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CONVENIENT SYNTHESIS OF NOVEL MACROCYCLIC URETHANES: ALKOXYCARBONYLATION OF AMINES AND RING-CLOSING METATHESIS STRATEGY

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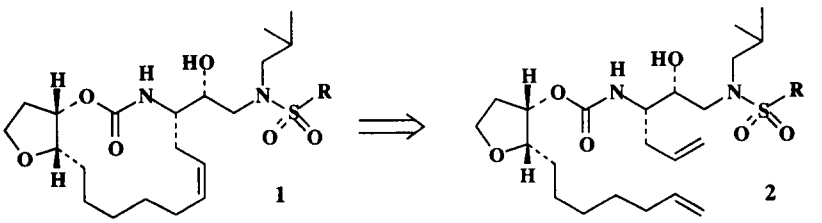
Abstract: Alkoxycarbonylation of amines followed by ring-closing metathesis of the resulting dienes with Grubbs catalyst (25-50 mol%) provided convenient access to 14-16 membered macrocyclic urethanes in very good yields.

We recently demonstrated the utility of various acyclic urethanes in the design and synthesis of structurally novel HIV protease inhibitors for the treatment of AIDS.[1] In this context, we have developed a number of efficient methodologies for the synthesis of acyclic urethanes.[2] As part of our continuing efforts in the design and synthesis of novel molecular probes for the HIV protease substrate binding site, we now require a general synthetic route to the 14-16 membered macrocyclic urethanes as exemplified in the designed inhibitor **1**. Unlike acyclic urethanes, thus far the biological significance of macrocyclic urethanes has not been explored due to the lack of effective synthetic methods. The advent of ring-closing metathesis reactions has now provided opportunity for the construction of these novel cyclourethanes for biological studies.[3] Already, the remarkable potential of this olefin-metathesis reaction has been demonstrated in the synthesis of numerous biologically important molecules with varied ring systems and diverse functionalities.[4, 5] In this letter, we report the synthesis of 14-16 membered macrocyclic urethanes utilizing commercially available N,N'-disuccinimidyl carbonate (DSC) promoted alkoxycarbonylation of amines followed by efficient ring-closing metathesis reactions of the resulting dienes with commercially available Grubbs catalyst.[6]



1 **2**

The synthetic sequence leading to the construction of various macrocyclic urethanes is illustrated in Scheme 1. Commercially available 9-decen-1-ol **3** was converted to alcohol **4** by Swern oxidation followed by reaction of the resulting aldehyde with MeMgBr in ether (70% yield). Treatment of the alcohols **3** and **4** with DSC (1.5 equiv) in the presence of Et_3N in dry acetonitrile at 23°C for 12 h furnished the mixed succinimide carbonates **6** and **7** respectively. These carbonates

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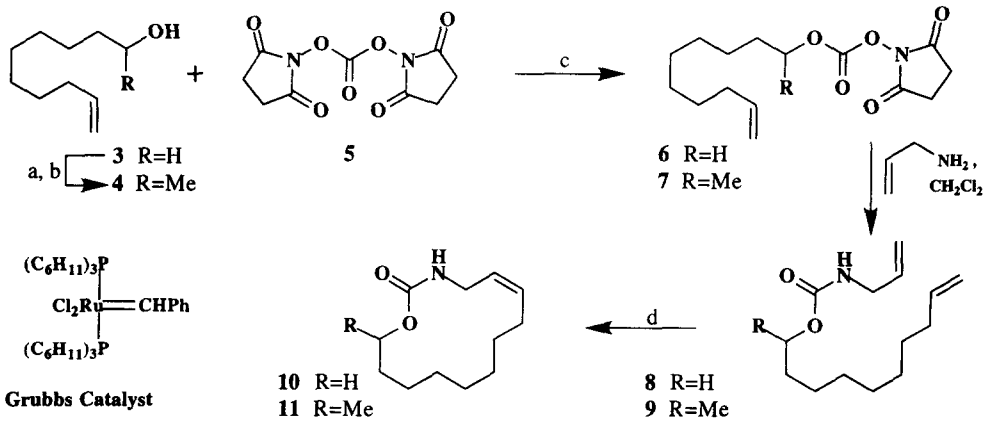
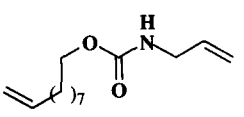
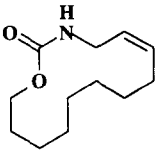
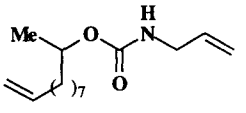
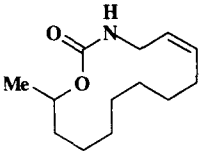
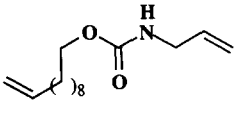
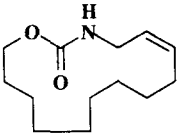
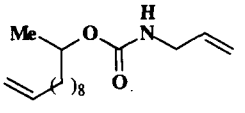
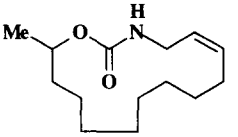
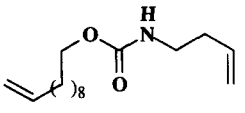
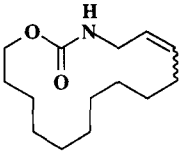
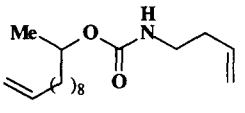
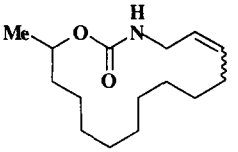
are quite stable and can be chromatographed if necessary. However, the crude mixed carbonates obtained after standard workup were reacted with allylamine to provide the corresponding urethanes **8** and **9** in excellent yield (94% and 80% respectively) after silica gel chromatography. The reactions of 3-butenylamine and various mixed carbonates under similar conditions also afforded the corresponding acyclic urethanes in excellent yields.



