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Regioselective alkylation of 3,4-dihydro-2*H*-pyran by xanthate-mediated free radical *nonchain* process

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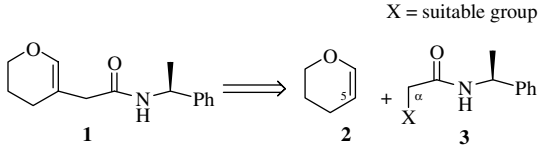
Abstract—An intermolecular xanthate-mediated free radical *nonchain* addition reaction is introduced for the regioselective alkylation of 3,4-dihydro-2*H*-pyran. Additionally, we observed that the free radical *nonchain* reaction depends on the nature of the radical precursor.

An ongoing project in our laboratory required the synthesis of an optically pure acetamide **1** as the starting material of a natural occurring compound. Accordingly, as **1** is a derived compound from inexpensive commercially available 3,4-dihydro-2*H*-pyran **2**, we envisioned the possibility of a regioselective coupling reaction between compounds **2** and **3** (Scheme 1).

By inspection on Scheme 1, we can realize that, in order to connect C5 and Cα in a direct way, a novel coupling reaction needs to be developed. The well-known Heck coupling reaction[1] or similar coupling reactions[2] cannot be applied herein because there is no halide atom present in the double bond of **2**. Apparently, a convenient way to accomplish the reaction is through a free radical addition onto the olefinic bond (e.g., halogen atom transfer) followed by a radical or ionic elimination reaction.[3] Thus, we turned our attention to a recent Zard and Miranda work,[4] where a xanthate-mediated 5-*endo* radical cyclization occurred under free radical *nonchain* process leading to the formation of isomeric unsaturated lactams **4–6** (Scheme 2).



Scheme 1.

In this presumably free radical *nonchain* reaction, the dilauroyl peroxide (DLP) was suggested to act as the radical initiator and as oxidant. Therefore, the isomeric lactams **4–6** were obtained by an intramolecular 5-*endo-trig* radical addition followed by oxidation of radical **B**, which after proton elimination afforded the isomeric lactams **4–6** (Scheme 2). If we take a look at the lactam **4**, we notice that it corresponds to a formal selective intramolecular alkylation at the alkenyl carbon of the enamine. Based on this, we now considered the possibility for obtaining the desired compound **1** by intermolecular radical addition of radical **E** onto **2** followed by radical oxidation and final proton elimination of the six-membered ring oxocarbenium ion **G** (Scheme 3).

Accordingly, *nonchiral* xanthate **9** was selected as a free radical model of study. Thus, this compound was prepared as depicted in Scheme 4. Bromoacetyl bromide **11** and benzylamine **12** were allowed to react in the presence of triethyl amine to give **14** quantitatively. Amide **14** was finally treated with potassium *O*-ethyl xanthate to afford **9** (Scheme 4).[5]

Xanthate **9** was submitted to different free radical reaction conditions. Modest yields of the analogous expected product **16** were observed with 10 equiv of 3,4-dihydro-2*H*-pyran **2**, and 2 equiv of DLP in refluxing 1,2-dichloroethane (Table 1, entry 3).[6]

Additionally, a direct xanthate reduction product **17** was obtained in low yield (Table 1). When peroxides,

