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A convenient synthesis of heterocyclic compounds containing 11-oxo-6,11,12,13-tetrahydrodibenzo[*b*,*g*][1,5]oxazonine fragment

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A convenient synthesis of rare diaryl-fused nine-membered heterocyclic scaffold using a novel modification of four-component Ugi condensation based on the usage of aromatic aldehyde-acid as bifunctional component is described.

Among a variety of physiologically active aryl- and heteroaryl-fused six- and seven-membered heterocyclic systems, including morpholines and oxazepines, nine-membered diaryl-fused heterocycles form a relatively little-explored group with a pronounced pharmaceutical importance. In many cases, their structures strongly resemble the specific composition of low-membered analogues according to the fundamental bioisosteric rules. Therefore, the biological activity of such compounds should be described jointly to illustrate key structural and topological features.

Differently substituted 5(3)-oxo-1,4-oxazepines were described as effective protease inhibitors,[1] non-peptidergic GPCR inhibitors,[2] integrin antagonists,[3] squalene synthase[4] and reverse transcriptase inhibitors.[5] Thus, several oxazepines and their bioisosteric analogues **I**,[1(*a*),6] **II**,[7,8] **III**[7,8] and **IV**[9] (Figure 1) were shown to have a wide spectrum of physiological activity while their carboxamide analogues are still in development or in early stages of pre-clinical trials.

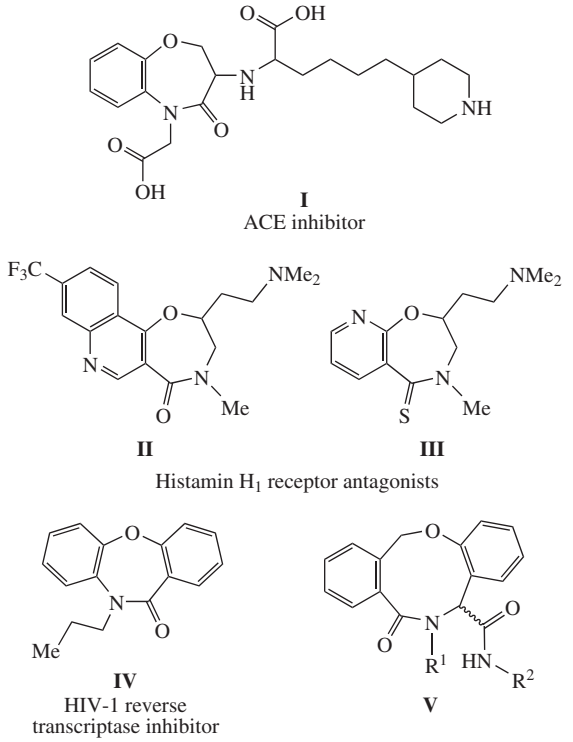


Figure 1 Examples of physiologically active aryl-fused 1,4-oxazepinones (structures **I**–**IV**) and compounds synthesized in this work (common structure **V**).

As shown in Figure 1, the compounds **V** we have obtained contain the core diaryl-fused nine-membered heterocyclic fragment, which is structurally very similar to several known aryl- and heteroaryl-fused 1,4-oxazepinones in terms of the fundamental bioisosteric rules. Furthermore, the carboxamide moiety of compounds **V** is in a close topological similarity with the peripheral alkyl fragments in structures of the above pharmacological agents. Here, we report the development of a novel Ugi-type multi-component reaction (MCR) for the synthesis of rare heterocyclic compounds belonging to this scaffold.

The Ugi reaction[10] was shown to be an effective approach to the assembly of diverse compound libraries, which can be readily applied in combinatorial chemistry format. An important modification of the classical four-component Ugi reaction includes the use of bifunctional reagents.[9,11(*a*)]

Recently, we have developed an advanced variant of Ugi MCR using heterocyclic keto- and aldehide-acids as one of the initial bifunctional components.[12–17] In particular, using this prospective strategy, we have developed efficient synthetic routes to aryl and/or heterocycle-fused six- and seven-membered carbamoyl-β-lactams **VI**[13] and **VII**,[14] **VIII**[15] and **IX**,[15] **X**[16] and **XI**[16] as well as **XII**[17] (Figure 2).

