Turkish Journal of Chemistry

Volume 42 | Number 1 Article 3

1-1-2018

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ÇINAR, SEDA and ÜNALEROĞLU, CANAN (2018) "Facile synthesis of heteroaryl substituted -lactams from nitrovinyl arenes," *Turkish Journal of Chemistry*: Vol. 42: No. 1, Article 3. https://doi.org/10.3906/kim-1705-25

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Turkish Journal of Chemistry
http://journals.tubitak.gov.tr/chem/
Research Article

Turk J Chem
(2018) 42: 29 – 35
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doi:10.3906/kim-1705-25

Facile synthesis of heteroaryl substituted γ-lactams from nitrovinyl arenes

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Received: 15.05.2017 • **Accepted/Published Online:** 10.08.2017 • **Final Version:** 08.02.2018

Abstract: Aliphatic nitroalkanes with different functional groups were synthesized from the Michael addition reactions of active methylene compounds **2** and nitrovinyl arenes **1** in high yields. The synthesized Michael adducts were subjected to intramolecular cyclization to give heteroaryl substituted γ-lactams in good to high yields under mild reaction conditions.

Key words: γ-Lactam, aliphatic nitroalkanes, Michael addition, nitrovinyl arenes

1. Introduction

Nitrogen-containing heterocycles attract chemists due to their utility in medicine. γ-Lactams among N-heterocycles constitute a synthetic challenge because of their important biological activities.[1] For this reason, different methodologies have been developed for their synthesis. These methods include ring expansion of β-lactams,[2] domino ring opening-cyclization of aziridines,[3] intramolecular cyclization,[4,5] [3+3] cycloaddition,[6,7] or radical cyclization reactions.[8,9]

The Michael addition reaction of nucleophiles to electron-deficient species serves as a synthetic tool to form a carbon–carbon bond within the synthesis of biologically active compounds. Okino et al. used γ-lactam formed from the cyclization of the Michael adduct of diethylmalonate and β-nitrostyrene in the total synthesis of (R)-(-)-baclofen.[10] Versatile functionality of the nitro group provides easy transformations into amine,[11,12] ketone,[13,14] oxime,[15,16] or nitrile oxide[17] structures. In this manner, nitro functionality-bearing Michael adducts are potential starting materials for the synthesis of biologically active molecules containing γ-lactam cores.

Herein, we report the formation of γ-lactams **4** from the intramolecular cyclization reactions of Michael adducts **3** obtained from the reaction of active methylene compounds **2** and nitrovinyl arenes **1** according to the retrosynthetic plan given in the Figure.

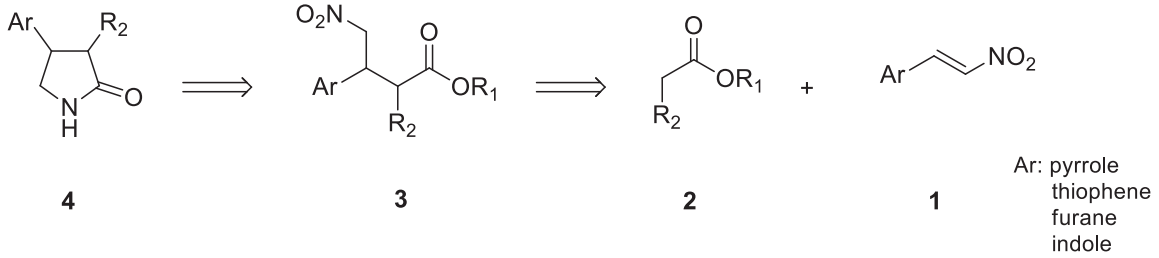

Figure. Retrosynthetic plan for the synthesis of γ-lactams **4**.

