SYNTHESIS OF 1-METHOXY-4-(2-MORPHOLINOETHYL)-3,3-DIPHENYLPRYRROLIDIN-2-ONE

Keywords: Doxapram, lactam, lactone, Mitsunobu reaction.

Doxapram has long been used as intravenously-administered drug for treatment of acute respiratory insufficiency [1]. As a part of our research program toward development of novel respiratory stimulants we were interested in synthesis of more potent Doxapram analogues. Herein we report a concise synthesis of N-methoxypyrrrolidinone 1.

The key step in the synthesis is transformation of lactone 4 into N-OMe lactam 7, which was elaborated to the target compound 1 in a straightforward three-step sequence.

The prerequisite lactone 4 was prepared in an iodotetraphenyl-α₅-stibane-catalyzed cycloaddition reaction between oxirane 3 and diphenyl ketene, generated from acid chloride 2 [2] prior to the cycloaddition [3]. Transformation of lactone 4 into lactam 7 was achieved in a two-step sequence. Initially, lactone 4 was converted to O-methylhydroxamic acid 5 in the Me₃Al-mediated [4] reaction with H₂NOMe·HCl. Because the hydroxamic acid 5 was unstable and readily cyclized back to lactone 4, it was used in the next step without purification. Cyclization of
compound 5 under Mitsunobu conditions [5] afforded the desired lactam 7 together with the isomeric O-methyl oxime 6 (ratio 7:6 = 1:3). The ratio of N- vs. O-cyclization products was improved to 1:1 by substitution of THF and CH₂Cl₂ by more polar DMF or NMP. Gratifyingly, the isomers could be separated by chromatography on silica gel. Furthermore, the undesired oxime 6 could be smoothly hydrolyzed back to the lactone 4 under acidic conditions [6] (81% yield) and reused in the synthesis of lactam 7.

Lactam 7 was elaborated to the target compound 1 in three-step sequence comprising hydroboration–oxidation [7] to alcohol 8, followed by conversion to chloride 9 and, finally, alkylation of morpholine [8, 9].

IR spectra were recorded on a Shimadzu IR Prestige21 FTIR spectrometer in thin film. ¹H and ¹³C NMR spectra were registered on a Varian Mercury 400 instrument (400 and 100 MHz, respectively) in CDCl₃, using the residual solvent peak as an internal reference (7.26 ppm for ¹H nuclei, 77.0 ppm for ¹³C nuclei). High resolution mass spectra (ESI) were obtained on Micromass microTOF-Q Mass Spectrometer. Elemental analyses were performed on Carlo Erba EA 1108 Analyzer. Melting points were determined by using an OptimMelt automated melting point system and are uncorrected.

3,3-Diphenyl-4-vinyldihydrofuran-2(3H)-one O-methyloxime (6) and 1-methoxy-3,3-diphenyl-4-vinylpyrrolidin-2-one (7).

2M Solution of Me₃Al in PhMe (7.77 ml, 15.55 mmol) is added dropwise to the cooled (0°C) solution of O-methylhydroxylamine hydrochloride (1.30 g, 15.55 mmol) in dry PhMe (18 ml) under Ar atmosphere. 3,3-Diphenyl-4-vinyldihydrofuran-2(3H)-one (4) (1.37 g, 5.18 mmol) is added and the reaction mixture stirred at 55°C for 20 h. Solvent is evaporated, the residue is dissolved in CH₂Cl₂ (15 ml), cooled to 0°C and saturated aq. NaHCO₃ (15 ml) is added. The resulting suspension is stirred at 0°C for 10 min, filtered through celite, the celite pad is washed with CH₂Cl₂ (10 ml). Layers are separated and the water phase is extracted with CH₂Cl₂ (2 × 15 ml). Combined organic extracts are washed with saturated aq. NaHCO₃ (40 ml) and dried over Na₂SO₄. Solvents are evaporated to give 3-hydroxy-N-methoxy-2,2-diphenylpent-4-enamide (5), which was used in the next step without purification.

Compound 5 is dissolved in NMP (20 ml), cooled to 0°C, DIAD (0.98 g, 4.85 mmol) and Ph₃P (1.27 g, 4.85 mmol) are added. The reaction mixture is stirred at room temperature for 2 h. Water (20 ml) is added to the reaction mixture and resulting suspension is extracted with t-BuOMe (3 × 15 ml). Volatiles are removed under reduced pressure. Purification of the crude mixture by column chromatography (10 to 50% EtOAc – petroleum ether) afforded pure compounds 6 and 7.

