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One-step assembly of carbamoyl substituted annulated 1,4-oxazepines

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Abstract—We present a convenient synthesis of heterocyclic scaffolds using a novel modification of four-component Ugi condensation. Two complementary variants of this useful synthetic strategy provide an efficient one-step assembly of four novel pharmaceutically relevant (hetero)aryl-fused 1,4-oxazepines with different substituents' profile.

Among a variety of physiologically active 5(3)-oxo-1,4-oxazepines the derivatives of their aryl-fused analogs represent a relatively little-explored group with interesting pharmaceutical properties. They were described as effective protease inhibitors,[1] non-peptidergic GPCR inhibitors,[2] integrin antagonists,[3] squalene synthase,[4] and reverse transcriptase inhibitors.[5] For example, 3-alkylamino-substituted 2,3-dihydro-5*H*-benzo[*b*][1,4]-oxazepin-4-one **I** is a strong inhibitor of angiotensin-converting enzyme (ACE),[1a] which plays a key role in the modern approaches to hypertension and diabetic nephropathy therapy, end-organ protection, and heart failure treatment.[6] 3,4-Dihydropyrido[3,4-*f*][1,4]oxazepin-5(2*H*)-one **II** and 3,4-dihydropyrido[3,2-*f*][1,4]-oxazepine-5(2*H*)-thione **III** represent a promising structural class of compounds possessing H_1 antihistaminic activity,[7] which can be used for the efficient therapy of some allergic reactions and dermatological affections.[8] Dibenz[*b*,*f*][1,4]oxazepin-11(10*H*)-one **IV** was found to selectively inhibit human immunodeficiency virus type 1 (HIV-1) reverse transcriptase.[9]

According to these examples, aryl- and heteroaryl-fused derivatives of 5(3)-oxo-1,4-oxazepine represent promising synthetic targets. Development of efficient synthetic approaches to these scaffolds may provide a valuable source of novel physiologically active agents. In this paper, we communicate our success in developing a novel four-component Ugi-type reaction for the synthesis of novel aryl- and heteroaryl-fused derivatives of 5-carboxamide-3-oxo-1,4-oxazepine **V** and 3-carboxamide-3-methyl-5-oxo-1,4-oxazepine **VI**–**VIII** (Fig. 1), which can be applied in combinatorial chemistry approaches.

In the reported synthetic approaches to the aryl-fused derivatives of oxo-1,4-oxazepines, the key reaction is the intermolecular cyclization of the appropriate aryl derivatives leading to the desired molecules.[10] However, the described synthetic strategies have found limitations mainly due to lack of versatility and a limited number of the appropriate initial reactants. In addition, the described approaches have not provided a robust method suitable for the production of combinatorial libraries. The Ugi reaction[11] was shown to be an effective approach to the assembly of diverse compound libraries, which can be readily applied in combinatorial chemistry format. One of the important modifications of the classical four-component Ugi reaction includes the use of bifunctional reagents.[12] One example of the use of the Ugi reaction to prepare annulated 1,4-oxazepines has been reported by Zhang et al.[12a]