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2. Results and discussion

The heteroaryl substituted adducts **3a**–**n** in Table 1 were synthesized from the reaction of active methylene compounds **2a**–**d** and pyrrole-, thiophene-, furan-, or indole-bearing nitrovinyl arenes **1a**–**d**, respectively, in the presence of $LiClO_4$/TEA according to the previously reported procedure.[18] Reactions of **2a** with nitrovinyl arenes **1a**–**d** gave addition products **3a**–**d** in 65%–80% yields (Table 1, entries 1–4). Reactions of ethyl acetoacetate (**2b**) among the active methylene compounds with **1a**–**d** gave **3e**–**h** in high yields (86–99%) (Table 1, entries 5–8). Moreover, addition of methyl cyanoacetate (**2c**) to nitrovinyl arenes **1a**–**c** produced **3i**–**k** in moderate yields (50%–71%) while no product was formed from the addition reaction to nitrovinyl indole **1d** (Table 1, entries 9–12). When phosphonate-containing **2d** was used, pyrrole-containing addition product **3l** was obtained in low yield (16%) (Table 1, entry 13). In our previous study, phosphonate bearing adducts **3m**,**n** were reported similarly in low yields through the synthesis of furan- or thiophene-substituted γ-lactams.[19] When the reaction was performed with nitrovinyl indole **1d**, formation of an adduct was not observed (Table 1, entry 16). In addition, no change in yield in this set of reactions was observed when longer reaction times or heating was applied. To the best of our knowledge, heteroaryl-bearing Michael adducts **3a**, **e**, **i**–**l** were synthesized for the first time through this work. Together with all these results, all addition products were obtained as diastereomeric mixture in 50:50 to 60:40 ratios calculated from the ^{1}H NMR and ^{31}P NMR analysis.

Transformation of nitro moiety into amine,[20] oxime,[21] or nitrile oxide[22] makes it a versatile functional group in organic synthesis. Thereby, reduction of the nitro group of Michael adducts provides an easy access to γ-lactams.[10,20] With Michael addition products in hand, we next applied this approach to nitro-substituted adducts **3a**–**n** by using the $NiCl_2.6H_2O/NaBH_4$ system as reducing reagent to obtain a γ-lactam skeleton.

Firstly, we studied cyclization reactions of malonate substituted adducts **3a**–**d**. Reduction of the nitro group of these compounds using $NiCl_2.6H_2O/NaBH_4$ in methanol resulted in the γ-lactams **4a**–**d**. Heteroaryl substituted lactams **4a**–**d** were obtained in moderate to excellent yields (50%–99%) (Table 2, entries 1–4). We applied the same procedure for **3e**–**h** to obtain keto-substituted γ-lactams. However, no cyclization products were obtained and the starting materials decomposed. Similar results were observed for the cyclization reactions of **3i**–**k** bearing a cyano group at the α-position of ester moiety. These results indicated that the existence of keto or cyano groups on Michael adducts **3e**–**k** hampered the cyclization reactions. Phosphonate group-bearing adducts produced the corresponding γ-lactams **4f**–**g** in moderate yields (Table 2, entries 5–7).

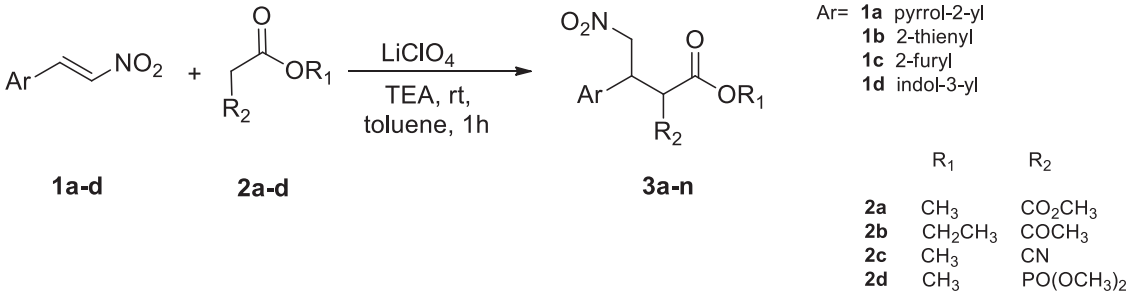
In summary, different functional groups bearing addition products **3** were obtained from the reaction of active methylenes with various nitrovinyl arenes. Intramolecular cyclization reactions of **3a**–**d**, **l**–**n** generated heteroaryl-substituted γ-lactams **4a**–**g** in the presence of $NiCl_2.6H_2O/NaBH_4$ under mild reaction conditions. Throughout the intramolecular cyclizations of Michael adducts with α-keto or cyano substituents **3e**–**k** failed to give γ-lactams. The method we applied provides access to a variety of heteroaryl substituted γ-lactams.

