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Tetrahedron Letters 45 (2004) 5857–5860
Tetrahedron Letters

IMDA cycloadditions of 3-alkynyl tethered 2-pyrones for the synthesis of medium-sized macrocycles

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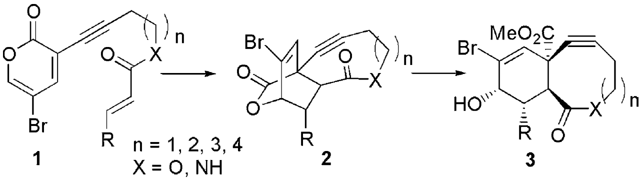
Received 26 April 2004; revised 27 May 2004; accepted 31 May 2004
Available online 19 June 2004

Abstract—Alkynyl tethered 2-pyrones underwent intramolecular Diels–Alder cycloadditions to provide bicyclolactone-fused medium-sized macrocycles in good overall yields. Lactone ring opening reactions furnished various ring fused medium-sized macrolactams and macroazanes with good overall yields.

As part of our ongoing research program on 3,5-dibromo-2-pyrone,[1] we have recently reported that it undergoes the Pd-catalyzed coupling reactions with terminal alkynes, regioselectively at C3-Br position.[1e] The resulting coupling products were shown to have ambient dienyl character, proceeding Diels–Alder cycloadditions with both electron-rich and electron-poor dienophiles.[1e] Further elaboration utilizing aforementioned regioselective coupling reactions would generate the 2-pyrones attached with dienophile partners for the subsequent intramolecular Diels–Alder (IMDA) cycloadditions to provide various polycyclic frameworks. Numerous precedents can be found in the literature effectuating the assembly of novel carbon skeletons, by employing various tether groups.[2] Due to the linear geometry, however, the alkyne groups are usually used as dienophiles,[3] not as tether groups.

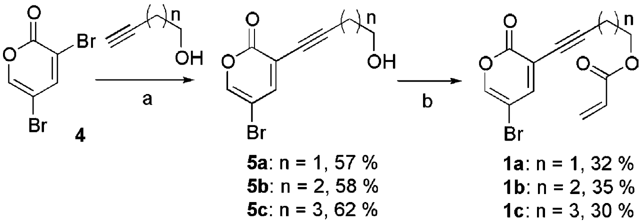
Intrigued by the high natural abundance and biological activities of various medium-sized macrocycles[4] as well as the uniqueness of the alkynyl tether group, we investigated IMDA cycloadditions of the alkynyl tethered 2-pyrones. For example, the precursor **1** may undergo IMDA cycloadditions to afford the tricyclolactone **2**. Subsequent opening of the bridgehead lactone would furnish the structurally novel macrocycle **3** (Scheme 1).



Scheme 1. IMDA cycloaddition of 2-pyrones.

For the preparation of the precursors **1a–c**, we first followed the steps described in Scheme 2, starting from **5a–c** as they are readily prepared from **4** via regioselective Sonogashira couplings with terminal alkynes. Subsequent acylations with acryloyl chloride provided the precursors **1a–c**, but in only moderate yields, as the pyrone moiety is somewhat labile under the reaction conditions.

Preassembly of the acryloyl alkynyl esters **6a–d** (70–80% from the alkynyl alcohol), followed by the coupling



Scheme 2. Preparation of alkynyl tethered 2-pyrones. Reagents and conditions: (a) $Pd(PPh_3)_2Cl_2/CuI/Et_3N/DMF/rt$; (b) acryloyl chloride/$Et_3N/DMAP/CH_2Cl_2/0\,°C$ to rt.

Keywords: IMDA; 2-Pyrone; Macrocycles.

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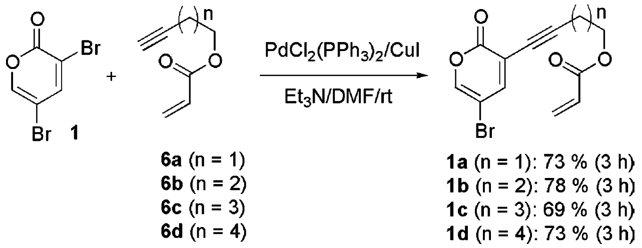
doi:10.1016/j.tetlet.2004.05.145

reactions with **4** provided the precursors **1a–d**, with much higher overall yields (Scheme 3).[5] It is worth noting that the coupling reaction at the alkyne is faster than the possible Heck coupling at the acrylate under the reaction conditions.

The precursors **1a–d** proceeded IMDA cycloadditions to the corresponding 8, 9, 10 and 11-membered lactones in fair yields, when heated in toluene (Table 1).[6]

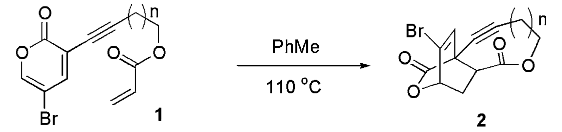
While **1a** gave a mixture of *endo*/*exo* products, **1b–d** provided only *endo*-adducts with no detectable *exo*-cycloadducts. The alkynyl tether in **1a** may not be long enough to allow the exclusive formation of the otherwise more favorable *endo*-TS. The IMDA cycloadditions of the similar systems with a substituent at β-position also afforded the corresponding cycloadducts, but in mid 30% yields after 48 h (Scheme 4).

