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Synthesis and Selective *N*,*O*-Functionalization of Pyrazolone-Fused 3-Aminoazepinones

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A new class of pyrazolone-fused 3-amino-1,3,4,7-tetrahydro-2*H*-azepin-2-ones was synthesized from azepane-based α,β-unsaturated esters. The latter compounds were obtained efficiently from 2-Cbz-amino-*N*-(2-bromoallyl)-4-pentenamide derivatives through initial Pd-catalyzed methoxycarbonylation followed by ring-closing metathesis. These new 3-aminotetrahydroazepinone esters were condensed with hydrazine and oxidized under mild conditions using $CuCl_2$. The resulting bicyclic pyrazolones were transformed into valuable building blocks for medicinal chemistry through *O*-triflation and through selective *N*-1- and *O*-alkylation of the pyrazolone core using (bis)electrophiles.

Introduction

3-Aminobenzazepinones of type **1** have been synthesized and successfully used as constrained phenylalanine derivatives for incorporation in bioactive peptidomimetic compounds. Related heterocyclic fused 3-aminoazepinone derivatives are not widespread (Figure 1).[1] Indole-fused analogues **2** are, for example, available through intramolecular cyclizations of tryptophan derivatives.[2] The lack of other types of heterocycles fused at the azepane core structure impedes a broader evaluation of these promising bicyclic compounds as building blocks for medicinal chemistry. Nonheterocyclic fused azepinones are generally synthesized through lactamizations or Pictet–Spengler reactions with electron-rich aromatics. Therefore, synthetic methods that enable the introduction of heterocycles at the azepane core through alternative pathways are of importance.

In this respect, we envisaged that new azepane esters **4** could serve as valuable precursors for new types of bicyclic compounds **3**, given the various transformations of α,β-unsaturated carbonyl compounds towards heterocycles.[3] The majority of 4,5-disubstituted pyrazolones are synthesized by reaction of hydrazines with β-keto esters or α,β-unsaturated esters. Several pyrazolones are known for their antipyretic and analgesic effects.[4] More recently, this heterocyclic motif has been successfully incorporated in molecules that are potent against diabetes and as selective GABA subtype receptor antagonists.[5] The presence of multiple, spatially separated sites that allow further orthogonal derivatization means that pyrazolone-fused azepinones **3** possess significant potential as novel building blocks.

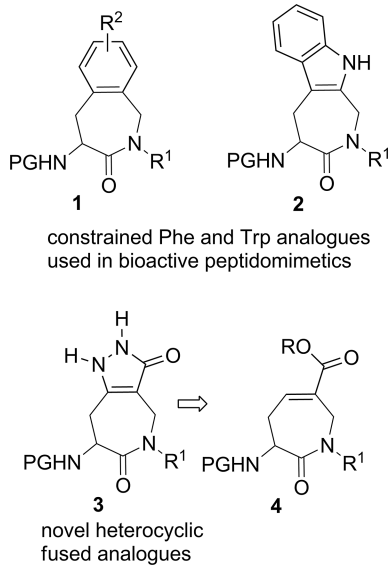

Figure 1. (Hetero)aromatic fused 3-amino-1,3,4,7-tetrahydro-2*H*-benzazepin-2-ones.

Results and Discussion

To obtain the proposed azepane esters **4** as starting points for the construction of bicyclic compounds **3**, a ring-closing metathesis (RCM) approach was evaluated. This was designed in analogy with our recently reported synthesis of polyheterocyclic 3-aminoazepinones via chlorinated azepinones.[6,7] At first, a Claisen rearrangement of *O*-allyl-*N*-Cbz-glycinate was used to prepare *N*-protected racemic