3. Experimental

3.1. General

All procedures were carried out under inert atmosphere. Chemicals and solvents were purchased from Sigma Aldrich and Acros Organics. Products were purified by silica gel flash column chromatography (0.05–0.63 nm 230–400 mesh ASTM, Merck). ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectra were recorded on a Bruker 400, Ultra Shield, high performance digital FT-NMR spectrometer. Peaks that represent both the major and minor diastereomers are indicated by an asterisk. Square brackets indicate the peaks arising from the minor

Table 1. Michael addition reaction of active methylene compounds **2a**–**d** with nitrovinyl arenes **1a**–**d**.



Entry		Ar	Active methylene compound	Michael adduct	Yield (%)[a]	dr[d]
1	**1a**	pyrrol-2-yl	**2a**	**3a**	71	-
2	**1b**	2-thienyl	**2a**	**3b**	80	-
3	**1c**	2-furyl	**2a**	**3c**	65	-
4	**1d**	indol-3-yl	**2a**	**3d**	76	-
5	**1a**	pyrrol-2-yl	**2b**	**3e**	90	58:42
6	**1b**	2-thienyl	**2b**	**3f**	99	50:50
7	**1c**	2-furyl	**2b**	**3g**	99	50:50
8	**1d**	indol-3-yl	**2b**	**3h**	86	58:42
9	**1a**	pyrrol-2-yl	**2c**	**3i**	71	60:40
10	**1b**	2-thienyl	**2c**	**3j**	50	55:45
11	**1c**	2-furyl	**2c**	**3k**	50	55:45
12	**1d**	indol-3-yl	**2c**	**-**	-	-
13	**1a**	pyrrol-2-yl	**2d**	**3l**	16[b]	55:45
14	**1b**	2-thienyl	**2d**	**3m**	25[b,c]	60:40
15	**1c**	2-furyl	**2d**	**3n**	22[b,c]	50:50
16	**1d**	indol-3-yl	**2d**	**-**	-[b]	-

Reaction conditions: nitrovinyl arene (0.60 mmol), active methylene compound (0.64 mmol), $LiClO_4$ (0.036 mmol), and Et_3N (0.007 mmol). [a] Isolated yields. [b] Reaction time was 24 h and temperature was 50 °C. [c] Previously reported literature.[19] [d] ^{1}H NMR and ^{31}P NMR analysis.

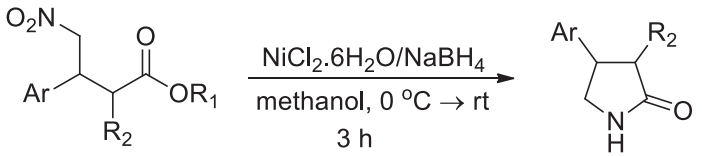
diastereomer, where applicable. FT-IR absorption spectra were recorded on an ATR (Nicolet iS10) spectrometer. Melting points were recorded using a Gallenkamp capillary melting point apparatus. Mass spectra were recorded on an Agilent 1200/6210 High Resolution Mass Time-of-Flight (TOF) LC/MS spectrometer.

3.2. General procedure for the synthesis of addition products 3a–n

A mixture of a nitrovinyl arene (0.60 mmol), active methylene compound (0.64 mmol), $LiClO_4$ (0.036 mmol), and Et_3N (0.007 mmol) in 1 mL of toluene was stirred at room temperature for 1 h (TLC monitoring). After completion of the reaction the solvent was removed under reduced pressure and the residue was purified by column chromatography using silica gel (EtOAc/hexane as eluent).

Dimethyl 2-(2-nitro-1-(1*H*-pyrrol-2-yl)ethyl)malonate (3a): Brown oil; Yield: 71%; R_f = 0.25 (EtOAc/hexane, 1:3); IR (ATR)(υ max/cm^{-1}): 3404, 2959, 1728, 1551, 1435, 1256, 1160, 933, 800, 726 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3/CCl_4$) δ = 3.69 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.86 (d, J = 5.5 Hz, 1H,

Table 2. Intramolecular cyclization reaction of Michael adducts **3a**–**d**, **l**–**n**.