We have clearly demonstrated the high efficacy and versatility of this coupling strategy for the production of combinatorial libraries of various heterocyclic structures representing promising pharmaceutically relevant synthetic targets. Note that, based on a bifunctional reagent, we have recently developed an analogous synthetic route to carbamoyl substituted 6-oxo-4,5,6,11-tetrahydropyrrolo[1,2-*b*][2,5]benzodiazocines using a novel Ugi-type MCR.[18]

In this work we have focused specifically on broadening the scope and synthetic potential of the modified Ugi four-center three-component reaction based on the use of bifunctional components (Figure 2). Following the current synthetic approach, we have obtained heterocyclic compounds **5a**,**b** based on 2-[(2-formylphenoxy)methyl]benzoic acid **4** (Scheme 1).

Thus, key bifunctional compound **4** was obtained from acid **1** and corresponding salicylaldehyde **2** using a modified approach reported by Guillaumel *et al.*[19] In the first step of our synthesis, aldehyde-ester **3** was easily obtained in 75% yield by the reaction of **1** with **2** in Me_3CN at 80 °C in the presence of K_2CO_3. Compound **3** was then easily hydrolyzed by 5% alkali in a mixture of ethanol and water (3:1, v/v), and resulting bifunc-

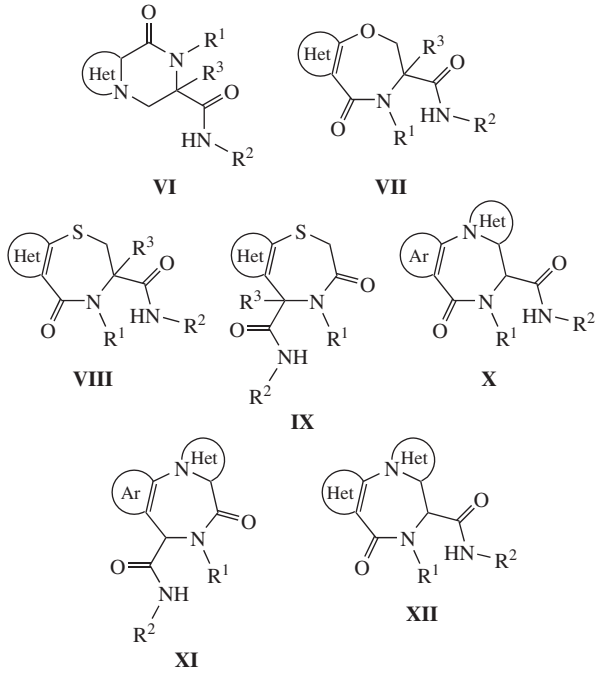
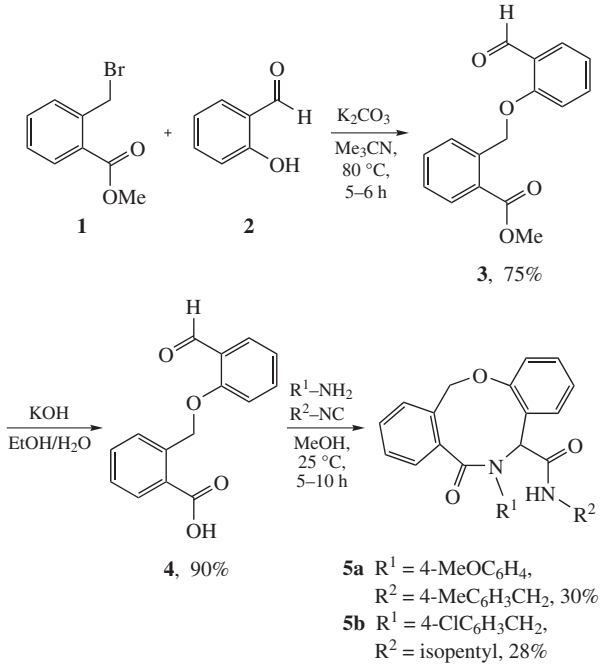


Figure 2 Examples of aryl and/or heterocycle-fused six- and seven-membered carbamoyl-β-lactams.

tional compound **4** was successfully isolated in 90% yield (for the detailed synthetic protocols for intermediate compounds **1**–**4**, see Online Supplementary Materials).