Scheme I: (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 , -50°C, 85%; (b) MeMgBr, Et_2O, 0°-23°C, 3 h, 82%; (c) Et_3N, CH_3CN, 23°C, 12 h; (d) 25 mol% Grubbs catalyst, CH_2Cl_2, 23°C, 20 h.

Exposure of the acyclic urethanes **8** and **9** to commercial Grubbs catalyst (25-50 mol%) in CH_2Cl_2 (0.003 M solution) at 23°C for 20 h afforded the macrocyclic urethanes **10** and **11** in 78% and 69% yield respectively after silica gel chromatography. When the ring-closing metathesis reaction of **8** was carried out in the presence of 10 mol% catalyst, a substantial amount of starting material remained after 24 h.[7] This synthetic protocol was employed to a series of six different types of acyclic urethanes and the results are summarized in Table I. As is evident, this procedure allows convenient access to the synthesis of a variety of structurally novel cyclo-urethanes from primary or secondary alcohols and suitable amines (yield 51-78%). Interestingly, 14- and 15-membered cyclo-urethanes (entries 1-4) were formed as a single cis isomer (J = 6-7 Hz) however, 16-membered cyclo-urethanes were formed as a cis/trans mixture by ^{1}H-NMR (400 MHz). Catalytic hydrogenation of the cis/trans mixture afforded saturated cyclo-urethane in near quantitative yields (98% yield).[8] In an effort to improve the catalyst loading as well as E/Z selectivity for the 16-membered cyclo-urethane, we have examined Schrock molybdenum catalyst (up to 30 mol%) in benzene at 55°C for 48 h.[6, 9] These reaction conditions resulted in a substantial decomposition of the starting acyclic urethane and only a trace amount of 16-membered cyclo-urethane was isolated. We have also attempted the same cyclization (entry 5) with 15 mol% catalyst in the presence of 2-equivalents of $Ti(OiPr)_4$ in CH_2Cl_2 at 23°C for 24 h then at 40°C for 24 h.[10] After this period, the 16-membered cyclo-urethane was obtained as a mixture (1:1) in 56% isolated yield and 38% starting material was recovered. The effect of solvents (THF, benzene and toluene) and temperature were surveyed and the choice of CH_2Cl_2 at 23°C provided the best results.

Table I. Synthesis of Macrourethanes by Ring-Closing Metathesis[a]

Entry	Urethane	mol% (cat)	Macrourethane	Ring Size	% Yield[b]
1.		25		14	78
2.		25		14	74[c]
3.		50		15	58
4.		50		15	69
5.		50		16	64[d]
6.		50		16	69[e]

[a]All reactions are carried out at 23°C for 22-26 h; [b]Yields refer to purified products; [c]About 25% starting material was recovered (74% yield based on recovery); [d]Mixture ratio 1:1; [e]Mixture ratio 1:1.6.

In summary, the known[4, 5] functional group tolerance of the olefin metathesis reaction as well as the ready availability of both DSC and Grubbs catalyst make the current methodology suitable for the synthesis of polyfunctional molecules for biological studies. Chemistry and biology of cyclo-urethane derived novel HIV protease inhibitors are the subject of our ongoing investigation. The following example is representative of this procedure.

Preparation of acyclic urethane 8: To a stirred solution of mixed carbonate **6** (267 mg, 0.9 mmol) in CH_2Cl_2 (2 mL) was added a solution of allylamine (0.134 mL, 1.8 mmol) in CH_2Cl_2 (1 mL) and the resulting mixture was allowed to stir at 23°C for 20 min. The reaction was quenched with saturated aqueous NH_4Cl solution (5 mL). The reaction mixture was then extracted with CH_2Cl_2 (2 x 15 mL).

The combined organic layers were washed with brine (20 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue which was purified by flash chromatography (silica gel, 10-15% EtOAc in hexanes) to afford **8** (202 mg, 94%) as an oil. ^{1}H-NMR($CDCl_3$, 200 MHz): δ, 5.85-5.73 (m, 2H), 5.22-4.99 (m, 4H), 4.71(s, 1H), 4.05 (t, J = 6.6 Hz, 2H), 3.79 (t,, 2H, J = 5.5 Hz), 2.01 (m, 2H), 1.65-1.56 (m, 2H), 1.36-1.29 (m, 10H).

Preparation of cyclo-urethane 10: To a stirred solution of **8** (148 mg, 0.62 mmol) in CH_2Cl_2 (220 mL, 0.0027 M) was added commercial Grubb`s catalyst {$[(C_6H_{11})_3P]_2Cl_2Ru$=CHPh} (127 mg, 25 mole%). The resulting was stirred under argon atmosphere for 20 h. After this period, the solvent was evaporated under reduced pressure and the residue was flash chromatographed (silica gel, 5-10% EtOAc/ hexanes) to afford **10** (103 mg, 79%) as a white solid. m.p 76-79°C; ^{1}H-NMR ($CDCl_3$, 200 MHz): δ , 5.51-5.44 (m, 2H), 4.8 (s, 1H), 4.15 (t, 2H, J = 4.97 Hz), 3.64 (t, 2H, J = 5.28 Hz), 1.99 (m, 2H), 1.56-1.51 (m, 2H), 1.32-1.24 (m, 10H); MS, m/z: 211 (M^+).

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6. DSC is available from Aldrich and Grubbs catalyst and Schrock catalyst (2,6-diisopropylphenylimido-neophylidenemolybdenum (VI) bis(hexafluoro-t-butoxide) are available from Strem Chemicals.
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