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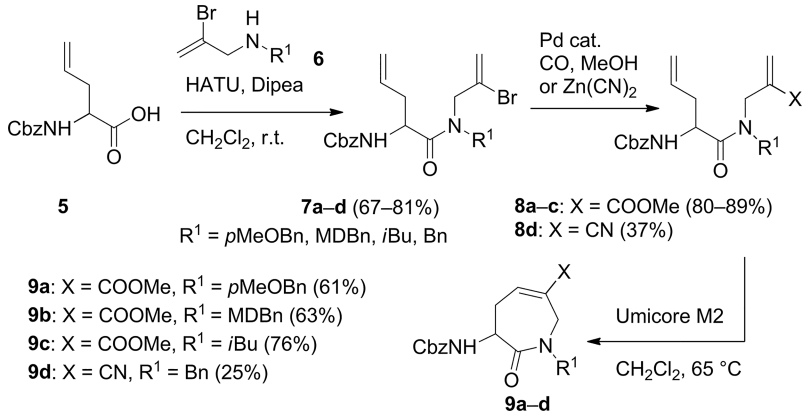
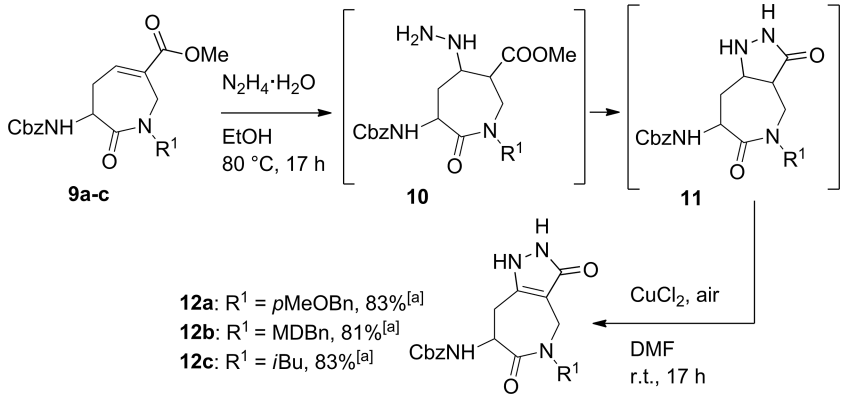


Scheme 1. Synthesis of 3-amino-1,3,4,7-tetrahydro-2*H*-azepin-2-ones **9a**–**d**.



Scheme 2. Condensation of α,β-unsaturated esters **9** with hydrazine towards new 3-aminoazepinone scaffolds **12**. [a] Conversions based on HPLC analysis.

allylglycine **5**,[8] which was transformed into the corresponding amides **7** (Scheme 1). Reported procedures using 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide (EDC) as coupling agent gave very low conversions in our hands,[9] but the use of 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate (HATU) gave access to amides **7a**–**d** in good yields. Unfortunately, these *N*-(2-bromoallyl)-4-pentenamides proved to be very poor substrates in RCM reactions, giving either no cyclization at all or giving very low yields even under high catalyst loading.[10] Therefore, it was decided to first transform the bromoallyl moiety of amides **7** prior to RCM. Methoxycarbonylation of **7a**–**c** by using $Pd(dppf)Cl_2$ (dppf = 1,1′-bis(diphenylphosphino)ferrocene) under CO atmosphere in MeOH/THF resulted in formation of the corresponding esters **8a**–**c** in excellent yields after one hour reaction at 75 °C. Analogous cyanation experiments using **7d**, $Zn(CN)_2$, and catalytic amounts of $Pd(PPh_3)_4$ resulted in **8d**, albeit in low isolated yields (37%). To cyclize the prepared dienes towards the envisaged 3-aminoazepinones **9**, the Umicore M2 ruthenium catalyst was used, which performed as well as Grubbs' II catalyst in these reactions. Cyano-substituted substrate **8d** only yielded 25% of the corresponding lactam **9d**, but the related esters **8a**–**c** nicely resulted in new seven-membered cyclic α,β-unsaturated esters **9a**–**c** in good yield (Scheme 2). Related azepinone-based α,β-unsaturated esters have, to our knowledge, only been prepared without a 3-amino substituent, through [3 + 4] cycloaddition, intramolecular cyclocarbonylation, or by ring opening of a nitrone followed by intramolecular cyclization.[11–13] Having in hand this new set of building blocks, the synthesis of new heterocyclic fused 3-aminoazepinones using bisnucleophiles was attempted.

Reactions of the obtained α,β-unsaturated esters **9a**–**c** with hydrazine monohydrate in EtOH at 80 °C furnished pyrazolidinones **11a**–**c** with high conversion according to HPLC/LCMS analysis. Slow oxidation was also observed, and minor amounts (< 10%) of the corresponding pyrazolones **12a**–**c** were found in the reaction mixture. Encouraged by these results, a one-pot protocol towards **12a**–**c** was evaluated. Several reaction conditions and oxidants were tested to force the oxidation to completion. The use of palladium on carbon either with or without prior isolation of the pyrazolidinone **11** from the reaction mixture only partially enhanced the oxidation. The use of MnO_2 and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) resulted in decomposition of the starting material, whereas treatment of **11** with $CuCl_2$ in *N*,*N*-dimethylformamide (DMF) in a reaction vessel open to air, completed the oxidation reaction after 17 h at room temperature.[14]