3a-d,l-n **4a-g**

Entry	Michael adduct	Ar	R_1	R_2	$\gamma-$Lactam	% Yield[a]
1	**3a**	pyrrol-2-yl	CH_3	$COOCH_3$	**4a**	50
2	**3b**	2-thienyl	CH_3	$COOCH_3$	**4b**	99
3	**3c**	2-furyl	CH_3	$COOCH_3$	**4c**	99
4	**3d**	indol-3-yl	CH_3	$COOCH_3$	**4d**	69
5	**3l**	pyrrol-2-yl	CH_3	$PO(OCH_3)_2$	**4e**	61
6	**3m**	2-thienyl	CH_3	$PO(OCH_3)_2$	**4f**	65[b]
7	**3n**	2-furyl	CH_3	$PO(OCH_3)_2$	**4g**	60[b]

Reaction conditions: Michael adduct (0.100 mmol), $NiCl_2.6H_2O$ (0.100 mmol), $NaBH_4$ (1.200 mmol). [a] Isolated yields. [b] Previously reported literature.[19]

$CHCO_2CH_3$), 4.28–4.33 (m, 1H, $CHCH_2NO_2$), 4.81 (dd, J = 13.4, 7.1 Hz, 1H, $CHHNO_2$), 4.90 (dd, J = 13.4, 7.4 Hz, 1H, $CHHNO_2$), 5.95 (bs, 1H, $H_{pyrrole}$), 6.06 (bs, 1H, $H_{pyrrole}$), 6.70 (bs, 1H, $H_{pyrrole}$), 9.00 (bs, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3/CCl_4$) δ = 36.4, 52.9, 53.0, 53.7, 76.6, 107.2, 108.5, 118.7, 125.3, 168.1, 168.5; HRMS (ESI): m/z calcd. for $C_{11}H_{15}N_2O_6$ $[M+H]^+$: 271.0930; found: 271.0941.

Dimethyl 2-(2-nitro-1-(thiophen-2-yl)ethyl)malonate (3b): Yellow oil; Yield: 80%. R_f = 0.30 (EtOAc/hexane, 1:3); the spectral data are in agreement with the previously reported literature.[23]

Dimethyl 2-(1-(furan-2-yl)-2-nitroethyl)malonate (3c): Yellow oil; Yield: 65%. R_f = 0.31 (EtOAc/hexane, 1:3); the spectral data are in agreement with the previously reported literature.[23]

Dimethyl 2-(1-(1*H*-indol-3-yl)-2-nitroethyl)malonate (3d): Yellow oil; Yield: 76%. R_f = 0.15 (EtOAc/hexane, 1:3); the spectral data are in agreement with the previously reported literature.[24]

Ethyl 2-acetyl-4-nitro-3-(1*H*-pyrrol-2-yl)butanoate (3e): Yellow oil; Yield: 90%; dr: 58:42; R_f = 0.34 (EtOAc/hexane, 1:3); IR (ATR)(υ max/cm^{-1}): 3413, 2988, 1714, 1552, 1375, 1180, 1024, 788, 723 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3/CCl_4$) δ = [1.16 (t, J = 7.1 Hz, 3H, OCH_2CH_3)], 1.23 (t, J = 7.1 Hz, 3H, OCH_2CH_3), [2.10 (s, 3H, $COCH_3$)], 2.23 (s, 3H, $COCH_3$), 3.94 (d, J = 6.0 Hz, 1H, $CHCOCH_3$), [3.96 (d, J = 7.5 Hz, 1H, $CHCOCH_3$)], 4.03–4.30 (m, 6H, OCH_2CH_3, $CHCH_2NO_2$)*, 4.68–4.83 (m, 4H, $CHHNO_2$)*, 5.89 (bs, 1H, $H_{pyrrole}$), [5.93 (bs, 1H, $H_{pyrrole}$)], 6.00–6.04 (m, 2H, $H_{pyrrole}$)*, 6.66 (bs, 2H, $H_{pyrrole}$)*, [8.82 (bs, 1H, NH)], 8.92 (bs, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3/CCl_4$) δ = 13.7, [13.8], 29.6, [30.2], 35.5, [36.3], [60.5], 61.1, 61.9, [62.0], 77.4*, 106.7, [106.8], 108.2, [108.5], 118.2, [118.3], 125.6, [125.8], 167.8*, 202.0, [202.2]. HRMS (ESI): m/z calcd. for $C_{12}H_{17}N_2O_5$ $[M+H]^+$: 269.1137; found: 269.1152.

