An Ugi-Type Condensation of α-Isocyanoacetamide and Chiral Cyclic Imine under a New Catalytic System

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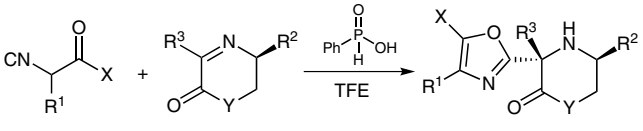
Abstract: A new catalytic Ugi-type condensation of α-isocyanoacetamide and chiral cyclic imine is developed, where the combination of phenyl phosphilic acid and trifluoroethanol is exploited to promote the Ugi-type condensation with α-isocyanoacetamide for the first time. Under this new catalytic system, the reaction using the cyclic imines as relatively inertial substrates proceed well, and chiral 3-oxazolyl-morpholin/piperazine-2-one derivatives are synthesized with high yield and stereoselectivity. Furthermore, transformation of the condensation product to a novel fused tricyclic structure is attempted initially by treatment with maleic anhydride.

Key words: catalytic Ugi-type condensation, α-isocyanoacetamide, oxazoles, phosphilic acid, asymmetric synthesis

The Ugi reaction and its many variants have been studied widely and show great potential in generating molecular complexity and diversity.[1] Among them, the Ugi-type condensation of α-isocyanoacetamide **1**, amine **2**, and oxo compound **3** furnish a highly efficient access to the synthesis of substituted oxazole derivatives **4** (Scheme 1).[2] The reaction could proceed without or with promoters depending on the reactivity of imine intermediate. The oxazole unit is found in many bioactive natural products and pharmaceutically relevant molecules,[2a,3] and structure **4** is applied in the design of important peptidomimetic platforms.[4] Moreover, based on abundant oxazole chemistry,[5] the products containing oxazoles are likely to be converted into other complex scaffolds.

Scheme 1 Representative Ugi-type reaction of an α-isocyanoacetamides, an amine, and an aldehyde

Similar to the stereochemical issues in other Ugi reaction,[6] although one chiral center is generated in the course of this reaction, highly stereoselective cases of this Ugi-type condensation are rare. Up to now, only one enantioselective catalytic version was achieved in the reaction of aldehyde, aniline, and α-isocyanoacetamide in 56–90% ee.[7] There has still not been a special study focused on the stereoselectivity when employing chiral substrates. A limited number of precedents with chiral amines showed low or no diastereoselectivity.[8] Exploration of asymmetric Ugi reactions permit the swift creation of diverse chiral molecule libraries with potential applicability in medical and agricultural chemistry, because optically pure compounds are of utmost importance during the development of most drugs. Recently, we reported an asymmetric Ugi reaction of isocyanide, carboxylic acid, and chiral cyclic imine **5**.[9] As a continuation of the study on developing asymmetric reactions using **5**, we report herein a catalytic Ugi-type condensation of **1** and **5** with excellent stereoselectivity, by which asymmetric syntheses of new 3-oxazolyl-morpholin/piperazine-2-one derivatives **6** are achieved (Scheme 2). Phenyl phosphilic acid (**7**) in trifluoroethanol (TFE), as a new system, is employed to catalyze this Ugi-type condensation of α-isocyanoacetamide for the first time.



1a: R^1 = H, X = morpholinyl
1b: R^1 = Bn, X = morpholinyl
1c: R^1 = *i*-Pr, X = morpholinyl
1d: R^1 = Me, X = morpholinyl
1e: R^1 = Ph, X = piperidinyl
1f: R^1 = Ph, X = pyrrolidinyl
1g: R^1 = Bn, X = piperidinyl
1h: R^1 = Bn, X = diethylamino

5a: R^2 = Bn, R^3 = Me, Y = O
5b: R^2 = *i*-Pr, R^3 = Me, Y = O
5c: R^2 = Ph, R^3 = Me, Y = O
5d: R^2 = *i*-Pr, R^3 = Et, Y = O
5e: R^2 = Bn, R^3 = Et, Y = O
5f: R^2 = Bn, R^3 = Me, Y = NMe
5g: R^2 = Bn, R^3 = Me, Y = N*n*-Bu

Scheme 2 Asymmetric synthesis of heterocycles **6** from **1** and **5**

In the Ugi-type condensation reported previously, unsubstituted α-isocyanoacetamides are used rarely despite their prospective utility, because of their inherent instability and the side reactions, caused by the competing nucleophilic methylene carbon, lead to more complexity and uncertainty.[10] Therefore, unsubstituted and substituted isocyanoacetamides **1a**,**b** were chosen to react with **5a** for the screening of suitable conditions that would work with both substrates. In the absence of an additive, the reaction