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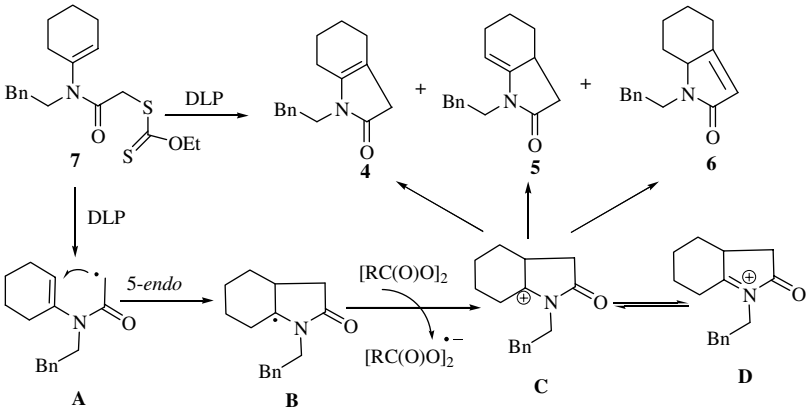
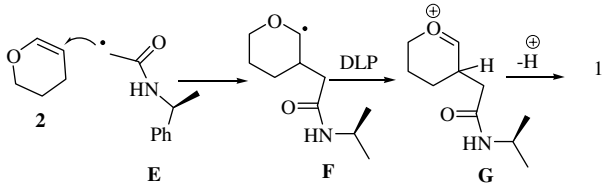
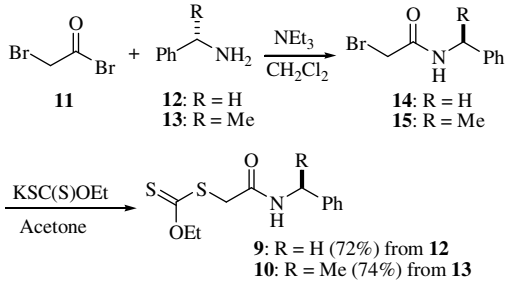


Scheme 2.



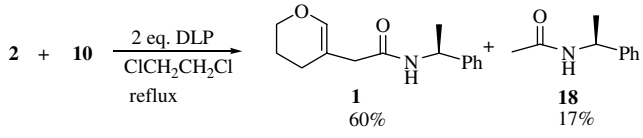
Scheme 3.



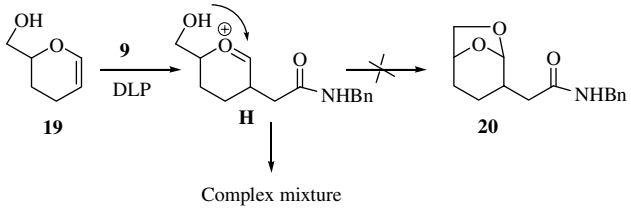
Scheme 4.

dicumyl peroxide (DCP), or dibenzyl peroxide (DBP) were used, neither the coupling product **16** nor the reduction product **17** was observed (entries 6–8).

Following the same route depicted in Scheme 4, optically pure xanthate (*S*)-**10** was synthesized and allowed to react under the condition reactions described in Table 1 (entry 4) to afford the expected product **1** along with the corresponding xanthate reduction product **18**[7] in 60% and 17% yield, respectively.

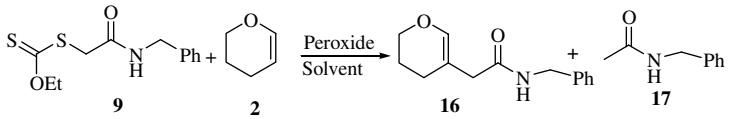


Scheme 5.



Scheme 6.

Table 1. Radical addition/proton elimination[a,b]