At first glance, the bridgehead lactone seemed to have a larger steric congestion than the lactone in the macrocycle. Attempted reactions with NaOMe at various temperatures, however, resulted in the cleavage of both lactones.

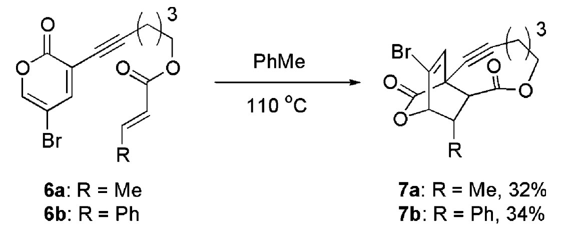


Scheme 3. Preparation of alkynyl tethered 2-pyrones.

Table 1. IMDA cycloadditions of **1**



Entry	3	Time (h)	*endo:exo*	Yield (%)
1	**1a** ($n = 1$)	48	**2a** (60:40)	31
2	**1b** ($n = 2$)	41	**2b** (100:0)	51
3	**1c** ($n = 3$)	13	**2c** (100:0)	55
4	**1d** ($n = 4$)	13	**2d** (100:0)	66



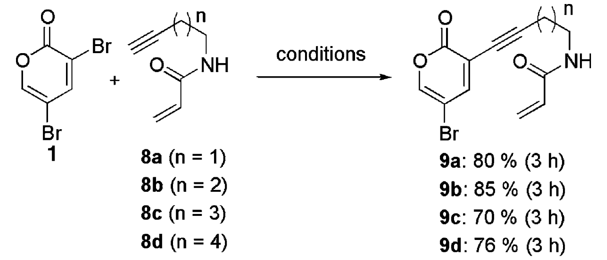
Scheme 4. IMDA cycloaddition of 2-pyrones.

Under the same protocol, we then prepared 2-pyrones bearing acrylamide group. Preassembly of **8a–d**, followed by the couplings with **1** afforded **9a–d** in good overall yields (Scheme 5). Again the Pd-catalyzed coupling reactions with the alkynyl acrylamide **8** proceeded chemoselectively at the alkynyl side and regioselectively at C3 position of the 3,5-dibromo-2-pyrone.

In contrast to **3a** bearing the same number of methylenes between the pyrone and dienophile, **9a** gave the cycloadduct in less than 10% yield.[7] Meanwhile, the IMDA cycloadditions of the precursors with longer tether group **(9b–d)** furnished tricyclolactams **10b–d** in good yields. Analogous to **3a**, the precursor with shorter tether (**10b**) provided a mixture of *endo*/*exo* adduct, while the ones with longer tether furnished *endo*-adduct only (Table 2).

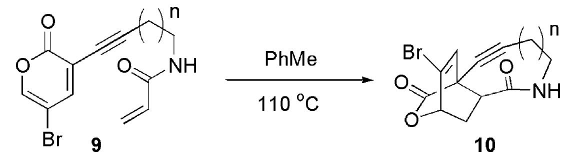
Interestingly, the *endo*-cycloadduct in entry 2 was isomerized into the *exo*-adduct during the silica-gel column chromatography. We presume such unusual *endo–exo* isomerization would take place because of the ring strain, through the process depicted in Scheme 6.

Protonation followed by C–C bond cleavage furnishes the intermediate **B**. The existence of the normally unstable carbocation, α to the ester, in the intermediate **B** may be rationalized by the stabilization with two adjacent allylic π-bonds. Subsequent bond rotation, followed by the ring closure would give rise to the *exo*-adduct. A simple molecular modeling suggests the *endo*-**10b** would be thermodynamically less stable than the *exo*-**10b**, due to the ring strain. Stirring the *endo*-adduct **10b**-*endo* in silica gel produced similar result.

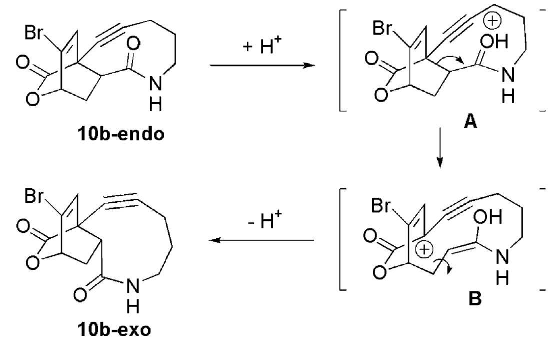


Scheme 5. Synthesis of **9a–d**. Conditions: $Pd(PPh_3)_2Cl_2/CuI/Et_3N/1,4$-dioxane/rt.