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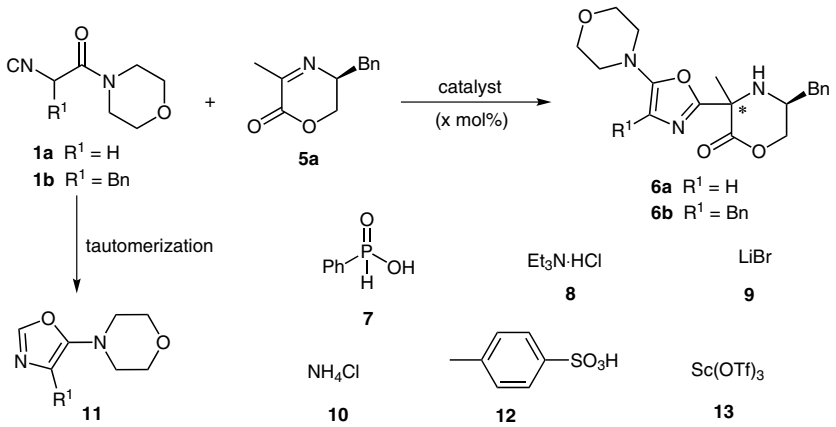
of **1** and **5** did not take place at all just by varying solvent and temperature. Under the previous (promoted) conditions for the Ugi-type reactions [Et_3N·HCl (**8**), LiBr (**9**), or NH_4Cl (**10**) as promoter, MeOH and toluene as solvent, from r.t. to reflux],[2b–d,8b,10a,11] the reaction was slow (Table 1, entries 1, 11, and 12). Simple prolongation of reaction time resulted in serious decomposition of imines **5** and tautomerization of **1** to 2*H*-oxazole **11**, and the desired product **6** was always obtained in low yield. This indicated that the Ugi-type condensation based on **5** proceeds with much more difficulty than the precedent reaction. It is possible that compounds **5**, as the imines from the condensation of a primary amine and a ketone, are less active than the iminium counterpart from the secondary amine and the imines from the aldehyde. So, a new efficient reaction system is required for the promotion of the slow reaction of **1** and **5**.

In 2008, a phenyl phosphilic acid (**7**) catalyzed Ugi reaction of aldehydes, amines, and isonitriles was reported.[12] However, the potential of **7** on development of new catalytic Ugi reactions did not receive attention after that. We found that in our case, the reaction could be activated effectively by **7**. In the presence of 25 mol% of **7**, the desired product **6a** was obtained in TFE at room temperature (Table 1, entry 2). Decreasing the amount of **7** or lowering the temperature could partially inhibit the tautomerization of **1** to give better yield (Table 1, entries 3 and 4). Replacement of **7** with *p*-toluenesulfonic acid (**12**), a stronger Brønsted acid, led to a remarkable drop in yield (Table 1, entry 5). Increase of concentration within an appropri-

Table 1 Optimization of the Ugi-Type Condensation with **5a** and **1a**,**b**[a]



Entry	R^1	Solvent	Time (h)	Catalyst (x mol%)	Temp (°C)	Yield (%)	Recovered **5a** (%)
1	H	MeOH	6	**8** (200)	60	trace	67
2	H	TFE	1.5	**7** (25)	r.t.	40	16
3	H	TFE	1.5	**7** (10)	r.t.	51	26
4	H	TFE	3	**7** (25)	–40	52	27
5	H	TFE	2.5	**12** (25)	–40	10	18
6	H	TFE	1.5	**13** (10)	–40	51	20
7	H	TFE	1	**9** (100)	r.t.	8	trace
8	H	TFE	1	**10** (150)	r.t.	12	0
9[b]	H	TFE	2.5	**7** (25)	–40	59	29
10[b,c]	H	TFE	1	**7** (10)	r.t.	86	0
11[b,c]	Bn	PhMe	24	**9** (100)	80	trace	69
12[b,c]	Bn	PhMe	72	**10** (150)	80	19	62
13[b,c]	Bn	PhMe	12	**7** (10)	80	trace	74
14[b,c]	Bn	TFE	4	**13** (10)	–40	30	45
15[b,c]	Bn	TFE	1	**7** (10)	r.t.	93	0

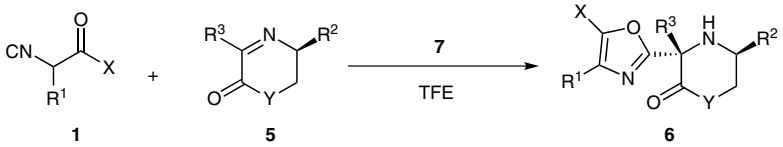
[a] General conditions: **5a**/**1** = 1:1, *c* 0.2 M.
[b] *c* 0.4 M.
[c] Additional **1** was supplemented in midway (0.8 equiv for **1a**, 0.4 equiv for **1b**).