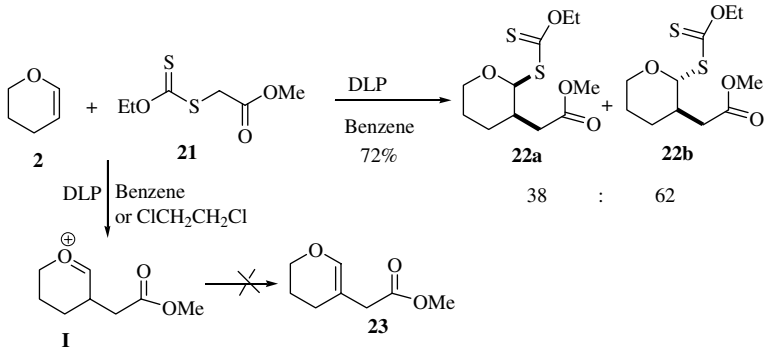


Entry	**2** (equiv)	Peroxide (equiv)	Solvent	**16** (Yield)	**17** (Yield)
1	2	DLP (0.5)	$ClCH_2CH_2Cl$	Trace	—
2	5	DLP (1)	$ClCH_2CH_2Cl$	10	Trace
3	10	DLP (1)	$ClCH_2CH_2Cl$	21	7
4	10	DLP (2)	$ClCH_2CH_2Cl$	58	12
5	10	DLP (2)	C_6H_6	Trace	—
6	10	DCP (2)	$ClCH_2CH_2Cl$	NR	—
7	10	DCP (2)	C_6H_6	NR	—
8	10	DBP (2)	$ClCH_2CH_2Cl$	NR	—

NR = no reaction.

[a] All reactions were carried out in refluxing solvents.

[b] Dilauryl peroxide (DLP), dibenzyl peroxide (DBP), and dicumyl peroxide (DCP).



Scheme 7.

The formation of the reduction product **18** (and also **17**) might correspond to a disproportionation product, as it would explain the formation of the olefinic double bond of **16** and **1**, however, the ratio of **16/17** or **1/18** should be equimolar or close to that (Scheme 5).

Thus, like Zard and Miranda, we propose that the reaction mechanism may occur through direct oxidation by the peroxide of the incipient radical **F** into oxocarbenium ion **G**, which then by proton elimination, the double bond is recovered (see Scheme 3).[4,8] In this regard, we attempted trapping the oxocarbenium ion by using an internal nucleophile with the expectation that cyclization might be competitive with proton elimination (Scheme 6).

Accordingly, 3,4-dihydro-2*H*-pyran-2-methanol **19** was allowed to react with xanthate **9** and 2 equiv of DLP in refluxing $ClCH_2CH_2Cl$, resulting in the formation of a rather complex reaction mixture. Unfortunately, we could not accomplish the ring closure onto oxocarbenium ion (compound **20**), which would be the unambiguous proof for the existence of oxocarbenium ion as the intermediate of this reaction (as well as the formation of the lactams, see Scheme 2).[9] On the other hand, a xanthic acid elimination (which should result from xanthate-mediated free radical chain reaction) is not supported because of an additional experiment between compound **2** and xanthate **21** under standard conditions afforded an inseparable mixture of products **22a** and **22b** (in a ratio of 48/62, respectively)[10] resulted from a xanthate-mediated free radical chain reaction (Scheme 7).[11]

Until now, we have not been able to find an explanation about the difference in reactivity among these two types of carbon-centered radicals α to a carbonyl group (from amides and esters), so a number of interesting questions are raised. Thus, more laboratory quality time as well as theoretic studies on this regard is in progress.

In conclusion, a novel intermolecular free radical *non-chain* addition reaction onto 3,4-dihydro-2*H*-pyran is reported. Although this reaction was developed for the synthesis of a specific compound, we anticipate very similar behavior for those with few variants into the framework.

Acknowledgements

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5. *Synthesis of the free radical precursors*: To a solution of amine (1 equiv) and triethylamine (1.2 equiv) in dry THF (approx 1 g/50 mL of THF) at 0 °C was added dropwise bromoacetyl bromide (1.1 equiv) dissolved in dry THF (approx 1 mL/20 mL). The reaction mixture was warmed to room temperature and allowed to react for 2 h, and then quenched with 50 mL of H_2O. The reaction mixture was extracted with ethyl acetate, washed with brine, dried over $NaSO_4$, and concentrated in vacuo to yield a colorless oil. The crude mixture was dissolved in 40 mL of acetone and cooled to 0 °C, and then potassium ethyl xanthate (1.5 equiv) was added. The reaction mixture was allowed to react for 4 h at room temperature and the solution was concentrated under reduced pressure. The resulting viscous oil was purified under chromatography with ethyl acetate and hexane as the eluant.
S-(*Benzylcarbamoyl*)*methyl O-ethyl carbonodithioate* **9**: Mp = 94–95 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (t, 3H, $J = 7.2$ Hz), 3.87 (s, 2H), 4.44 (d, 2H, $J = 5.6$ Hz), 4.62 (q, 2H, $J = 7.2$ Hz), 6.69 (br, 1H), 7.27 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.6, 39.0, 43.8, 71.0, 127.5, 127.6, 128.6, 137.6, 166.8, 212.8; MS (EI): $m/z = 148$ (54%, M^+−EtOCSS), 269 (12%, M^+); (FAB-HRMS) $m/z = 270.0622$ (calcd for $C_{12}H_{16}NO_2S_2$: 270.0616).

