

A New Synthetic Route to 12-Oxo-1, 15-pentadecanlactam

Jia Xing HUANG, Xiao Mei LIANG, Dao Quan WANG*

Key Laboratory of Pesticide Chemistry and Application Technology,
Department of Applied Chemistry, China Agricultural University, Beijing 100094

Abstract: 12-Oxo-1, 15-pentadecanlactam **7** was synthesized from cyclododecanone with a total yield of 36% in a seven-step reaction. The azide **5** to 12-nitro-1, 15-pentadecanlactam **6** is the key step featured by direct ring expansion.

Keywords: Macrolactam, synthesis, ring enlargement.

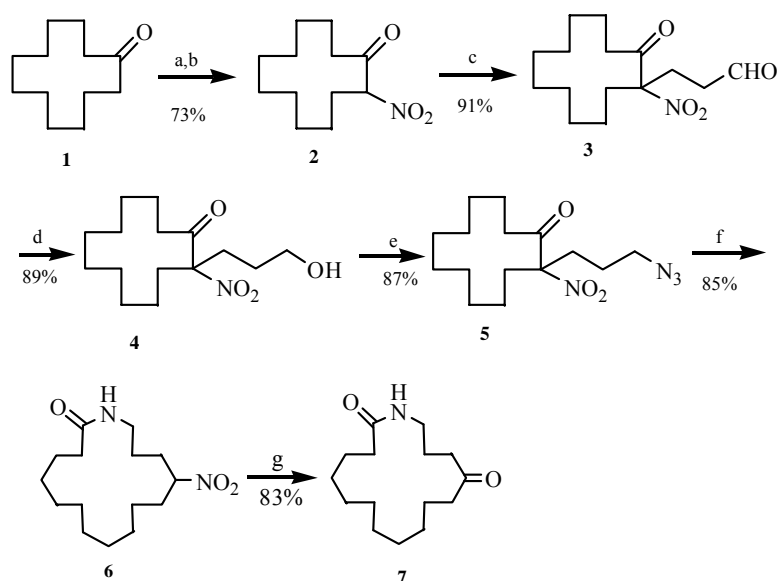
12-Oxo-1,15-pentadecanlactam is an important synthetic intermediate. Von Rudolf Walchli *et al.*^{1,2} had obtained it by selective reductive amination of the aldehyde group of **3**, but the yield is low. Catherine Goulaouic-Dubois *et al.*³ reported the synthesis of 12-cyano-1,15-pentadecanlactam from 2-cyanocyclododecanone through an azide intermediate with good yield. But the reduction of the azide group with lindlar catalyst led to the bicyclic intermediate, indicating that the nitrile group does not withdraw the electron strongly enough to activate the carbonyl group to induce the direct ring expansion.

The nitro group withdraws electron stronger than azide group and can afford the direct ring enlargement. Further more the nitro group can be converted to the expected oxo group. With this in mind we designed a new route to the 12-oxo-1, 15-pentadecanlactam from the cyclododecanone. In this route, **5** converts to **6** is a key step (**Scheme 1**).

2-Nitrocyclododecanone **2**^{4,5}, prepared from cyclododecanone **1**, was allowed to react with acrolein to give **3**^{6,7}. The aldehyde group of **3** was selectively reduced by NaBH₄ to afford **4**⁸, which was converted to the azide **5**⁹ via reaction of the corresponding mesylate with NaN₃ in the presence of phase-transfer catalyst. Catalytic hydrogenation of azide **5** with Lindlar catalyst afforded **6**⁹ successfully without any byproduct. Then through Nef reaction the 12-oxo-1,15-pentadecanlactam **7**⁹ was obtained. The total yield from cyclododecanone was 36%.

* E-mail: wangdq@cau.edu.cn

Scheme 1



a) Ac_2O , TsOH, reflux; b) Ac_2O , CCl_4 , concentrated H_2SO_4 , concentrated HNO_3 , AcOH;
 c) $\text{CH}_2=\text{CHCHO}$, Et_3N , THF; d) NaBH_4 , MeOH, 0 °C, 40 min; e) MeSO_2Cl , Et_3N , toluene,
 0 °C, 40 min then NaN_3 , Bu_4NBr , H_2O , 60 °C; f) H_2 /Lindlar catalyst, EtOH, rt; g) NaOMe,
 MeOH then 4 mol/L HCl.

References and Notes

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- 5**: white solid, m.p.89~90 °C; ^1H NMR, δ_{H} ppm: 0.80~1.60 (m, 17H), 2.0~2.5 (m, 6H), 2.75~2.95 (m, 1H), 3.25~3.45 (m, 2H); δ_{C} ppm: 201.1, 100.7, 50.8, 32.3, 29.9, 29.4, 26.3, 26.2, 23.3, 22.7, 22.6, 21.9, 21.7, 21.3, 19.0. **6**: white solid, m.p. 96~97 °C; ^1H NMR, δ_{H} ppm: 1.13~2.20 (m, 24H), 2.20~2.30 (m, 2H), 3.12~3.30 (m, 1H), 3.48~3.65 (m, 1H), 4.47~4.63 (m, 1H), 5.60 (s, 1H). **7**: white solid, m.p.103~104 °C; ^1H NMR, δ_{H} ppm: 1.18~2.37 (m, 13H), 1.52~1.71 (m, 4H), 1.71~1.82 (m, 2H), 2.17 (t, 2H, $J=6.9\text{Hz}$), 2.41 (t, 2H, $J=6.7\text{Hz}$), 2.58(t, 2H, $J=6.5\text{Hz}$), 3.2~3.39 (m, 2H), 6.09 (s, 1H); Anal. Calcd. for $\text{C}_{15}\text{H}_{27}\text{NO}_2$: C 71.10, H 10.74, N 5.53; Found: C 71.12, H 10.93, N 5.75; EIMS m/z (%): 253(M^+ , 28), 225(7), 44 (100).

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