An attempt was made to investigate whether pyrazolidinone formation occurred through initial addition of hydrazine to the double bond or through initial transformation of the ester function. To this end, a mixture of the α,β-unsatu-

rated ester **9a** and hydrazine hydrate was stirred in CH_3CN at room temperature. The change in solvent was required for solubility reasons. This converted the starting material cleanly into the Michael adduct in a few hours, as confirmed by LCMS and ^1H NMR analyses (see the Supporting Information). Evaporation of the liquids, dissolving the crude material in EtOH followed by heating to 80 °C, resulted in the formation of a mixture of the original Michael acceptor **9a**, Michael adduct **10a**, and pyrazolidinone **11a**. This result, combined with the low temperature required for the condensation reaction, indeed suggests a reversible Michael addition and a subsequent ring formation through a 5-*exo*-*trig* cyclization, which is consistent with previous reports.[15]

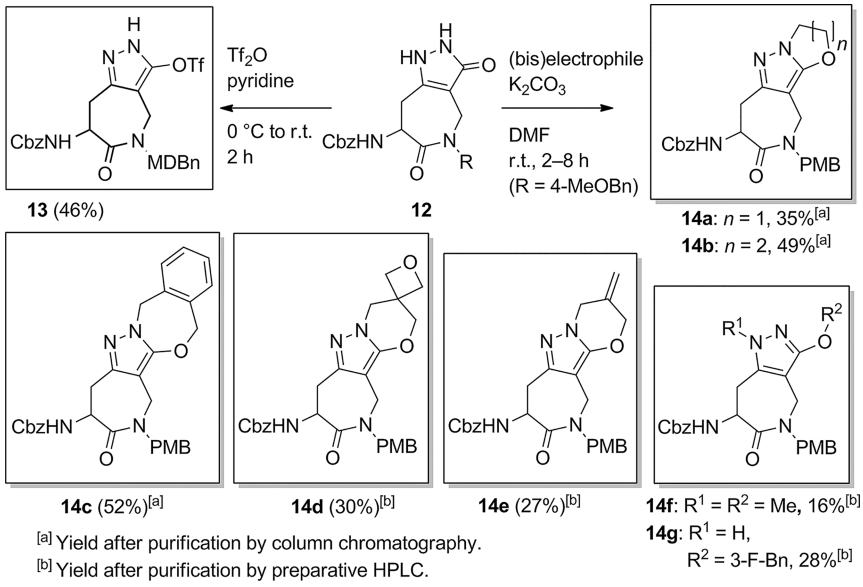
Although several examples of condensation reactions of substituted hydrazines with α,β-unsaturated esters have been reported,[16] this was unsuccessful when performed on substrate **9a**. The use of benzyl or methyl hydrazine either with or without a base, gave mainly starting material with minor amounts of the Michael adduct (ca. 5% based on HPLC analysis). Even conducting reaction in a microwave at 225 °C for 60 min only gave starting material and side products. The use of other bisnucleophiles such as amidines, guanidines, or hydroxylamine did not result in clean formation of the corresponding imidazolidines or oxazolidines.

It should be noted that pyrazolones **12a**–**c** are relatively insoluble in standard organic solvents such as CH_2Cl_2, EtOAc, alcohols, and ethers. For the envisaged further pyrazolone transformations, crude reaction mixtures of **12** were used. Analytical samples were purified by preparative HPLC prior to characterization.

To investigate the reactivity of substrates **12**, acylation reactions of the pyrazolone moiety were attempted. Reactions with several different acyl chlorides did not give rise to acylated pyrazolones and, instead, resulted in complex reaction mixtures. The use of one equivalent of Ac_2O resulted in a mixture of starting material and double acylation products, according to HPLC/LCMS analysis. When an excess of Ac_2O was used even triple acylation took place. To evaluate a selective deacylation of these overacylated compounds towards isolable monoacylated **12a**, the obtained mixture was treated with nucleophiles. A full deacylation towards starting material **12a** was observed when hydroxide or benzylamine was used at room temperature. In all, selective deacylation proved impossible and the isolated trace amounts of acylated compounds even slowly converted into starting materials **12** upon standing. To transform pyrazolones **12** into building blocks that were equipped with multidirectional diversification points, pyrazolone **12b** was treated with Tf_2O and pyridine at 0 °C. This provided valuable new building blocks **13** for further Pd-catalyzed functionalizations. Treatment of pyrazolones **12** with $POCl_3$ towards analogous building blocks unfortunately did not result in the corresponding chlorinated pyrazolones.