Ethyl 2-acetyl-4-nitro-3-(thiophen-2-yl)butanoate (3f): Brown oil; Yield: 99%; R_f = 0.44 (EtOAc/hexane, 1:3); the spectral data are in agreement with the previously reported literature.[25]

Ethyl 2-acetyl-3-(furan-2-yl)-4-nitrobutanoate (3g): Brown oil; Yield: 99%; R_f = 0.46 (EtOAc/hexane, 1:3); the spectral data are in agreement with the previously reported literature.[18]

Ethyl 2-acetyl-3-(1*H*-indol-3-yl)-4-nitrobutanoate (3h): Brown oil; Yield: 86%; R_f = 0.21 (EtOAc/hexane, 1:3); the spectral data are in agreement with the previously reported literature.[26]

Methyl 2-cyano-4-nitro-3-(1*H*-pyrrol-2-yl)butanoate (3i): Brown oil; Yield: 71%; dr: 60:40; R_f = 0.24 (EtOAc/hexane, 1:3); IR (ATR)(υ max/cm^{-1}): 3389, 2929, 2255, 1755, 1700, 1562, 1385, 1270, 1010, 723 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3/CCl_4$) δ = 3.79 (s, 3H, OCH_3), [3.81 (s, 3H, OCH_3)], [3.98 (d, J = 5.1 Hz, 1H, CHCO$_2$CH$_3$)], 4.06 (d, J = 4.3 Hz, 1H, CHCO$_2$CH$_3$), [4.22–4.27 (m, 1H, CHCH$_2$NO$_2$)], 4.32–4.37 (m, 1H, CHCH$_2$NO$_2$), 4.76–5.00 (m, 4H, CHHNO$_2$)*, 6.12–6.15 (m, 2H, H$_{pyrrole}$)*, 6.17 (bs, 2H, H$_{pyrrole}$)*, 6.73 (bs, 2H, H$_{pyrrole}$)*, 8.38 (bs, 2H, NH)*; ^{13}C NMR (100 MHz, $CDCl_3/CCl_4$) δ = 36.7, [37.2], [40.8], 41.2, 54.0*, 75.5, [75.7], [107.7], 108.2, 109.4*, 114.1, [114.7], 119.2, [119.3], 123.0, [124.1], [164.9], 165.0. HRMS (ESI): m/z calcd. for C$_{10}$H$_{12}$N$_3$O$_4$ [M+H]$^+$: 238.0828; found: 238.0838.

Methyl 2-cyano-4-nitro-3-(thiophen-2-yl)butanoate (3j): Yellow oil; Yield: 50%; dr: 55:45; R_f = 0.38 (EtOAc/hexane, 1:3); IR (ATR)(υ max/cm^{-1}): 2972, 2263, 1746, 1557, 1437, 1377, 1217, 1010, 912, 785 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3/CCl_4$) δ = 3.77 (s, 3H, OCH_3), [3.83 (s, 3H, OCH_3)], [4.01 (d, J = 4.9 Hz, 1H, CHCO$_2$CH$_3$)], 4.14 (d, J = 5.0 Hz, 1H, CHCO$_2$CH$_3$), 4.49–4.58 (m, 2H, CHCH$_2$NO$_2$)*, 4.79–5.04 (m, 4H, CHHNO$_2$)*, 7.00–7.03 (m, 2H, H$_{thiophene}$)*, [7.09 (d, J = 3.4 Hz, 1H, H$_{thiophene}$)], 7.12 (d, J = 3.4 Hz, 1H, H$_{thiophene}$), 7.30 (d, J = 5.1 Hz, 2H, H$_{thiophene}$)*; ^{13}C NMR (100 MHz, $CDCl_3/CCl_4$) δ = 38.5, [38.8], 42.0*, 53.8, [54.0], 76.4*, 113.6, [113.8], [126.3], 126.4, 127.1*, [127.3], 127.6, 134.8, [136.3], 164.0, [164.2]. HRMS (ESI): m/z calcd. for C$_{10}$H$_9$N$_2$O$_4$S [M–H]$^-$: 253.0283; found: 253.0305.