Keywords: Ugi condensation; 5-Oxo-1,4-oxazepine-3-carboxamide; 3-Oxo-1,4-oxazepine-5-carboxamide; Parallel synthesis; Compound library.
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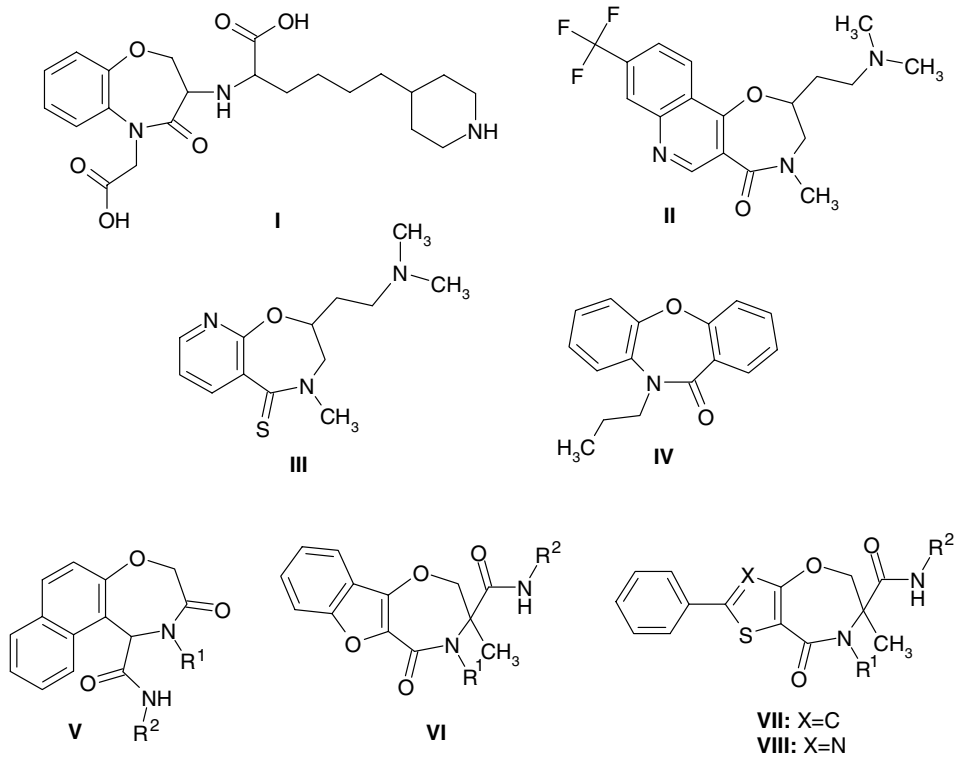
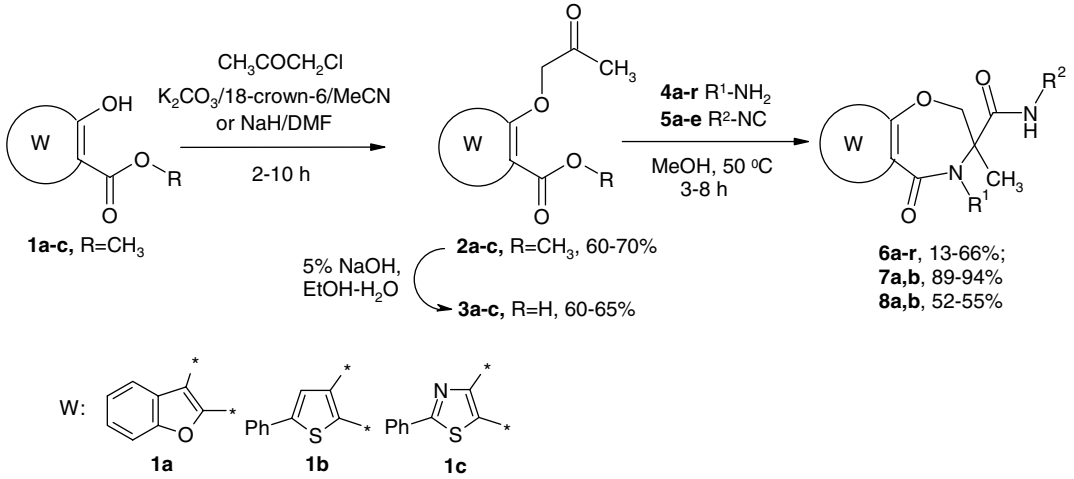


Figure 1. Examples of physiologically active aryl-fused 1,4-oxazepinones (structures **I**–**IV**) and compounds synthesized in this work (structures **V**–**VIII**).

Recently, we have described a convenient synthetic approach to novel aryl(heteroaryl)-fused pyrazines using a modification of four-component Ugi condensation with 2-oxoethylamino-acetic acid fragment as a bifunctional component.[13] As a further modification of this prospective methodology, we developed an efficient synthetic route to novel aryl and heteroaryl-fused derivatives of 3-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*][1,4]diazepine heterocyclic structures based on Ugi-type reaction of bifunctional reagents bearing *N*-(carboxyaryl)-2-formyl fragment of corresponding pyrroles with isonitriles and amines.[14] In the mentioned works, we demonstrated the efficacy and versatility of this efficient coupling strategy for the production of combinatorial libraries of heterocyclic structures representing promising pharmaceutically relevant synthetic targets.

In this work, we have focused on broadening the scope of the developed method and synthesized four novel heterocyclic templates **V**–**VIII**, which were not described before in the literature. Key bifunctional keto acids **3a**–**c** for the synthesis of heteroaryl-fused 5-oxo-1,4-oxazepines **6**–**8** (Scheme 1) were obtained from the corresponding hydroxy-substituted heteroaryl carboxylates



Scheme 1. Synthesis of novel aryl and heteroaryl-fused derivatives of 3-methyl-5-oxo-1,4-oxazepine-3-carboxamides **6a**–**r**, **7a**,**b**, and **8a**,**b** (Table 2).

