDS facilitated the formation of both the enol triflate and BARAC, we then investigated the one-pot BARAC formation from the ketolactam **4a** (Scheme 3). Thus, a THF solution of ketolactam **4a** and $PhNTf_2$ was treated with 2.5 equivalents of KHMDS at −78°C for 1 h to provide the desired N-Me BARAC **6a** in 74% isolated yield. The reaction temperature proved important in achieving high yields. When the reaction was carried out at 0 °C, a complex mixture of unidentified products was obtained. The desired N-Me BARAC **6a** was observed in the crude material; however, in 6% ^{1}H NMR yield.



Scheme 3 One-pot formation of N-Me BARAC **6a** from ketolactam **4a**

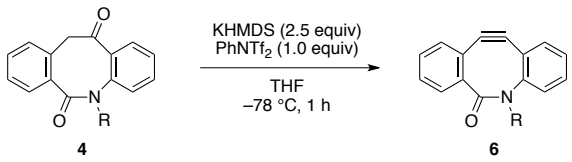
To gain insight into the sequential reaction, we further examined the relative rates of the two reactions in the one-pot BARAC formation by reducing the stoichiometric amount of KHMDS. This was because cyclic enol triflate **5a** was not observed in the ^{1}H NMR spectrum of the crude material in Scheme 3. When the reaction was performed using 0.8 equivalents of KHMDS at −78 °C for 1 h, both enol triflate **5a** and N-Me BARAC **6a** were obtained in 36% and 11% ^{1}H NMR yields, respectively (Scheme 4). These results indicate that the reaction rates of triflate formation and β-elimination of the triflate group are comparable.

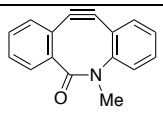
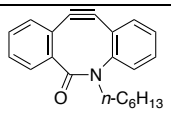
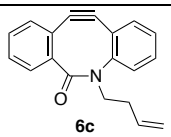
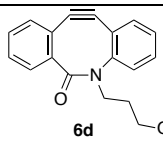
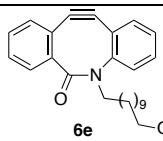


Scheme 4 One-pot BARAC formation with sub-stoichiometric KHMDS

Having established the optimal conditions for the one-pot formation of the BARAC skeleton, we then investigated the scope of the possible substituents on the nitrogen atom for conjugation with a fluorescent functional group. Our approach enables gram-scale preparation of N-Me BARAC **6a** in 95% isolated yield (Table 2, entry 1).[11] Moreover, **6a** is solid and stable at room temperature, whereas several BARACs in liquid form started to decompose within 24 h at room temperature. Ketolactam **4b** bearing an *n*-hexyl group on the nitrogen atom also underwent the one-pot formation of the corresponding BARAC **6b** in 63% yield (entry 2). In addition, the described conditions were applicable to the synthesis of BARAC **6c** bearing a butenyl group on the nitrogen atom in 84% (entry 3). The synthesis of BARAC **6d** containing a triisopropylsilyl (TIPS) ether group was also achieved in 90% yield. It is noteworthy that the synthesis of this compound is challenging using the method employing silyl enol triflate as a substrate (entry 4). Furthermore, the ketolactam **4e** bearing a longer side chain was also converted to the corresponding BARAC **6e** in 91% yield under the optimal conditions (entry 5).

Table 2 Scope of the functionality of nitrogen atom in the one-pot BARAC formation

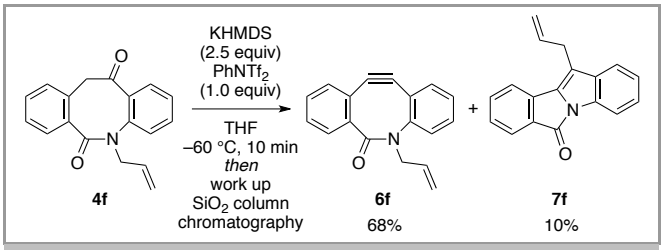


Entry	Product	yield (%)[a]
1	 **6a**	74 95[b]
2	 **6b**	64
3	 **6c**	84
4	 **6d**	90[c]
5	 **6e**	91[b,d]

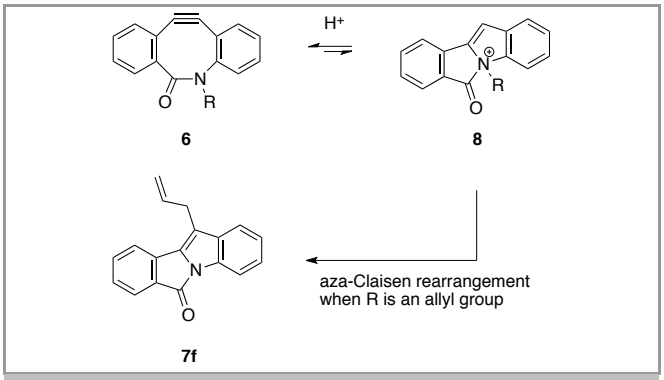
[a] Isolated yield. [b] Gram scale. [c] Reaction time: 2.5 h. [d] Reaction conditions: 1.5 h, KHMDS 3.0 equiv, $PhNTf_2$ 1.5 equiv.

We also performed a one-pot BARAC formation of ketolactam **4f** bearing an allyl group on nitrogen, which was previously reported to be converted to tetracyclic compound **7f** through the acid-promoted intramolecular cyclization and subsequent aza-Claisen rearrangement of BARAC **6f** (Scheme 5).[12] We initially performed the reaction at −78 °C for 2 h; however, the desired product was obtained in 32% ^{1}H NMR yield, with several unidentified products. Nevertheless, when the reaction was conducted at −60 °C for 10 min, all of the starting material was consumed and the desired BARAC **6f** was obtained in 68% yield after silica gel column chromatography, with the tetracyclic compound **7f** present in 10% yield as a result of the rearrangement. BARAC **6f** was completely converted to **7f** upon standing for 4 h at room temperature under atmospheric conditions. Apart from the N-allylated BARAC **6f**, other BARAC derivatives **6a**–**6e** were not transformed to the corresponding tetracyclic compounds **7** at room temperature.