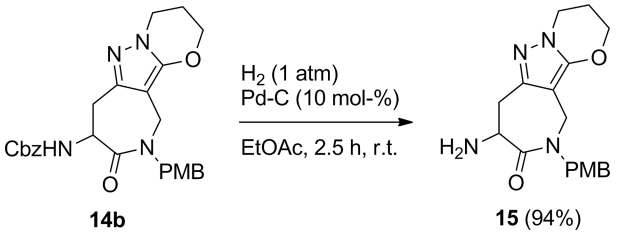
Next, the selectivity of *N*- vs. *O*-alkylation was evaluated. This selectivity in pyrazolone alkylation is known to be dependent on the substrate, alkylating reagent, and reaction conditions.[17,18] For instance, double deprotonation of pyrazolones using 2 equiv. of strong base followed by treatment with 1 equiv. of alkyl halides can give selective *N*-1-alkylated pyrazolones. Analogous reactions using K_2CO_3 in CH_3CN give rise to mixtures of mono- and different dialkylated products.[19] To regioselectively alkylate a pyrazolone at oxygen, Boc-protection of the most reactive N-1 nitrogen is often required.[20]

To verify the reactivity of bicyclic pyrazolones **12** in alkylation reactions, **12a** was treated with 3-fluorobenzylbromide. After reaction in DMF for 2 h at room temperature, 50% yield of monofluorobenzylated pyrazolone **14g** was formed and could be separated from the double benzylated pyrazolone (20%) by preparative HPLC in 28% isolated yield (Scheme 3). In contrast, the alkylation reaction using MeI gave rise to a mixture of mono- and double-methylated



Scheme 3. Synthesis of (poly)heterocyclic fused 3-aminoazepinones **14a**–**g**.

compounds (mono/double ratio 1:19; LCMS). Only the major double alkylated pyrazolone **14f** could be isolated in high purity. NMR (^{1}H, ^{13}C, HSQC and HMBC) data of the obtained alkylated pyrazolones were compared with reported data to determine whether *O*-, *N*-1- or *N*-2-alkylation took place. Reference data were chosen from reports in which related pyrazolones were synthesized unambiguously through intramolecular cyclizations, condensation of β-keto esters with substituted hydrazines, or cycloaddition of dienes to 3*H*-pyrazol-3-ones (i.e., different from *N*- or *O*-alkylations of the pyrazolone). This suggested the formation of **14f** and **14g**.[21] Given that both alkylation reactions did not seem promising in terms of isolated yield, the use of biselectrophiles was evaluated to establish selective and preparatively useful pyrazolone derivatizations. Most reported data show that when pyrazolones are treated with 1,2-dibromoethane or 1,3-dibromopropane, alkylation proceeds at the O and at N-1, forming oxazolines or the corresponding six-membered rings, respectively.[16,22] However, reactions of pyrazolones with biselectrophiles giving *N*-1/*N*-2-alkylation[23] or regioisomeric mixtures of alkylation products are also reported.[24] Related benzo-fused pyrazolones such as 1,2-dihydro-3*H*-indazol-3-ones, react with 1-bromo-3-chloropropane to give mainly the *N*-1/*N*-2-alkylated product.[25] In our hands, the reaction of biselectrophiles with pyrazolones **12a** resulted in selective *N*-1 and *O*-alkylation towards oxazolidine (**14a**), oxazane (**14b**), and benzoxazepane (**14c**) fused heterocycles. No *N*-2,*N*-1-alkylation was observed, as was demonstrated by NMR analysis and comparison with reported data. The scope of the reaction was further elaborated by making use of dichloroisobutene and 3,3-bis(bromoethyl)oxetane, resulting in the corresponding new polyheterocycles **14e** and **14d**. To verify the possibility of deprotecting the N-atoms of the obtained compounds orthogonally, **14b** was treated with hydrogen gas under Pd-C catalysis. This resulted in clean formation of **15** in 94% yield (Scheme 4). Subsequent acylation reactions of the free amino group of **15** using HATU as coupling agent gave good conversions towards the corresponding acylated compounds, as evidenced by HPLC and HRMS analyses. Unfortunately, because of troublesome purification by silica gel chromatography, the latter derivatives could not be isolated and fully characterized (see the Supporting Information for details).



14b **15** (94%)

Scheme 4. Deprotection of *N*-Cbz-3-aminoazepinone **14b**.