Table 1. Synthesis of ketoesters **2a–c**

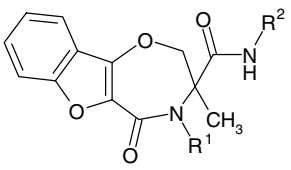
Initial reagent	**1a**[15a]	**1b**[15b]	**1c**[15c]
Reaction conditions	1.2 mol equiv of K_2CO_3, 0.01 mol equiv of 18-crown-6, MeCN, 10 h at reflux	2 mol equiv of K_2CO_3, 0.01 mol equiv of 18-crown-6, MeCN, 2 h at reflux	1.1 mol equiv of NaH, DMF, 8 h at 50 °C
Purification	Extraction with EtOAc, recrystallization from EtOH	Crystallization from the reaction mixture, recrystallization from MeOH	Extraction with $CHCl_3$, recrystallization from EtOH–water (2:1)
Yield of **2a–c**	70%	60%	60%

1a–c, which are readily available from commercial sources or synthetically.[15] At the first step, ketoesters **2a–c** were obtained by using the reaction of **1a–c** with chloroacetone. The optimal reaction and purification conditions significantly varied according to the nature of the initial bifunctional reactant (Table 1). The reaction led to the desired ketoesters **2a–c** in 60–70% yield. The latter were hydrolyzed by 5% alkali in a mixture of ethanol and water (3:1, v/v), and the resulting keto acids **3a–c** were isolated in 60–65% yield.

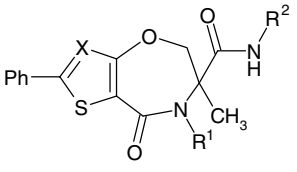
We have found that reaction of keto acids **3a–c** with various amines **4a–r** and isocyanides **5a–e** in methanol at 50 °C led to novel heteroaryl-fused derivatives of 3-methyl-5-oxo-1,4-oxazepine-3-carboxamides **6a–r**, **7a**,**b**, and **8a**,**b** (Table 2). Typically, the full conversion of initial keto acids was achieved within 3–8 h, depending on the structure of the keto acid. 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. With respect to the amine component, various cycloaliphatic and aromatic primary amines, such as substituted anilines, benzyl and phenyl amines, linear and branched aliphatic amines, were tolerated without any limitations. As isonitrile reagents, we used five different isonitriles **5a–e** available from commercial sources.

For assembly of the aryl-fused 3-oxo[1,4]oxazepine-5-carboxamide heterocyclic system, we explored the possibility of the use of formyl carboxylate **9** as an alternative bifunctional reagent in a similar condensation (Scheme 2). Compound **9** was prepared as reported by Hullar and Failla.[16] The reaction of **9** with amines **4a–w** and cyclopentylisocyanide **5a** in methanol at 50 °C led to a medium-sized library of novel N-substituted 3-oxo-naphtho[1,2-*f*][1,4]oxazepine-5-cyclopentylcarboxamides **10a–w** in 14–74% yield. This condensation proceeded more slowly than reaction of **3a–c** with isocyanides and amines; typically, the complete conversion of initial reactants was achieved within 16–18 h.

Table 2. Structures and yields of the synthesized compounds **6a–r**, **7a**,**b**, and **8a**,**b**