ate range might further improve the yield (Table 1, entry 9). Nevertheless the consumption of **1** is always faster than **5**, therefore supplement of **1** in midway is very effective for thorough conversion of **5** and high yield of **6** (Table 1, entries 10 and 15). In other solvents including toluene,[12] the catalytic effect of **7** clearly decreased (Table 1, entry 13). Some other additives were also tried in TFE (Table 1, entries 7 and 8), and only $Sc(OTf)_3$ (**13**) promoted the reaction of **1a** (Table 1, entry 6). However, for the substituted isocyanoacetamide **1b**, the catalytic effect of **13** was inferior than for the unsubstituted isocyanoacetamide **1a** (Table 1, entry 14 vs. entry 6).

The generality of this new catalytic Ugi-type condensation was next examined. Gratifyingly, under the mild conditions the reaction of various compounds **1** and **5** all proceeded quickly to give the desired products **6**[13] in good to excellent yields, whether R^1 on oxazole is a hydrogen, alkyl, or aryl group (Table 2). When the amino function (X) in **1** is morpholinyl, most reactions were finished after approximately one hour in high yield. For some isocyanoacetamide units with other amino groups, the reaction process seemed somewhat slow, and a higher amount of catalyst was needed to accelerate it. Cyclic imines **5** showed excellent stereoinduction for the new chiral quaternary carbon, and quite a few products were obtained as the single stereoisomer. In some cases another diastereoisomer was detected in small amount, nevertheless, dr values were all at least 10:1, as judged by NMR spectra (**6a**–**c**,**g**,**h**) or separation (**6k**). The diastereoselectivity in this reaction is better than in our previously reported three-component Ugi reaction.[9] The NOESY NMR spectra of **6c** and **6f** were analyzed to determine the stereochemistry of the products. The NOE correlation not between Me-3 and H-5 signals but between Me-3 and aromatic or benzylic hydrogen illustrates the *trans*-relationship of the C-3 oxazolyl and C-5 alkyl (R^3) group, namely an *S*-configuration at C-3 (Figure 1). It is reasonable that isocyanoacetamide **1** as nucleophile preferentially approach imine **5** from the side opposite to the R^1 group to generate predominant the *trans* product.[9,14] Structurally, compounds **6** may be regarded as varied derivatives of chiral α,α-disubstituted oxazole-containing amino acids, which are of importance for the design and synthesis of various conformationally restricted and biologically active pseudopeptides including galmic.[15]

On the basis of reactivity of 5-aminooxazoles as electron-rich azadienes with dienephiles,[16] some strategies to combine the Ugi-type condensation and the Diels–Alder cycloaddition have been developed to construct interesting and complex scaffolds.[8b,17] However, the asymmetric tan-

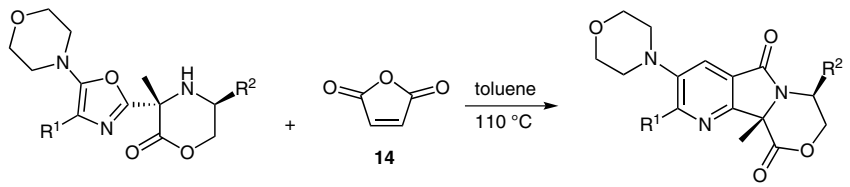
Table 2 Synthesis of 3-Oxazolyl-morpholin/piperazine-2-one Derivatives **6a**–**n**[a]



1 **5** **6**

Entry	R^1	R^2	R^3	Y	X	Time (h)	Product	Yield (%)	dr
1	H	Bn	Me	O	morpholinyl	1	**6a**	86	14:1
2	Bn	Bn	Me	O	morpholinyl	1	**6b**	93	19:1
3	*i*-Pr	Bn	Me	O	morpholinyl	1.25	**6c**	93	12:1
4	Me	Bn	Me	O	morpholinyl	1	**6d**	92	single
5	Bn	*i*-Pr	Me	O	morpholinyl	1.25	**6e**	87	single
6	*i*-Pr	Ph	Me	O	morpholinyl	1.25	**6f**	84	single
7	*i*-Pr	*i*-Pr	Et	O	morpholinyl	1.25	**6g**	88	14:1
8	*i*-Pr	Bn	Et	O	morpholinyl	1.25	**6h**	78	10:1
9	*i*-Pr	Bn	Me	NMe	morpholinyl	1	**6i**	64	single
10	*i*-Pr	Bn	Me	N*n*-Bu	morpholinyl	1	**6j**	81	single
11[b]	Ph	Bn	Me	O	piperidinyl	4	**6k**	90	13:1
12[b]	Bn	Bn	Me	O	piperidinyl	4	**6l**	73	single
13[b]	Ph	Bn	Me	O	pyrrolidinyl	1.5	**6m**	85	single
14[c]	Bn	Bn	Me	O	diethylamino	2	**6n**	78	single