S-[(*S*)-*1-Phenylethylcarbamoyl]methyl O-ethyl carbonodithioate* **10**: Mp = 59–60 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (t, 3H, $J = 7.2$ Hz), 1.47 (d, 3H, $J = 7.2$ Hz), 3.79 (d, 1H, $J = 15.9$ Hz), 3.85 (d, 1H, $J = 15.9$ Hz), 4.61 (m, 2H), 5.11 (sept, 1H, $J = 6.8$ Hz), 6.58 (br d, 1H, $J = 6.2$ Hz), 7.28 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.6, 21.6, 39.1, 49.1, 71.0, 126.0, 127.4, 128.6, 142.6, 165.9, 212.9; MS (EI): $m/z = 162$ (45%, M^+−EtOCSS), 283 (8%, M+); (FAB-HRMS) $m/z = 283.0700$ (calcd for $C_{13}H_{17}NO_2S_2$: 283.0701).

6. *General procedure*: 2 equiv of DLP dissolved in dichloroethane (2 mL/100 mg) were added portionwise to a solution of xanthate and 10 equiv of 3,4-dihydro-2*H*-pyran dissolved in dichloroethane (5 mL/100 mg of xanthate) at reflux over 4 h (0.5 equiv/1 h). The reaction mixture was cooled to room temperature and solvent removed under reduced pressure. The resulting viscous oil was purified under chromatography with ethyl acetate and hexanes as the eluant.
N-Benzyl-2-(5,6-dihydro-4H-pyran-3-yl)acetamide **16**: Mp = 96–97 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.85 (m, 2H,), 1.99 (m, 2H), 2.83 (s, 2H), 3.91 (apparent t, 2H, $J = 5.1$ Hz), 4.43 (d, 2H, $J = 5.7$ Hz), 6.10 (br, 1H), 6.37 (s, 1H), 7.27 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.1, 23.3, 41.3, 43.5, 65.3, 107.4, 127.4, 127.5, 128.7, 138.3, 142.8, 171.0; MS (EI): $m/z = 231$ (64%, M+); (FAB-HRMS) $m/z = 232.1330$ [M+H$^+$] (calcd for $C_{14}H_{17}NO_2$: 232.1338).
(*S*)-*2-(5,6-Dihydro-4H-pyran-3-yl)-N-(1-phenylethyl)acetamide* **1**: $[\alpha]_D$ −27.5 (*c* 1, $CHCl_3$); mp = 93–94 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ: 1.47 (d, 3H, $J = 6.8$ Hz), 1.85 (m, 2H), 1.95 (m, 2H), 2.77 (dd, 1H, $J = 16.4$, 3.2 Hz), 2.82 (dd, 1H, $J = 16.2$, 2.9 Hz), 3.92 (apparent t, 2H, $J = 5.6$ Hz), 5.13 (sept, 1H, $J = 6.8$ Hz), 5.97 (d, 1H, $J = 6.8$ Hz), 6.38 (s, 1H), 7.28 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.8, 22.3, 23.3, 41.5, 48.5, 65.4, 107.5, 125.8, 127.2, 128.5, 142.6, 142.9, 169.9; MS (EI): $m/z = 245$ (58%, M+); (FAB-HRMS) $m/z = 246.1490$ [M+H$^+$] (calcd for $C_{15}H_{20}NO_2$: 246.1494).
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