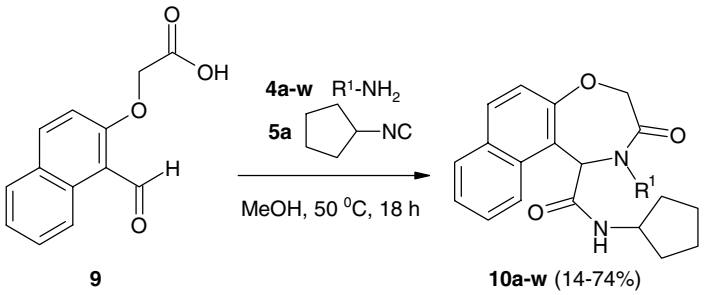


6a-r



7a,b: X = CH
8a,b: X = N

No.	R^1	R^2	Yield, %
6a	3-Cl–C_6H_4–CH_2	C_6H_5–CH_2	25
6b	C_6H_5–$(CH_2)_3$	2-MeO–C_6H_4–CH_2	34
6c	MeO–$(CH_2)_2$	2-MeO–C_6H_4–CH_2	29
6d	2-Cyclohex-1-en-1-ylethyl	2-MeO–C_6H_4–CH_2	45
6e	2-F–C_6H_4–CH_2	2-MeO–C_6H_4–CH_2	64
6f	2-Me–C_6H_4–$(CH_2)_2$	2-MeO–C_6H_4–CH_2	22
6g	3-Br–C_6H_4–CH_2	*c*-C_5H_9	29
6h	2-Me–C_6H_4–$(CH_2)_2$	*c*-C_5H_9	18
6i	4-Me–C_6H_4–CH_2	*c*-C_5H_9	66
6j	Bn	*c*-C_5H_9	55
6k	*n*-Bu	C_6H_5–CH_2	44
6l	*n*-Pr	2-MeO–C_6H_4–CH_2	52
6m	Bn	*c*-C_5H_9	61
6n	2-F–C_6H_4–CH_2	*c*-C_5H_9	34
6o	4-EtO–C_6H_4–CH_2	*c*-C_5H_9	38
6p	2-Me–C_6H_4–CH_2	*c*-C_5H_9	64
6q	4-*i*-Pr–C_6H_4–CH_2	*c*-C_5H_9	21
6r	3-F–C_6H_4–CH_2	*c*-C_5H_9	48
7a	4-Me–C_6H_4–CH_2	*c*-C_7H_{13}	89
7b	4-Me–C_6H_4–CH_2	*c*-C_8H_{15}	94
8a	Bn	*c*-C_6H_{11}	52
8b	C_6H_5–$(CH_2)_2$	*c*-C_6H_{11}	55



9 **10a-w** (14-74%)

Scheme 2. Synthesis of novel N-substituted derivatives of 3-oxo-naphtho[1,2-*f*][1,4]oxazepine-5-cyclopentylcarboxamide **10a–w** (Table 3).

Table 3. Structures and yields of the synthesized compounds **10a–w**

No.	R^1	Yield, %
10a	2-Cyclohex-1-en-1-ylethyl	64
10b	3-F–C_6H_4–CH_2	68
10c	4-Me–C_6H_4–CH_2	75
10d	4-Et–C_6H_4–CH_2	46
10e	4-F–C_6H_4–CH_2	56
10f	1,3-Benzodioxol-5-ylmethyl	37
10g	*c*-C_5H_9	15
10h	*c*-C_6H_{11}	24
10i	2-Me–C_6H_4	55
10j	2-Et–C_6H_4	74
10k	2-F–C_6H_4	52
10l	2-Cl–C_6H_4	14
10m	2-Br–C_6H_4	72
10n	2-MeOC(O)–C_6H_4	65
10o	3-F–C_6H_4	21
10p	2,3-Di-Me–C_6H_3	24
10q	2,5-Di-F–C_6H_3	64
10r	3,5-Di-MeO–C_6H_3	35
10s	2,5-Di-MeO–C_6H_3	26
10t	3,4-Di-MeO–C_6H_3–$(CH_2)_2$	54
10u	4-Br–3-MeO–C_6H_3	48
10v	3-Cl–4-MeO–C_6H_3	39
10w	3-Cl–4,6-di-MeO–C_6H_2	72

In both condensation variants, the desired products usually precipitated from the reaction mixtures after the reaction was cooled to room temperature. Structures and yields of the synthesized compounds are shown in Tables 2 and 3. These reactions afforded the desired products in moderate to high yields, depending on the nature of the coupling components. The precipitates could be purified by flash column chromatography on silica gel. The assignment of all synthesized structures was made on the basis of ^{1}H NMR, ^{13}C NMR, and high-resolution mass-spectroscopy data. Thus, two non-equivalent methylene protons of the oxazepine ring of compounds **6–8** can be seen as two doublets in the range of δ 4.0–4.5 and δ 4.7–5.0 ppm with the geminal spin–spin coupling constants in the range of 13.6–14.1 Hz. The characteristic signals from methylene protons of oxazepine ring of compounds **10a–w** are usually located in the same region. Mass-spectra of **6–8** and **10** revealed the presence of molecular ions and other large fragments consistent with the assigned structures.

In summary, we have developed a convenient synthetic strategy to the assembly of the aryl(heteroaryl)-fused derivatives of 5(3)-oxo-1,4-oxazepine heterocyclic structures based on a novel modification of the Ugi four-component reaction. As a synthetic tool for creating diverse compound libraries, the four-component condensation used in this work offers a large number of potential input reactants and resulting products and can be used in a combinatorial format.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.01.158.

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