**Compound 6.** Yield 400 mg (26%), white powder, mp 165–167°C (MeOH), Rᵣ 0.48 (EtOAc – petroleum ether, 1:3). IR spectrum, ν, cm⁻¹: 1666 (C=O). ¹H NMR spectrum, δ, ppm: 3.81 (3H, s, OCH₃); 3.94–4.02 (2H, m, 5-CH₂, 4-CH); 4.35–4.43 (1H, m, 5-CH₃); 5.13–5.18 (1H, m) and 5.26–5.34 (2H, m, CH=CH₂); 7.05–7.10 (2H, m, H Ph); 7.21–7.36 (6H, m, H Ph); 7.46–7.51 (2H, m, H Ph). ¹³C NMR spectrum, δ, ppm: 49.8; 59.2; 62.5; 71.5; 119.6; 127.0; 127.2; 127.7; 127.8; 128.8; 132.3; 132.7; 140.3; 141.2; 161.1. Found, %: C 77.55; H 6.58; N 4.72. C₁₉H₁₉NO₂. Calculated, %: C 77.79; H 6.53; N 4.77.

**Compound 7.** Yield 410 mg (27%), white powder, mp 115–117°C (MeOH), Rᵣ 0.27 (EtOAc – petroleum ether, 1:3). IR spectrum, ν, cm⁻¹: 1717 (C=O). ¹H NMR spectrum, δ, ppm (J, Hz): 3.31–3.40 (1H, m) and 3.75 (1H, dd, J = 7.2, J = 8.2, 5-CH₂); 3.79–3.90 (1H, m, 4-CH₂); 3.87 (3H, s, OCH₃); 5.07 (1H, dd, J = 1.4, J = 10.0 and 5.24 (1H, dd, J = 1.4, J = 17.2, CH=CH₂); 5.36 (1H, dd, J = 8.0, J = 10.0, J = 17.2, CH=CH₂); 6.92–6.98 (2H, m, H Ph); 7.18–7.39 (6H, m, H Ph); 7.63–7.78 (2H, m, H Ph). ¹³C NMR spectrum, δ, ppm: 43.6; 47.8; 58.1; 62.4; 118.2; 127.0; 127.2; 128.0; 128.1; 128.3; 134.9; 140.2; 141.0; 172.0. Found, %: C 77.43; H 6.52; N 4.73. C₁₉H₁₉NO₂. Calculated, %: C 77.79; H 6.53; N 4.77.

4-(2-Hydroxyethyl)-1-methoxy-3,3-diphenylpyrrolidin-2-one (8). 1M Solution of BH₃ in THF (2.81 ml) is added to the solution of 1-methoxy-3,3-diphenyl-4-vinylpyrrolidin-2-one (7) (0.41 g, 1.40 mmol) in dry THF (10 ml) at 0°C under Ar atmosphere.
The reaction mixture is stirred at room temperature for 4 h, then cooled to 0°C, 1N NaOH (3 ml) and 35% H₂O₂ (3 ml) are added. The mixture is stirred at room temperature for 2 h, and then saturated aq. NH₄Cl (10 ml) is added. The resulting suspension is extracted with CH₂Cl₂ (3 × 15 ml). Combined organic extracts are washed with saturated aq. NH₄Cl (20 ml), dried over Na₂SO₄. Volatiles are evaporated. Purification of the crude product by column chromatography (20 to 90% EtOAc – petroleum ether) afforded product 8. Yield 180 mg (41%), white foam, Rₚ 0.23 (EtOAc – petroleum ether, 1:1). IR spectrum, ν, cm⁻¹: 1696 (C=O). ¹H NMR spectrum, δ, ppm (J, Hz): 0.79–0.90 (1H, m) and 1.67 (1H, dddd, J = 3.2, J = 5.7, J = 8.3, J = 14.4, CH₂CH₂OH); 1.40–1.50 (1H, m, OH); 3.15–3.21 (1H, m) and 3.81 (1H, dd, J = 7.0, J = 8.2, 5-CH₃); 3.32–3.42 (1H, m, CH₉O₉); 3.78 (3H, s, OCH₃); 6.79–6.87 (2H, m, H Ph); 7.11–7.32 (6H, m, H Ph); 7.48–7.54 (2H, m, H Ph). ¹³C NMR spectrum, δ, ppm: 32.6; 35.2; 48.1; 57.8; 60.4; 62.3; 126.9; 127.3; 128.0; 128.1; 128.5; 128.7; 140.4; 140.8; 172.3. Found, m/z: 312.1592 [M+H⁺]. C₁₉H₂₁NO₃. Calculated, m/z: 312.1594.