[a] General conditions: TFE (0.4 M of **5**), r.t., phenylphosphinic acid (0.1 equiv), **1a** (1.0 + 0.8 equiv) or **1b**–**h** (1.0 + 0.4 equiv).
[b] Conditions: 0.25 equiv phenylphosphinic acid were used.
[c] Conditions: 0.5 equiv phenylphosphinic acid were used.



6d R^1 = Me, R^2 = Bn
6e R^1 = Bn, R^2 = *i*-Pr

15a R^1 = Me, R^2 = Bn, 43%
15b R^1 = Bn, R^2 = *i*-Pr, 40%

Scheme 3 Synthesis of fused tricyclic system **15** from **6** and **14**

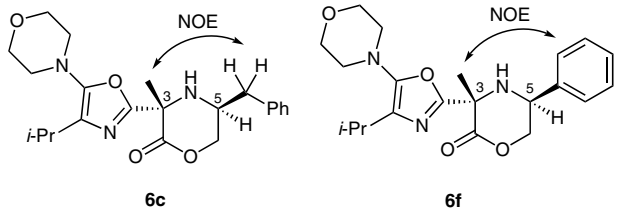


Figure 1 Configuration determination of products **6** by NOESY analysis

dem strategy to produce chiral heterocycles has not been reported. Thus, the reaction of oxazoles **6d** and **6e** with maleic anhydride (**14**) were initially attempted. After primary screening, heating a mixture of **6** and **14** in toluene produced a kind of novel tricyclic framework **15** as the single isomer, incorporating a pyrrolopyridine unit as well as a morpholine (Scheme 3). The pyrrolopyridine, as an analogous structure to the isoindolinones, nicotinamide, etc., is a potential pharmacophore and synthetic intermediate.[18] Heterocycles **15**, which incorporate the medically relevant morpholinone[19] unit, may possess interesting bioactivity.

In summary, the combination of phenyl phosphilic acid and TFE was developed to catalyze the Ugi-type condensation of α-isocyanoacetamide **1**. Under the conditions, asymmetric condensation of **1** and the relatively inert imine **5** proceeded smoothly leading to 3-oxazolyl-morpholin or piperazine-2-one derivatives **6**, in which excellent stereoselectivity of the new chiral center was achieved. The new reaction system showed potential to explore more Ugi-type condensations of α-isocyanoacetamides, particularly those in which some inert substrates were used. Moreover, aminooxazoles **6** reacted with maleic anhydride to form novel fused heterocycles **15**. Further investigation on the post-transformation of **6** to interesting chiral heterocycles such as **15** is ongoing.

Acknowledgment

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(13) **Typical Procedure for the Synthesis of 6**
To a mixture of imine **5a** (42 mg, 0.21 mmol) and isocyanides **1d** (35 mg, 0.21 mmol) in TFE (0.5 mL) was added phenyl phosphilic acid (3 mg, 0.021 mmol) at r.t. under stirring. After 20 min, additional **1d** (14 mg, 0.084 mmol) was added, and the mixture was stirred for another 40 min. The reaction was quenched with aq $NaHCO_3$, and extracted with CH_2Cl_2. The organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (PE–EtOAc = 3:2) to afford product **6d**; yield 92%; colorless gel; $[\alpha]_D^{20}$ –31 (*c* 0.7, in CH_2Cl_2). IR (neat): 3312, 2922, 2854, 1744, 1213, 1116, 753, 701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.22–7.33 (m, 5 H), 4.33 (dd, *J* = 3.5, 10.5 Hz, 1 H), 4.19 (t, *J* = 10.4 Hz, 1 H), 3.72–3.78 (m, 4 H), 3.46–3.55 (m, 1 H), 2.88–2.93 (m, 4 H), 2.76 (dd, *J* = 5.1, 13.7 Hz, 1 H), 2.59 (dd, *J* = 8.7, 13.7 Hz, 1 H), 2.06 (s, 3 H), 1.73 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.8, 157.1, 151.7, 136.3, 128.9, 128.8, 127.0, 121.3, 74.3, 66.8, 60.8, 50.7, 49.6, 37.7, 25.9, 11.2 ppm. HRMS (ESI^+): *m/z* calcd for $C_{20}H_{25}N_3O_4Na$ [M + Na]$^+$: 394.1743; found: 394.1749.
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