Conclusions

It can be stated that an efficient CO-insertion and RCM approach resulted in the formation of new 3-aminotetrahydroazepinonecarboxylates. These substrates proved to be suitable for condensation reactions with hydrazine towards the corresponding tetrahydroazepinone-fused pyrazolones. These compounds can be regarded as a new class of heterocyclic analogues of related benzazepinones, which have been successfully used in bioactive peptidomimetics. The regioselective reaction of the obtained pyrazolones with (bis)electrophiles resulted in a range of new substituted polyheterocycles with potential use as building blocks in medicinal chemistry.

Experimental Section

6-{[(Benzyloxy)carbonyl]amino}-1-methyl-7-oxo-2,5,6,7-tetrahydro-1*H*-azepine-3-carboxylates 9a–d; Typical RCM Procedure for 9c: Diene **8c** (1.0 equiv., 2.23 mmol) was dissolved in freshly distilled and degassed CH_2Cl_2 to a final concentration of 0.01 M. The Ruthenium Umicore M2 catalyst {[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene] dichloro(3-phenyl-1*H*-inden-1-ylidene)(tricyclohexylphosphine)ruthenium(II), 0.1 equiv., 0.22 mmol} was added and degassing was continued for 5 min. The mixture was then heated to reflux (65 °C) and stirred for 16 h under a N_2 atmosphere. The solvent was removed under reduced pressure, and the residue was purified by silica column chromatography (EtOAc/petroleum ether, 3:1→2.5:1) to give **9c** (0.471 g, 63%) as brown crystals; m.p. 94.7–97.5 °C. IR (ATR): $\tilde{\nu}$ = 3251, 2953, 2924, 1705, 1645, 1526, 1437, 1252 and 1044 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.84 (d, J = 6.3 Hz, 3 H), 0.87 (d, J = 6.3 Hz, 3 H), 1.80–1.88 (m, 1 H), 2.34–2.41 (m, 1 H), 2.95–3.02 (m, 1 H), 3.14 (dd, J = 13.7, 3.6 Hz, 1 H), 3.41 (dd, J = 13.7, 3.6 Hz, 1 H), 3.77 (s, 3 H), 4.14 (d, J = 17.6 Hz, 1 H), 4.39 (dd, J = 17.6, 2.6 Hz, 1 H), 4.98–5.03 (m, 1 H), 5.9 (d, J = 12.3 Hz, 1 H), 5.11 (d, J = 12.3 Hz, 1 H), 6.18 (br. d, J = 6.0 Hz, 1 H), 7.04 (br. t, J = 4.9 Hz, 1 H), 7.29–7.35 (m, 5 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 19.9, 20.1, 27.4, 33.7, 44.7, 49.5, 52.4, 56.0, 66.8, 128.0, 128.1 (2×), 128.5 (2×), 129.1, 136.4, 141.5, 155.5, 166.2, 171.2 ppm. HRMS: *m*/*z* calcd. for [$C_{20}H_{26}N_2O_5$ + H$^+$] 375.1914; found 375.1925; calcd. for [$C_{20}H_{26}N_2O_5$ + Na$^+$] 397.1734; found 397.1756.

Synthesis of Pyrazolones 12a–c. Typical Procedure for 12b: α,β-Unsaturated ester **9b** (1.0 equiv., 1.19 mmol) was suspended in degassed EtOH, and hydrazine monohydrate (2.4 equiv., 2.91 mmol, 65 wt.-% in water) was added. The reaction mixture was stirred for 15 h at 80 °C under a N_2 atmosphere. The resulting solution was left to cool to room temperature, after which the solvent was removed under reduced pressure. The residue was dissolved in DMF and $CuCl_2 \cdot 2H_2O$ (0.2 equiv., 0.24 mmol) was added. The reaction mixture was stirred open to the atmosphere for 8 h, after which the DMF was removed under reduced pressure to give a green residue. The limited solubility of these pyrazolones meant that the obtained crude residue was used in the next step for further derivatization with (bis)electrophiles without purification. An analytical sample was purified by preparative HPLC to afford **12b** as a white powder; m.p. 203.5–205.4 °C (decomp.). IR (ATR): $\tilde{\nu}$ = 3246, 2924, 2356, 2341, 1716, 1634, 1522, 1493, 1445, 1248, 1197, 1127, 1024 cm^{-1}. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 2.67 (app. t, J = 15.5 Hz, 1 H), 2.90 (dd, J = 8.3, 4.5 Hz, 1 H), 3.87 (d, J = 16.8 Hz, 1 H), 4.18 (d, J = 15.3 Hz, 1 H), 4.46 (d, J = 16.8 Hz, 1 H), 4.72 (d, J = 15.3 Hz, 1 H), 4.79–4.84 (m, 1 H), 5.06 (s, 2 H), 5.96 (s, 2 H), 6.69–6.73 (m, 2 H), 6.81–6.82 (m, 1 H), 7.30–7.38 (m, 5 H), 7.54 (d, J = 7.0 Hz, 1 H), 8.42 (br. s, 1 H) ppm. ^{13}C NMR (126 MHz, [D$_6$]-DMSO): δ = 27.9, 40.4, 50.6, 51.1, 66.0, 98.5, 101.3, 108.3, 108.6,

