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Ugi/xanthate cyclizations as a radical route to lactam scaffolds

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Abstract—The combination of Ugi reaction and xanthate radical cyclization onto alkenes allows an easy access to various highly functionalized heterocycles. The addition of chloroacetic acid to primary amines, aldehydes and isocyanides in methanol followed by the treatment with potassium ethyl xanthate, affords the xanthate Ugi adducts in good yields. These adducts were then submitted to radical cyclization conditions with dilauroyl peroxide as initiator. The choice of an alkene function properly located on the amine or the aldehyde permits the formation of 5- to 8-membered rings in moderate to good yields.

The Ugi reaction is among the most efficient multicomponent reactions available and has found wide applications in the synthesis of large arrays of complex targets.[1] In order to reach scaffolds of a higher structural complexity and improved biological tolerance, the Ugi reaction has very often been associated with further synthetic conversions (known as post-condensation reactions). Ugi couplings followed by cycloadditions,[2] Heck reactions,[3] cyclocondensations[4] or RCM[5] have thus been developed to allow the formation of various heterocyclic cores. On the other hand, radical cyclization reactions have emerged as a powerful tool for the construction of heterocyclic systems.[6] The development of various tin free methods has further increased the potential of these processes. Over the last decade, Zard et al. have demonstrated the efficiency of xanthate chemistry for the formation of C–C bonds in both intra and intermolecular fashions.[7] To the best of our knowledge, the use of radical cyclizations on Ugi adducts has not yet been documented yet.

Interested by both radical and isocyanide chemistry, we thus contemplated the formation of complex structures by the coupling of radical xanthate cyclizations and Ugi condensations.

The use of four components in Ugi reactions offers multiple solutions for the introduction of an alkene moiety prone to xanthate transfer cyclization. Indeed, xanthate-Ugi adducts can be readily prepared by the use of α-chlorocarboxylic acid as the acidic component in the Ugi reaction followed by the nucleophilic displacement of chlorine with potassium *O*-ethyl xanthate.

When isovaleraldehyde, allylamine, chloroacetic acid and *t*-butylisocyanide were mixed in methanol, the Ugi adduct was obtained after several hours at room temperature. Next, the addition of potassium *O*-ethyl xanthate (1.1 equiv) furnished the Ugi-xanthate adduct **1a** in a good yield after 1 h at room temperature. Heating **1a** under radical cyclization conditions (reflux in 0.3 M 1,2-dichloroethane with 15 mol % dilauroyl peroxide) gave the expected lactam **2a**, as a 1:1 mixture of separable diastereoisomers in a 70% isolated yield (Scheme 1).

Various aldehydes and isocyanides behaved similarly with allylamine and chloroacetic acid to give the corresponding Ugi-xanthate adducts **1b**,**c** which underwent 5-*exo*-trig cyclizations to furnish pyrrolidinones **2b**,**c**, in good yields (Scheme 1). Related pyrrolidinone structures have shown interesting biological activities in the treatment of conditions such as epilepsy.[8]

The degeneracy of radical additions to xanthates allows successful reactions even with slow radical processes, which are poorly compatible with tin hydride chemistry.

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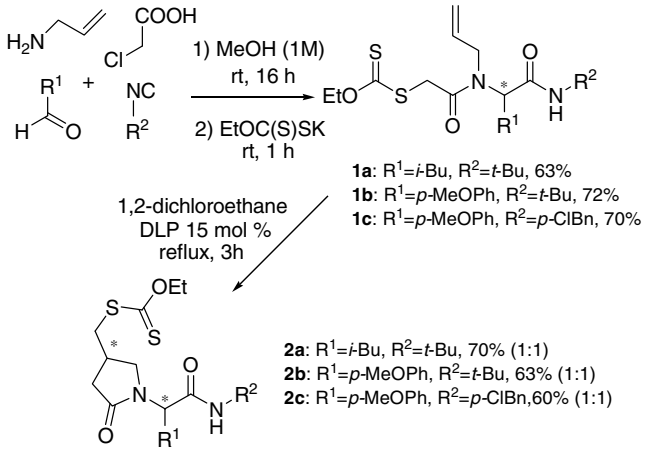
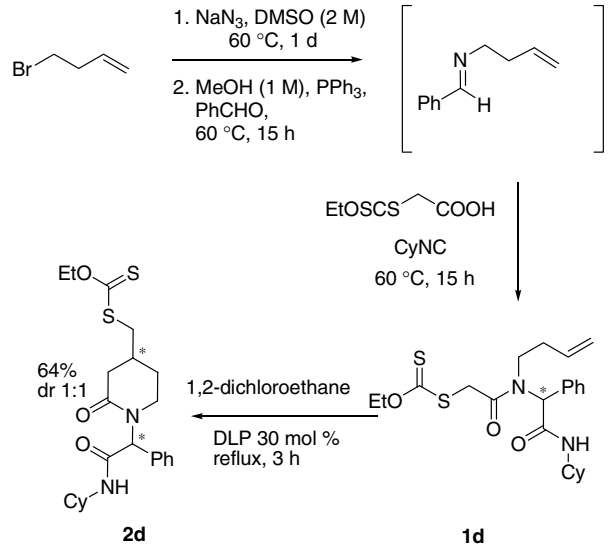