We have further found that the reaction of aromatic aldehyde-acid **4** with amines and isonitriles in methanol at 25 °C led to 11-oxo-6,11,12,13-tetrahydrodibenzo[*b*,*g*][1,5]oxazonine-13-carboxamides **5a**,**b** (Scheme 1).† Typically, the full conversion of initial reactants was achieved within 5–10 h, depending on the structure of the initial amines and isonitriles. The process presumably follows the same initial course as the classical Ugi condensation with an intermediate imine being attacked by the isonitrile to give a nitrilium intermediate, which then undergoes intramolecular cyclization.



Scheme 1 Ugi-type synthesis of N-substituted 11-oxo-6,11,12,13-tetrahydrodibenzo[*b*,*g*][1,5]oxazonine-13-carboxamides **5a**,**b**.

In the performed condensation, the desired cyclic products usually precipitated from the reaction mixtures after the reaction was cooled to room temperature. These reactions afforded the desired products in relatively low yields, depending on the nature of coupling components. However, note that the yields of reactions leading to such heterocyclic systems depend directly on the size of the cycle assembled.[20]

The obtained precipitate was purified by flash column chromatography on silica gel. All compounds were obtained as racemic mixtures of enantiomers. The assignment of all synthesized structures was made on the basis of ^{1}H NMR and high-resolution mass-spectrometry data.‡

To determine the structures of the resulting compounds accurately, pure crystalline substances were obtained for compounds **5a**,**b**, thus allowing the analysis of individual compounds through X-ray crystallography. Thus, the structure of **5a** was unambiguously established as 12-(4-methoxyphenyl)-*N*-(4-methylbenzyl)-11-oxo-6,11,12,13-tetrahydrodibenzo[*b*,*g*][1,5]oxazonine-13-carboxamide (Figure 3) by single-crystal X-ray analysis. Single crystals of compounds suitable for X-ray analysis were grown by slow evaporation from diethyl ether. The corresponding bond angles and lengths of these molecules in the asymmetric unit are the same within three standard deviations§ (for details see Online Supplementary Materials). As shown in Figure 3, the space orientation of two bulky substituents derived from amine and isonitrile components is completely different. The inner oxazonine space turn can also be clearly recognized.

† *General procedure for preparation of compounds* **5a**,**b**. Aldehyde-acid **4** (1.0 mmol) and the corresponding primary amine (1.5 mmol) were dissolved in methanol (3 ml). The solution was kept for 10 min at room temperature; then, isonitrile (1.5 mmol) was added and the resulting mixture was stirred at 25 °C for 5–10 h. The reaction was followed by TLC (5% MeOH in CH_2Cl_2). On completion, the reaction mixture was cooled to room temperature, the formed precipitate was filtered off, washed with methanol and, if required, purified by recrystallization from diethyl ether of by chromatography on silica gel, eluting with CH_2Cl_2. Target compounds **5a**,**b** were obtained as colourless solids in comparatively low yields (28 and 30%, respectively) as the mixture of corresponding enantiomers.

‡ *Analytical data for compounds* **5a**,**b**. ^{1}H NMR spectra were recorded on a Bruker AMX-400 or Varian spectrometer in [$^2H_6$]DMSO (300 MHz, CCl_4 as an internal standard). High-resolution mass spectra were recorded using electrospray ionization time-of-flight reflectron experiments (ESI-TOF) on an Agilent ESI-TOF mass spectrometer. Samples were electrosprayed into the TOF reflectron analyzer at an ESI voltage of 4000 V and a flow rate of 200 μl min^{-1}.