The plausible reaction mechanism for the rearrangement is illustrated in Scheme 6. According to the report by the Pezacki group, equilibrium between BARAC **6** and ammonium salt **8** should exist, though ammonium salt **8** was not detected in the ^{1}H NMR spectrum. When the substituent R is an allyl group, the ammonium salt **8f** underwent aza-Claisen rearrangement to provide the corresponding tetracyclic compound **7f**.



Scheme 5 Synthesis of *N*-allylated BARAC with generation of tetracyclic compound



Scheme 6 Plausible reaction mechanism for the formation of the tetracyclic indole through an aza-Claisen rearrangement

Finally, we applied our method for the synthesis of a coumarin-tethered BARAC derivative (Scheme 7). Desilylation of the TIPS ether group in ketolactam **4e** provided the desired alcohol **9** in 88% yield. Subsequent transformation to an azide was conducted in a two-step sequence, namely mesylation and azide substitution, to provide the corresponding azide **10**. The resulting azide was then subjected to copper-catalyzed triazole formation with 7-ethynylcoumarin (**11**) in the presence of $CuSO_4$ and sodium ascorbate[13] to yield ketolactam **12**. The established conditions were also applicable to the ketolactam to provide the corresponding BARAC **13** bearing tethered coumarin moiety in 51% yield, in a prolonged reaction time.

In conclusion, we have developed a one-pot BARAC synthesis from the corresponding ketolactam by employing KHMDS as a base. The described protocol allows not only the direct synthesis of BARACs but also the construction of the BARAC skeleton from the corresponding ketolactam without the introduction of a silyl group, unlike the one previously report by the Bertozzi group. The robustness of the ketolactam enables various functionalization of the side chain on the nitrogen atom prior to the formation of the BARAC skeleton, which could be applied to provide a direct access to BARACs bearing various functional groups such as the fluorescent coumarin moiety.

Funding Information

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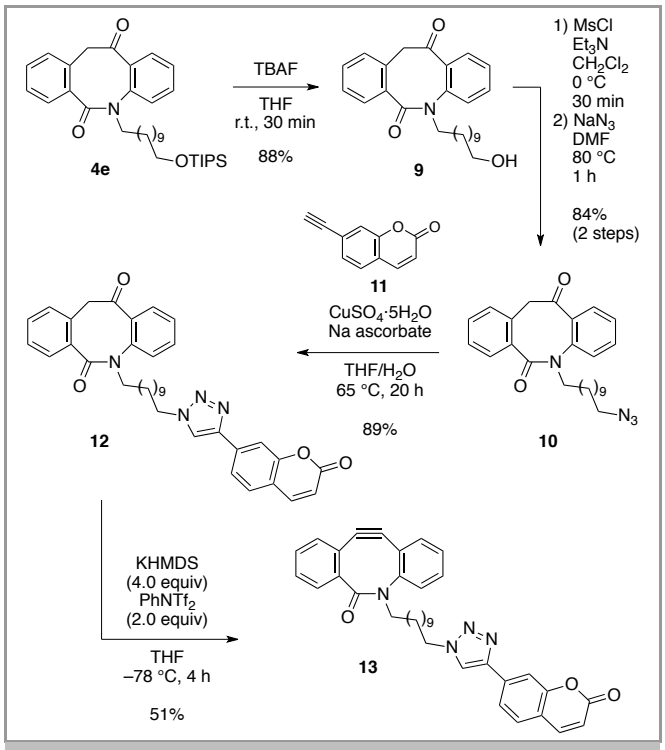
Supporting Information

Yes



Scheme 7 Synthesis of coumarin-tethered BARAC **13**

Primary Data

No

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(11) **Experimental procedures and characterization data**. A flame-dried 500-mL two-necked flat-bottomed flask equipped with a Teflon-coated magnetic stirring bar, a rubber septum, and an inlet adapter with a three-way stopcock was charged with ketolactam **4a** (1.65 g, 6.56 mmol) and $PhNTf_2$ (2.35 g, 6.56 mmol) in THF (39 mL). After the resulting solution was cooled to –78 °C, KHMDS (0.50 M in toluene, 32.8 mL, 16 mmol) was added dropwise over 6 min. After stirring at –78 °C for 1 h, the reaction mixture was treated with water (80 mL) and diluted with diethyl ether (30 mL). The mixture was allowed to warm to room temperature for 15 min. The aqueous layer was extracted twice with diethyl ether (15 mL × 2). The combined organic extracts were washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexane/diethyl ether = 1:3) to afford N-methyl BARAC **6a** (1.45 g, 6.22 mmol, 95%) as a brown solid. R_f = 0.38 (hexane/diethyl ether = 1:3); M.p. decomp. (120 °C); IR (ATR, cm^{-1}): 2924, 1657, 1468, 1447, 1333, 1214, 1180, 1079, 1039, 761, 715, 630; ^1H NMR (400 MHz, $CDCl_3$): δ 7.65–7.58 (m, 2H), 7.50–7.35 (m, 6H), 2.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.9, 156.6, 149.4, 130.0, 129.5, 129.4, 128.9, 128.2, 127.6, 126.5, 125.6, 122.31, 122.27, 109.5, 108.7, 38.8; HRMS (DART$^+$) *m/z*: calcd. for $C_{16}H_{12}NO$, 234.0919 $[M+H]^+$; found, 234.0928.

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