Methyl 2-cyano-3-(furan-2-yl)-4-nitrobutanoate (3k): Yellow oil; Yield: 50%; dr: 55:45; R_f = 0.44 (EtOAc/hexane, 1:3); IR (ATR)(υ max/cm^{-1}): 2960, 2255, 1746, 1558, 1436, 1377, 1337, 1215, 1012, 747 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3/CCl_4$) δ = 3.83 (s, 6H, OCH_3)*, [4.05 (d, J = 5.2 Hz, 1H, CHCO$_2$CH$_3$)], 4.10 (d, J = 5.5 Hz, 1H, CHCO$_2$CH$_3$), 4.34–4.42 (m, 2H, CHCH$_2$NO$_2$)*, 4.80–4.95 (m, 4H, CHHNO$_2$)*, 6.35–6.37 (m, 4H, H$_{furan}$)*, 7.41 (bs, 2H, H$_{furan}$)*; ^{13}C NMR (100 MHz, $CDCl_3/CCl_4$) δ = 37.4*, [39.5], 39.7, 53.9, [54.0], [74.1], 74.3, [109.2], 109.5, 110.9, [111.0], [113.3], 113.5, [143.5], 143.6, 147.0, [147.6], 164.1*. HRMS (ESI): m/z calcd. for C$_{10}$H$_9$N$_2$O$_5$ [M–H]$^-$: 237.0511; found: 237.0533.

Methyl 2-(dimethoxyphosphoryl)-4-nitro-3-(1*H*-pyrrol-2-yl)butanoate (3l): Pale yellow oil; Yield: 16%; dr: 55:45; R$_f$ = 0.52 (EtOAc); IR (ATR)(υ max/cm^{-1}): 1747, 1554, 1432, 1239, 1030, 912, 786, 750, 731, 648 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3/CCl_4$) δ = 3.61–3.81 (m, 20H, CO$_2$CH_3, CHCO$_2$CH$_3$, PO(OCH_3)$_2$)*, 4.21–4.34 (m, 2H, CHCH$_2$NO$_2$)*, [4.78 (dd, J = 28.9, 7.3 Hz, 1H, CHHNO$_2$)], 4.81 (dd, J = 29.9, 7.3 Hz, 1H, CHHNO$_2$), 4.97 (dd, J = 23.4, 7.5 Hz, 1H, CHHNO$_2$), [5.00 (dd, J = 24.0, 7.5 Hz, 1H, CHHNO$_2$)], 5.99 (bs, 2H, H$_{pyrrole}$)*, 6.02–6.05 (m, 2H, H$_{pyrrole}$)*, 6.70 (bs, 2H, H$_{pyrrole}$)*, [9.42 (bs, 1H, NH$_{pyrrole}$)], 9.58 (bs, 1H, NH$_{pyrrole}$); ^{13}C NMR (100 MHz, $CDCl_3/CCl_4$) δ = 35.4, 35.6, 46.6 (d, J = 133.7 Hz, CHCO$_2$CH$_3$), [47.4 (d, J = 134.6 Hz, CHCO$_2$CH$_3$)], 52.8*, 52.9, 53.3 (d, J = 6.5 Hz), 53.9 (d, J = 6.6 Hz), [54.0 (d, J = 6.9 Hz)], 76.8, 77.1, [107.7], 108.4, [118.5], 118.7, 125.6, [125.9], 128.6, [129.0], 168.0 (d, J = 4.2 Hz, C =O), [168.5 (d, J = 3.9 Hz, C =O)]; ^{31}P NMR (162 MHz, $CDCl_3/CCl_4$): δ = [23.1], 23.2; HRMS (ESI): m/z calcd. for C$_{11}$H$_{16}$N$_2$O$_7$P [M–H]$^-$: 319.0701; found: 319.0715.

Methyl 2-(dimethoxyphosphoryl)-4-nitro-3-(thiophen-2-yl)butanoate (3m): Pale yellow oil; Yield: 25%; R_f = 0.49 (EtOAc); the spectral data are in agreement with the previously reported literature.[19]

Methyl 2-(dimethoxyphosphoryl)-3-(furan-2-yl)-4-nitrobutanoate (3n): Pale yellow oil; Yield: 22%; R_f = 0.46 (EtOAc); the spectral data are in agreement with the previously reported literature.[19]

3.3. General procedure for the synthesis of γ-lactams 4a–g

A mixture of Michael adduct (0.100 mmol) and $NiCl_2.6H_2O$ (0.100 mmol) in 1 mL of methanol was stirred at 0 °C under argon atmosphere for 30 min. Next, $NaBH_4$ (1.200 mmol) was added at 0 °C and the mixture stirred for a further 3 h at rt. The reaction was terminated by adding saturated NH_4Cl (5 mL) and extracted with chloroform (3 × 10 mL). The extract was dried over $MgSO_4$, the solvent was removed under reduced pressure, and the residue was purified by column chromatography using silica gel (EtOAc/hexane as eluent).