5a: yield 30%, mp 211–213 °C. ^{1}H NMR, δ: 2.30 (s, 3H, Me), 3.82 (s, 3H, OMe), 4.19, 4.46 (dd, 2H, CH_2N, J 12.6 Hz), 4.76, 5.37 (dd, 2H, CH_2O, J 12 Hz), 5.56 (br. s, 1H, NH), 6.20 (s, 1H, CH), 6.48–6.58 (m, 1H, Ar), 6.78–6.94 (m, 4H, Ar), 6.99, 7.07 (dd, 4H, Ar, J_1 5.58 Hz, J_2 6.6 Hz), 7.20–7.38 (m, 3H, Ar), 7.52–7.64 (m, 3H, Ar), 7.74–7.84 (m, 1H, Ar). HRMS: 493.2121 (calc. for $C_{31}H_{28}N_2O_4$: 493.2122).

5b: yield 28%, mp 214–216 °C. ^{1}H NMR, δ: 0.86 (d, 6H, 2Me, J 6.6 Hz), 1.20–1.35 (m, 2H, CH_2), 1.39–1.52 (m, 1H, CH), 3.07–3.36 (m, 2H, CH_2NH), 4.47, 5.11 (dd, 2H, CH_2N, J_1 14.8 Hz, J_2 12.0 Hz), 4.47–4.55 (m, 1H, CH_2O), 5.08–5.33 (m, 2H, CH_2O + NH), 5.83 (s, 1H, CH), 6.74 (d, 2H, Ar, J 7.8 Hz), 7.05 (d, 2H, Ar, J 8.1 Hz), 7.20–7.24 (m, 2H, Ar), 7.40–7.45 (m, 1H, Ar), 7.47–7.53 (m, 4H, Ar), 7.63 (m, 1H, Ar). HRMS: 477.1934 (calc. for $C_{28}H_{29}ClN_2O_3$: 477.1939).

§ *Crystal structure of* **5a**: empirical formula, $C_{31}H_{28}N_2O_4$, M = 492.55, orthorhombic, space group *Pbca*, a = 21.819(3), b = 9.3072(12) and c = 25.577(3) Å, Z = 8, μ = 0.084 mm^{-1}. 29578 reflections were measured, 5089 independent reflections. R_{int} = 0.0816; R_1 = 0.1330, wR_2 = 0.2141; final R indices: R_1 = 0.0797, wR_2 = 0.1770; R indices (all data): R_1 = = 0.1330, wR_2 = 0.2141.

CCDC 746913 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2009.

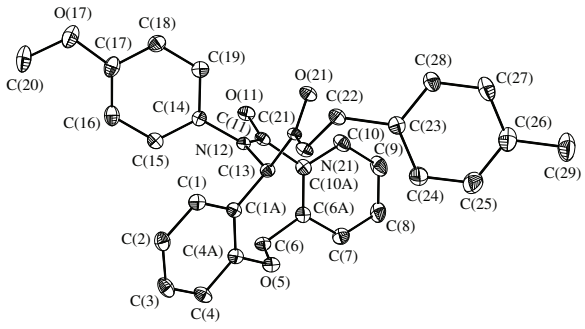


Figure 3 ORTEP plots (50% probability thermal ellipsoids) of compound **5a**. Hydrogen atoms are omitted. Selected bond lengths (Å): C(1A)–C(13) 1.495(5), N(12)–C(13) 1.479(4), C(6)–C(6A) 1.503(5), O(5)–C(6) 1.459(4); selected bond angles (°): N(12)–C(13)–C(1A) 111.2(2), O(5)–C(6)–C(6A) 109.5(3).

In summary, we have developed a convenient synthetic strategy to the assembly of the diaryl-fused derivatives of 1,5-oxazonine heterocyclic scaffold based on a novel modification of the Ugi-type four-component reaction. As a synthetic tool for creating diverse compound libraries, the four-component condensation presented in this work is quite acceptable for the usage of a large number of potential input reactants. Therefore, it can be comprehensively applied in a combinatorial format. Considering the ease of the preparation of initial reactants, convenient synthesis and isolation of products, this synthetic route provides a new valuable entry to rare nine-membered heterocyclic systems, which can be reasonably regarded as unique bioisosteric analogues of related biologically active seven-membered heterocyclic agents. The obtained compounds represent valuable starting points for the development of compounds of biological interest.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2009.09.020.

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