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A *p*-toluenesulfinic acid-catalyzed three-component Ugi-type reaction and its application for the synthesis of α-amino amides and amidines

Biswajit Saha, Brendan Frett, Yuanxiang Wang, Hong-yu Li *

College of Pharmacy, Department of Pharmacoloy and Toxicology, The University of Arizona, Tucson, USA
BIO5 Oro Valley, The University of Arizona, Oro Valley, AZ 85737, USA

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ABSTRACT

A mild, cost-effective, and simple three-component Ugi-type reaction using *p*-toluenesulfinic acid (*p*TSIA) as the acid catalyst has been developed to synthesize α-amino amides and α-amino amidines. Employing 1 equiv of amine used in the reaction generated α-amino amides exclusively, while 2 equiv of amines, especially with more nucleophilic aniline such as *p*-anisidine, yielded the α-amino amidines as the major product. This methodology would be suitable for the synthesis of natural or unnatural amino acids and drug-like amidine analogues.

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Multicomponent reactions (MCRs) are powerful tools for the synthesis of complex, biologically relevant heterocyclic molecules.[1] The atom economy of MCRs, their convergent character, operational simplicity, and the structural diversity and complexity of the resulting molecules make this chemistry exceptionally useful for discovery and optimization processes in the pharmaceutical industry.[2] Recently MCRs for the synthesis of heterocyclic molecules have emerged as valuable tools for both academic and industrial research.[3] Among MCRs, the Ugi reaction[4] is the most widely used methodology for the synthesis of diverse molecules.[5] In recent years, several modifications of the classical four-component Ugi reaction have been reported, in particular the Zhu and Dömling groups[6] have contributed significantly to the advancement of this transformation.[7] Another important modification is the three-component Ugi-type reaction (Scheme 1), where an aldehyde, a primary amine, and an isocyanide are used for various transformations.[8] The three-component Ugi reaction was first discovered by Weber et al. in 2000 during the synthesis of library compounds.[9] Later List et al. reported this reaction using phosphinic acid as the acid catalyst in toluene at high temperature.[10] In 2012, Khan reported a three-component Ugi-type condensation reaction for the synthesis of amidines in high yields with bromodimethylsulfonium bromide.[7f]

In view of our continued interest in the synthesis of drug-like molecules through MCRs,[11] we initially intended to perform a four-component Ugi reaction with *p*TSIA as the acid component, but we obtained a three-component Ugi-type product **4a** and a minor compound **5a** (Fig. 1). Herein we report the first *p*TSIA catalyzed three-component (aldehyde, amine, and isocyanide) Ugi-type reaction for the synthesis of α-amino amides and α-amino amidines.

The advantage of this methodology is that the reaction requires mild reaction conditions at room temperature, an inexpensive catalyst, and simple methanol as a solvent. Even if water is used as a solvent, moderate yields can be obtained (40–45%). We have prepared *p*TSIA from the sodium salt of *p*TSIA, which is commercially available, by acidification with 2 N HCl just before a reaction.

First, we carried out a reaction with benzaldehyde (1 equiv), *p*-anisidine (1 equiv), *t*-butyl isocyanide (1 equiv), and *p*TSIA (1 equiv) in methanol at rt for 12 h. The progress of the reaction was monitored by TLC and LCMS, and two new products were identified in the reaction by LCMS. These products were further separated by column chromatography and characterized by LCMS, NMR analysis, and X-ray diffraction crystallographic studies. One of the products, with a lower R_f on TLC, was obtained in 64% isolated yield and was determined to be the three-component Ugi-type product **4a** (Scheme 1). The second component, with a higher R_f, was obtained in 12% isolated yield and was identified by X-ray diffraction crystallographic studies as the α-amino amidine **5a.** The X-ray structure of **5a** is shown in Figure 1.

Next we optimized the conditions of catalyst loading, reaction time, and solvent to maximize the yield for the synthesis of compound **4i** with 4-fluoro benzaldehyde (**1i**, 1 equiv), *p*-anisidine (**2i**, 1 equiv), and pentyl-2-isocyanide (**3i**, 1 equiv). It was found that the reaction with 20 mol % of *p*TSIA catalyst for 24 h was

* Corresponding author. Tel.: +1 520 626 0794.
E-mail address: hongyuli@pharmacy.arizona.edu (H. Li).

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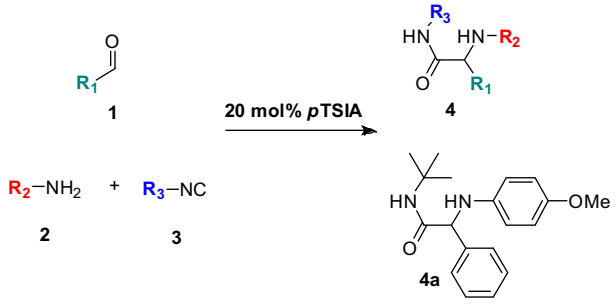


Scheme 1. Three-component Ugi-type reaction.

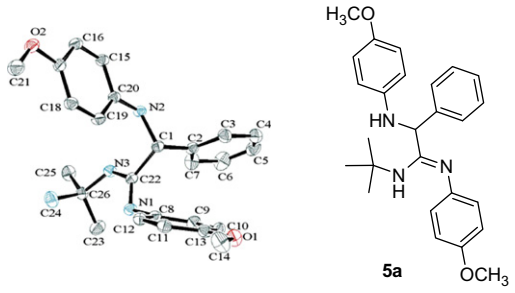


Figure 1. X-ray structure of **5a**.

optimal (Table 1, entry 8). Different solvents such as dichloromethane, water, and ethanol were tested, but methanol generally gave best yields.