Methyl 2-oxo-4-(1*H*-pyrrol-2-yl)pyrrolidine-3-carboxylate (4a): Brown crystal; Yield: 50%; mp: 135–136 °C; R_f = 0.69 (EtOAc/hexane, 1:3); IR (ATR)(υ max/cm^{-1}): 3323, 3263, 1739, 1684, 1428, 1333, 1278, 1203, 1164, 1038, 999, 743, 656 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3/CCl_4$) δ = 3.39 (d, J = 10.6 Hz, 1H, C*H*CO$_2$CH$_3$), 3.52–3.57 (m, 1H, C*H*HNH), 3.71–3.76 (m, 1H, C*H*HNH), 3.84 (s, 3H, OC*H*$_3$), 4.09–4.11 (m, 1H, C*H*CH$_2$NH), 5.96 (s, 1H, H$_{pyrrole}$), 6.09 (s, 2H, H$_{pyrrole}$, NH$_{lactam}$), 6.68 (s, 1H, H$_{pyrrole}$), 8.40 (bs, 1H, NH$_{pyrrole}$); ^{13}C NMR (100 MHz, $CDCl_3/CCl_4$) δ = 37.4, 44.9, 53.0, 54.6, 104.8, 108.8, 117.8, 129.6, 170.0, 171.2. HRMS (ESI): m/z calcd. for $C_{10}H_{13}N_2O_3$ $[M+H]^+$: 209.0926; found: 209.0934.

Methyl 2-oxo-4-(thiophen-2-yl)pyrrolidine-3-carboxylate (4b): Pale yellow crystal; Yield: 99%; mp: 106–107 °C; R_f = 0.63 (EtOAc/hexane, 1:3); IR (ATR)(υ max/cm^{-1}): 2929, 1708, 1349, 1227, 1156, 1097, 695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3/CCl_4$) δ = 3.45–3.52 (m, 2H, C*H*CO$_2$CH$_3$, C*H*HNH), 3.78–3.86 (m, 4H, OC*H*$_3$, C*H*HNH), 4.34–4.41 (m, 1H, C*H*CH$_2$NH), 6.91–6.95 (m, 2H, H$_{thiophene}$), 7.02 (bs, 1H, NH), 7.19 (d, J = 5.0 Hz, 1H, H$_{thiophene}$); ^{13}C NMR (100 MHz, $CDCl_3/CCl_4$) δ = 40.0, 48.1, 52.9, 56.1, 124.5, 124.8, 127.2, 142.7, 168.9, 171.8. HRMS (ESI): m/z calcd. for $C_{10}H_{12}NO_3S$ $[M+H]^+$: 226.0538; found: 226.0549.

Methyl 4-(furan-2-yl)-2-oxopyrrolidine-3-carboxylate (4c): Pale yellow crystal; Yield: 99%; mp: 85–86 °C; R_f = 0.63 (EtOAc/hexane, 1:3); IR (ATR)(υ max/cm^{-1}): 3275, 2968, 1712, 1432, 1349, 1215, 1160, 1006, 676 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3/CCl_4$) δ = 3.48–3.52 (m, 1H, C*H*HNH), 3.59 (d, J = 9.4 Hz, 1H, C*H*CO$_2$CH$_3$), 3.71–3.77 (m, 1H, C*H*HNH), 3.81 (s, 3H, OC*H*$_3$), 4.15–4.21 (m, 1H, C*H*CH$_2$NH), 6.14 (d, J = 3.2 Hz, 1H, H$_{furan}$), 6.28–6.29 (m, 1H, H$_{furan}$), 6.95 (bs, 1H, NH), 7.34 (s, 1H, H$_{furan}$); ^{13}C NMR (100 MHz, $CDCl_3/CCl_4$) δ = 37.9, 45.1, 52.7, 52.9, 106.5, 110.5, 142.3, 152.5, 169.0, 171.9. HRMS (ESI): m/z calcd. for $C_{10}H_{12}NO_4$ $[M+H]^+$: 210.0766; found: 210.0768.