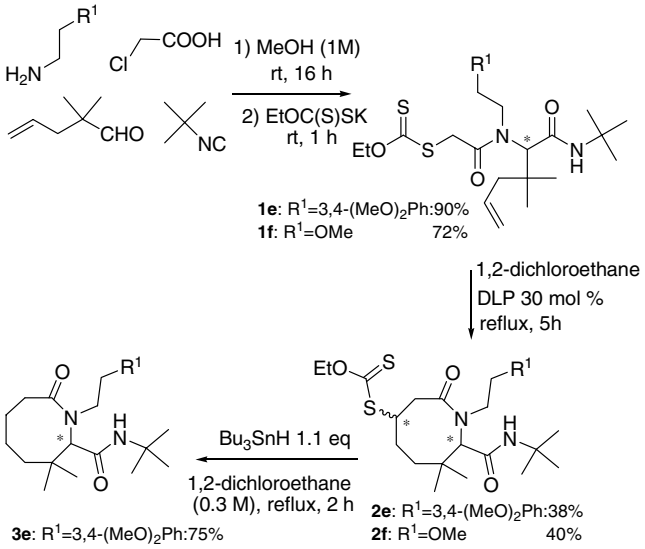
Scheme 1.

We thus turned our attention to the formation of lactams of higher ring size. Six-membered ring compounds could be obtained by a similar Ugi coupling with homoallyl amines. Overkleeft et al. reported a convenient formation of homoallyl Ugi adducts using a Staudinger/aza-Wittig tandem process.[9] We applied their procedure in a one-pot formation of Ugi xanthate adduct **1d** directly from 1-bromobutene in a 50% overall isolated yield. Thus, after azide formation in DMSO, MeOH was added to perform the aza-Wittig reaction followed by the Ugi coupling. For the latter transformation, 2-xanthyl acetic acid was used directly in place of chloroacetic acid, making the process shorter and demonstrating the compatibility of the xanthate moiety with the Ugi coupling conditions. Next, **1d** was transformed efficiently into the piperidinone **2d** via a 6-*exo* radical cyclization in a 64% isolated yield (Scheme 2).

For the construction of 8-membered ring lactams, we chose to introduce the alkene moiety through the aldehyde component. Commercial 2,2-dimethyl-4-pentenal was thus coupled with chloroacetic acid, *t*-butylisocyanide and homoveratrylamine to form **1e** in a high yield (Scheme 3). When xanthate **1e** was submitted to the radical cyclization with 30 mol % of dilauroyl peroxide, we were pleased to observe the formation of lactam **2e** as a single diastereoisomer via an 8-*endo*-trig cyclization. The absence of any 7-*exo* cyclization product was compatible with the selectivity reported on related systems.[10] The structure of xanthate **2e** was further confirmed by the reduction to **3e** with Bu_3SnH (Scheme 3).[11]



Scheme 2.



Scheme 3.

In conclusion, we have disclosed a new multicomponent two-step procedure to form lactams using an Ugi reaction, followed by a radical cyclization. This strategy further demonstrates the interest of the xanthate radical process for the fast assembly of complex cyclic structures with high diversity. We will report further investigations on the coupling of radical chemistry with Ugi reactions in due course.

References and notes

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11. Typical procedure for **1f**: 2,2-dimethyl-4-pentenal (272 μL, 2.0 mmol), 2-methoxyethylamine (174 μL, 2.0 mmol), chloroacetic acid (189 mg, 2.0 mmol) and *t*-butyl isocyanide (226 μL, 2.0 mmol) were mixed in methanol (2 mL) at room temperature for 16 h. When the starting material was totally consumed, potassium *O*-ethyl xanthate was added and the resultant mixture was stirred at room temperature for 1 h. Extraction and purification by flash column chromatography (silica gel; petroleum ether–diethyl ether, 30:70) furnished **1f** as a white solid (72% yield). A solution of this Ugi adduct **1f** (242 mg, 0.56 mmol) was then refluxed in 1,2-dichloroethane (1 mL) for 15 min under argon. Dilauroyl peroxide (DLP) was then added (10%) to the refluxing solution, followed by additional portions (5% every 90 min). When the starting material had been totally consumed (after addition of 30% of DLP), the crude mixture was cooled to room temperature, concentrated under reduced pressure and purified by flash column chromatography (silica gel; petroleum ether–ethyl acetate, 60:40) to afford **2f** as a yellow oil (40% yield). R_f: 0.3 (60:40 petroleum ether/ethyl acetate).^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45 (br s, 1H), 4.68 (q, 2H, $J = 7.1$ Hz), 4.42 (dt, 1H, $J = 14.3$, 2.2 Hz), 4.06 (td, 1H, $J = 10.6$, 2.2 Hz), 3.80–3.73 (m, 1H), 3.48 (s, 1H), 3.40 (s, 3H), 3.41–3.39 (m, 1H), 3.01–2.98 (m, 1H), 2.98–2.96 (m, 1H), 2.97–2.93 (m, 1H), 2.45 (ddd, 1H, $J = 18.1$, 12.9, 5.4 Hz), 2.20 (ddd, 1H, $J = 12.9$, 5.4, 2.6 Hz), 1.78 (tdd, 1H, $J = 12.9$, 5.4, 2.6 Hz), 1.56 (d, 1H, $J = 15.4$ Hz), 1.44 (t, 3H, $J = 7.1$ Hz), 1.31 (s, 9H), 1.25 (s, 3H), 1.14 (s, 3H).^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 213.6, 174.9, 170.2, 72.5, 71.9, 70.0, 59.3, 54.4, 51.2, 43.6, 42.3, 41.2, 34.4, 32.0, 31.0, 28.9, 28.3, 14.2. MS (ID, ICP NH_3) *m*/*z* 433 ($M+H^+$). HRMS calcd for $C_{20}H_{36}N_2O_4S_2$: 432.2116, found: 432.2123.