Table 2. IMDA cycloadditions of **9a–c**



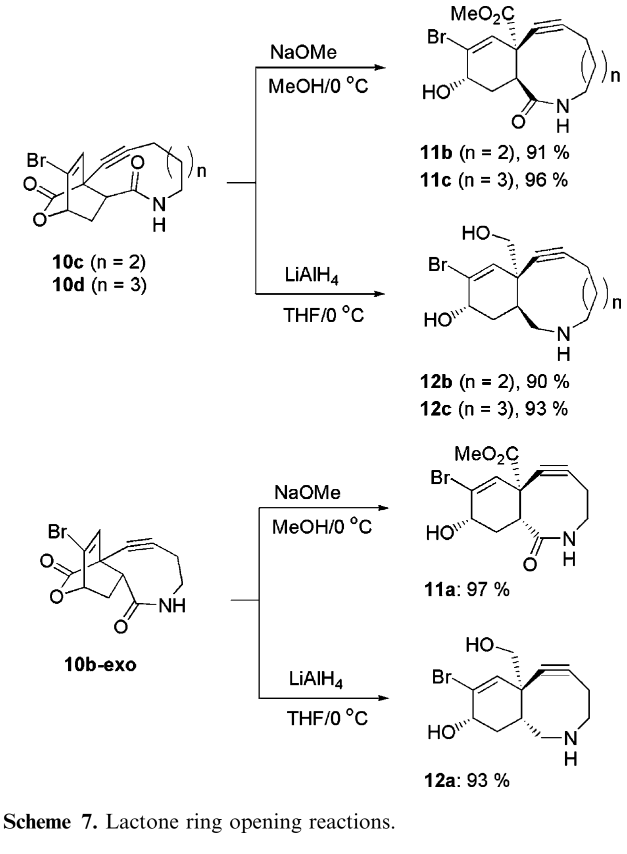
Entry	9	Time (h)	*endo:exo*	Yield (%)
1	**9a** ($n = 1$)	24	**10a** (N/A)	10
2	**9b** ($n = 2$)	13	**10b** (47:53)	46
3	**9c** ($n = 3$)	13	**10c** (100:0)	53
4	**9d** ($n = 4$)	11	**10d** (100:0)	69



Scheme 6. Suggested mechanism for the isomerization.

Lactone ring opening reactions of **10b–d** with NaOMe provided the cyclohexene fused macrolactams **11b–d**. The ring opening of **10b–d** with LiAlH$_4$ afforded the macrocyclic azanes **12b–d** in excellent yields (Scheme 7).

In summary, we have found that the 2-pyrones attached with acrylate or acrylamide dienophiles through alkynyl tethers undergo facile IMDA cycloaddition reactions to provide tricyclolactones[8] in good to fair yield. Subsequent treatment of the tricyclolactones bearing amide linkage with NaOMe or LiAlH$_4$ furnished the structurally unique cyclohexene ring fused macrocyclic lactams or azanes. Applications of our method to the related macrocyclic natural product systems are under current investigation.



Scheme 7. Lactone ring opening reactions.

Acknowledgements

This work was supported by a grant of the Korea Health 21 R&D Project, Ministry of Health & Welfare, South Korea (01-PJ1-PG1-01CH03-0003). J.-T.S. thanks the BK21 program for the financial support.

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5. Representative procedure: An oven-dried flask was charged with 3,5-dibromo-2-pyrone (**1**, 60 mg, 0.273 mmol), CuI (9 mg, 0.2 equiv), PdCl$_2$(PPh$_3$)$_2$ (17 mg, 0.1 equiv), acrylic acid pent-4-ynyl ester (**6a**, 66 mg, 2.0 equiv), Et$_3$N (0.07 mL, 2.0 equiv) and DMF (3.0 mL) at rt. After 3 h at rt under Ar atmosphere, the reaction mixture was partitioned into H$_2$O and ether. The separated organic layer was dried over MgSO$_4$, concentrated and purified by silica-gel column chromatography (hexanes:EtOAc = 10:1) to provide 54 mg of **1a** (73% yield) as a yellow viscous liquid.

6. Representative procedure: A solution of **1a** (33 mg, 0.1 mmol) in 5.0 mL of anhydrous toluene was heated at 110 °C for 13 h. The reaction mixture was cooled to rt, concentrated and purified by silica-gel column chromatography (hexanes:EtOAc = 4:1) to provide 17 mg of **2b** (51% yield) as a white solid.
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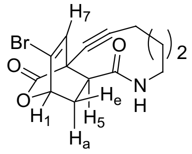
8. Stereochemical assignments of the cycloadducts were made based on the ^{1}H NMR chemical shifts and coupling constants of H_1, H_7, H_a, H_e and H_5 as well as by comparison to the related acyclic cycloadducts as exemplified with **10c**.



chemical shift (ppm)	coupling (Hz)
H_7: 6.28	H_1-H_e: 1.5
H_1: 5.15	H_1-H_a: 2.6
H_e: 2.47	H_e-H_a: 14.1
H_a: 2.58	H_a-H_5: 9.7
H_5: 2.73	H_e-H_5: 4.2