4-(2-Chloroethyl)-1-methoxy-3,3-diphenylpyrrolidin-2-one (9). The mixture of 4-(2-hydroxyethyl)-1-methoxy-3,3-diphenylpyrrolidin-2-one (8) (0.24 g, 0.76 mmol), SOCl₂ (3 ml) and DMF (50 µl) is stirred at room temperature for 20 h. Excess of SOCl₂ is removed under reduced pressure. The mixture is cooled to 0°C and treated with sat. NaHCO₃ (15 ml), then extracted with t-BuOMe (3 × 10 ml). The combined organic extracts are washed with water (20 ml), brine (20 ml) and dried over Na₂SO₄. Volatiles are evaporated. Purification of the crude product by column chromatography (10 to 35% EtOAc – petroleum ether) afforded product 9. Yield 210 mg (84%), white powder, mp 123–125°C (MeOH), Rₚ 0.23 (EtOAc – petroleum ether, 1:3). IR spectrum, ν, cm⁻¹: 1710 (C=O). ¹H NMR spectrum, δ, ppm (J, Hz): 1.11–1.21 (1H, m) and 1.95 (1H, dddd, J = 3.4, J = 10.3, J = 14.9, CH₂CH₂Cl); 3.19–3.25 (1H, m) and 3.88 (1H, dd, J = 7.1, J = 8.1, 5-CH₂); 3.45 (1H, ddd, J = 4.3, J = 10.3, J = 11.3, CH₂Cl); 3.51–3.64 (2H, m, CH₂Cl, 4-CH); 3.87 (3H, s, OCH₃); 6.87–6.91 (2H, m, H Ph); 7.20–7.41 (6H, m, H Ph); 7.57–7.61 (2H, m, H Ph). ¹³C NMR spectrum, δ, ppm: 32.6; 35.3; 42.7; 47.5; 57.6; 62.4; 127.2; 127.4; 128.2; 128.3; 128.4; 128.6; 140.1; 140.7; 172.2. Found, %: C 68.99; H 6.07; N 4.21. C₁₉H₂₀ClNO₂. Calculated, %: C 69.19; H 6.11; N 4.25.

1-Methoxy-4-(2-morpholinoethyl)-3,3-diphenylpyrrolidin-2-one (1). The reaction mixture of 4-(2-chloroethyl)-1-methoxy-3,3-diphenylpyrrolidin-2-one (9) (118 mg, 0.36 mmol) and morpholine (0.20 ml, 2.27 mmol) in EtOH (5 ml) is heated in the closed vial at 105°C for 48 h. Volatiles are evaporated and water (10 ml) is added. The resulting suspension is extracted with EtOAc (3 × 12 ml). The combined organic extracts are washed with water (30 ml), brine (20 ml) and dried over Na₂SO₄. Purification of the crude product by column chromatography (50 to 100% EtOAc – petroleum ether) afforded product 1. Yield 100 mg (76%), white foam, Rₚ 0.23 (EtOAc – CH₂Cl₂, 1:9). IR spectrum, ν, cm⁻¹: 1706 (C=O). ¹H NMR spectrum, δ, ppm (J, Hz): 0.78–0.90 (1H, m) and 1.57–1.68 (1H, m, CHCH₂CH₂N); 2.27–2.46 (6H, m, CH₂N(CH₂)₂); 3.19–3.26 (1H, m) and 3.84 (1H, dd, J = 7.0, J = 8.0, 5-CH₂); 3.27–3.38 (1H, m, 4-CH); 3.66–3.75 (4H, m, CH₂OCH₂); 3.86 (3H, s, OCH₃); 6.87–6.93 (2H, m, H Ph); 7.18–7.38 (6H, m, H Ph); 7.54–7.61 (2H, m, H Ph). ¹³C NMR spectrum, δ, ppm: 26.8; 36.4; 48.3; 53.9; 56.8; 58.0; 62.3; 66.9; 127.0; 127.3; 128.1 (2C); 128.5; 128.7; 140.8; 140.8; 172.3. Found, %: C 72.29; H 6.57; N 7.23. C₂₃H₂₈N₂O₃. Calculated, %: C 72.61; H 7.42; N 7.36.

REFERENCES
ПОЛУЧЕНИЕ ПИРИДИЛЗАМЕЩЁННЫХ МОНОАЗАТРИФЕНИЛЕНов

Ключевые слова: азатрифенилены, енамин, 1,2,4-триазин, реакция Дильса–Альдера, циклоприсоединение.


В данном сообщении мы предлагаем эффективный метод синтеза циклоалкенаннелированных производных моноазатрифениленов, основанный на реакции аза-Дильса–Альдера ранее не охарактеризованного 3-(пиридин-2-ilphenантр[9,10-e][1,2,4]триазина (1) [14] с 1-морфолинилциклоалkenами. Методика получения разнообразных производных пиридина в результате превращения соответствующих моноядерных 1,2,4-триазинов известна уже давно [15–17]. В настоящей работе эта методика впервые применена для одностадийного синтеза маладоступных пиридилизамещённых моноазатрифениленов 2a,b.

![Diagram](image-url)