121.2, 128.0, 128.3 (2×), 128.8 (2×), 131.8, 137.5, 146.8, 147.8 (2×), 156.1, 160.4, 172.1 ppm. HRMS: *m*/*z* calcd. for [$C_{23}H_{22}N_4O_6$ + H^+] 451.1612; found 451.1619.

Synthesis of Pyrazolones 14a–e. Typical Procedure for 14a: Pyrazolone **12a** (1.0 equiv., 0.229 mmol) was added to a suspension of K_2CO_3 (3.5 equiv., 0.802 mmol) in DMF (2.3 mL), and 1-bromo-2-chloroethane (1.2 equiv., 0.275 mmol) was added. The mixture was heated at 80 °C for 3 h, then the solvent was removed under reduced pressure. The residue was taken up in CH_2Cl_2 (10 mL) and this solution was washed with H_2O (3 × 5 mL) and brine (3 × 5 mL). The organic phase was dried with $MgSO_4$ and the solvents were evaporated. The resulting residue was purified by silica gel column chromatography (2% MeOH in petroleum ether/EtOAc, 1:2) to afford **14a** (22 mg, 35%) as an off-white oil. IR (ATR): $\tilde{\nu}$ = 3312, 2915, 2846, 1686, 1632, 1608, 1507, 1443, 1246, 1210 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 2.79 (dd, *J* = 16.3, 6.9 Hz, 1 H), 3.31 (dd, *J* = 16.3, 1.9 Hz, 1 H), 3.78 (s, 3 H), 3.82 (d, *J* = 10.6 Hz, 1 H), 4.42 (d, *J* = 10.63 Hz, 1 H), 4.16 (dt, *J* = 7.5, 2.5 Hz, 2 H), 4.35 (d, *J* = 15.0 Hz, 1 H), 4.80 (d, *J* = 15.0 Hz, 1 H), 4.92 (dt, *J* = 7.5, 5.0 Hz, 2 H), 4.99–5.09 (m, 1 H), 5.14 (s, 2 H), 6.20 (d, *J* = 7.5 Hz, 1 H), 6.81 (d, *J* = 10.0 Hz, 2 H), 7.12 (d, *J* = 10.0 Hz, 2 H), 7.32–7.38 (m, 5 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 32.5, 39.7, 45.4, 50.1, 50.6, 55.3, 66.8, 75.2, 89.1, 114.0 (2×), 128.0, 128.1, 128.5 (2×), 128.6, 129.1, 129.5 (2×), 136.5, 152.5, 155.0, 155.5, 159.1, 171.8 ppm. HRMS: *m*/*z* calcd. for [$C_{25}H_{26}N_4O_5$ + H^+] 463.1976; found 463.1965.

Acknowledgments

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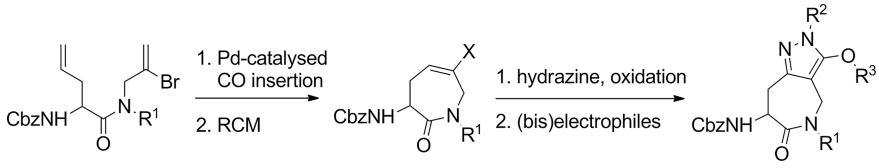
Heterocyclic Fused-Ring Systems



The synthesis of new pyrazolone-fused 3-amino-1,3,4,7-tetrahydro-2*H*-azepin-2-ones starting from azepane-based α,β-unsaturated esters is described. Initial methoxycarbonylation of 2-Cbz-amino-*N*-(2-bromoallyl)-4-pentenamides was followed by ring-closing metathesis and condensation with hydrazine. The pyrazolones were alkylated regioselectively, yielding polyheterocyclic fused 3-aminoazepinones.

Keywords: Fused-ring systems / Nitrogen heterocycles / Regioselectivity / Alkylation / Metathesis