Methyl 4-(1*H*-indol-3-yl)-2-oxopyrrolidine-3-carboxylate (4d): Pale yellow oil; Yield: 69%; R_f = 0.33 (EtOAc); IR (ATR)(υ max/cm^{-1}): 3393, 2955, 1698, 1434, 1351, 1161, 1006, 751, 673 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3/CCl_4$) δ = 3.53–3.58 (m, 1H, C*H*HNH), 3.71–3.77 (m, 4H, C*H*CO$_2$CH$_3$; OC*H*$_3$), 3.83–3.87 (m, 1H, C*H*HNH), 4.36–4.42 (m, 1H, C*H*CH$_2$NH), 7.04–7.09 (m, 2H, H$_{indole}$; NH), 7.11–7.15 (m, 1H, H$_{indole}$), 7.19–7.24 (m, 1H, H$_{indole}$), 7.39 (d, 1H, J = 7.8 Hz, H$_{indole}$), 7.56 (d, 1H, J = 8.1 Hz, H$_{indole}$), 8.37 (bs, 1H, NH$_{indole}$); ^{13}C NMR (100 MHz, $CDCl_3/CCl_4$) δ = 36.8, 46.9, 52.9, 54.2, 111.6, 114.7, 118.9, 119.9, 121.3, 122.7, 125.9, 136.7, 170.0, 172.6. HRMS (ESI): m/z calcd. for $C_{14}H_{14}N_2NaO_3$ $[M+Na]^+$: 281.0902; found: 281.0878.

Dimethyl (2-oxo-4-(1*H*-pyrrol-2-yl)pyrrolidin-3-yl)phosphonate (4e): Pale yellow oil; Yield: 61%; R_f = 0.59 (MeOH/EtOAc/hexane, 1:1:1); IR (KBr)(υ max/cm^{-1}): 3433, 2924, 1694, 1451, 1237, 1033,

803, 727 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ = 3.12–3.19 (m, 2H, C*H*PO$(OCH_3)_2$, C*H*HNH), 3.48 (d, J = 10.9 Hz, 3H, PO(OCH_3)), 3.53–3.58 (m, 1H, C*H*HNH), 3.64 (d, J = 10.9 Hz, 3H, PO(OCH_3)), 3.71–3.82 (m, 1H, C*H*CHPO$(OCH_3)_2$), 5.92 (bs, 2H, $H_{pyrrole}$), 6.65 (bs, 1H, $H_{pyrrole}$), 7.98 (bs, 1H, NH_{lactam}), 10.74 (bs, 1H, $NH_{pyrrole}$); ^{13}C NMR (100 MHz, DMSO) δ = 35.6, 46.2 (d, J = 141.5 Hz, O=P–*C*H), 48.1 (d, J = 9.2 Hz, O=PCH–*C*H), 52.8 (d, J = 6.6 Hz, O*C*H_3), 53.5 (d, J = 6.2 Hz, O*C*H_3), 105.3, 107.7, 117.7, 131.7 (d, J = 7.0 Hz, $C(2)_{pyrrole}$), 171.1 (d, J = 2.8 Hz, *C* =O); ^{31}P NMR (162 MHz, $CDCl_3/CCl_4$) δ = 26.8; HRMS (ESI): m/z calcd. for $C_{10}H_{16}N_2O_4P$ $[M+H]^+$: 259.0848; found: 259.0874.

Dimethyl (2-oxo-4-(thiophen-2-yl)pyrrolidin-3-yl)phosphonate (4f): Pale yellow oil; Yield: 65%; R_f = 0.68 (MeOH/EtOAc/hexane, 1:1:1); the spectral data are in agreement with the previously reported literature.[19]

Dimethyl (4-(furan-2-yl)-2-oxopyrrolidin-3-yl)phosphonate (4g): Pale yellow oil; Yield: 60%; R_f = 0.66 (MeOH/EtOAc/hexane, 1:1:1); the spectral data are in agreement with the previously reported literature.[19]

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