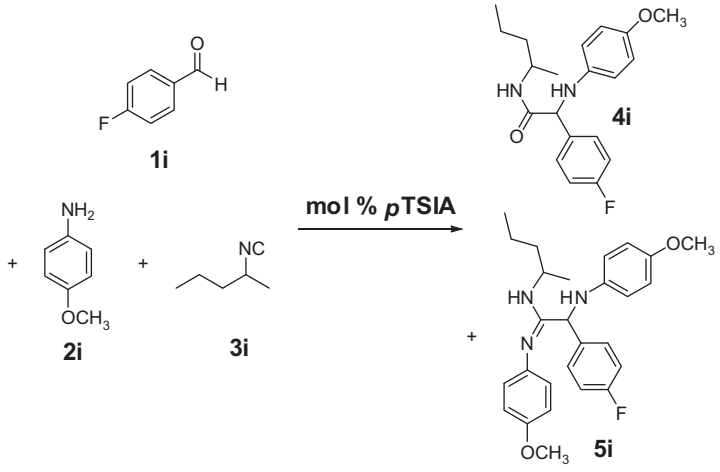
Using *p*TSIA as the acid catalyst and methanol as a solvent, we initiated a study to explore the scope of this three-component reaction by synthesizing 25 compounds (Table 2) with a variety of different aldehydes (1 equiv), amines (1 equiv), and isocyanides (1 equiv) with moderate to good yields (Table 2).[13]

Interestingly, when *p*-anisidine was used in excess (1.5 equiv), compound **5a** (Table 3) was obtained as the major product (~50%). Subsequently, we carried out reactions using 2 equiv, 3 equiv, 5 equiv, and 10 equiv of *p*-anisidine with 20 mol % of *p*TSIA to optimize the yield for the synthesis of amidine analogues. Although 5 equiv of *p*-anisidine (5 equiv) afforded the best yield (70%), further increasing the *p*-anisidine concentration beyond 2 equiv did not drastically improve the overall yield of the amidine analogues. Amidine yields using excess *p*-anisidine generally ranged from 60% to 70%.

We next investigated the scope and the mechanism of this reaction with 2 equiv of different anilines (Table 3). In the case with *p*-nitro aniline, the formation of **4.5** is slightly favored. The nucleophilicity of aniline is completely diminished generating mechanistic difficulty to produce compound **5.5** (Scheme 2). Anilines that contained *ortho* and *para* deactivating bromines also displayed a tendency to generate compounds **4.3** and **4.4** in higher yields than seen with activated anilines. With activated anilines, and choice of aldehyde (**1**) and isocyanide (**3**), the reaction scope is broadly open to generate a variety of amidine analogues (**5**) in good yield (~60%).

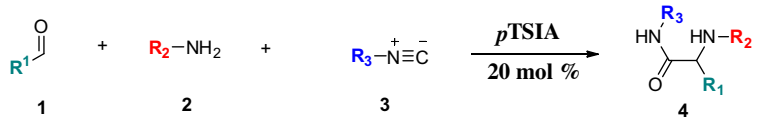
From the studies of Table 3, a plausible mechanism for the formation of **4** and **5** could be assumed to be similar to the Ugi reaction and proceeds via the formation of **6** from the amine and the aldehyde. Subsequent formation of the iminium ion **9** in the presence of *p*TSIA, followed by the nucleophilic addition of isocyanides **3** with its terminal carbon atom produces the nitrilium **10**.[12] The second nucleophilic addition takes place at this intermediate with the acid anion **8** to the in situ generation of intermediate **11** (Scheme 2). Since the *p*-toluenesulfinate is a good leaving group, it can be replaced by a nucleophile of either a water molecule, generated in the course of imine formation, or an amine molecule. The nucleophilic replacements also depend on the concentration of water and amine molecules, and the nucleophilicity of the amine. This can be easily understood, because when 1 equiv of amine is used, most of the amine molecule is consumed in the first step and the resulting water molecule acts predominantly as a

Table 1
Optimization of the three-component Ugi-type reaction



Entry	Mol % of catalyst	Time (h)	**4i**, Yield (%)	**5i**, Yield (%)
1	0	12	0	0
2	5	12	30	5
3	10	12	45	7
4	15	12	47	9
5	20	12	52	12
6	25	12	57	18
7	20	16	65	17
8	20	24	71	22

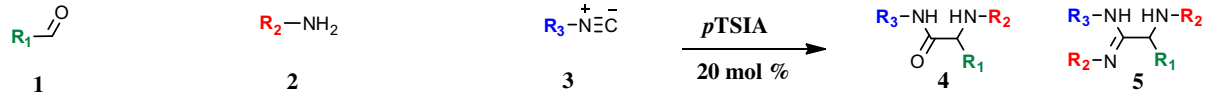
Table 2
Synthesis of α-amino amides



1 2 3 4

Entry	R_1	R_2	R_3	P	Yield (%)
1	C_6H_5–	4-$CH_3OC_6H_4$–	*t*-Butyl	**4a**	70
2	4-FC_6H_4–	4-$CH_3OC_6H_4$–	*n*-Butyl	**4b**	70
3	4-FC_6H_4–	4-$CH_3OC_6H_4$–	Benzyl	**4c**	67
4	4-FC_6H_4–	4-$CH_3OC_6H_4$–	Cyclopentyl	**4d**	62
5	4-FC_6H_4–	4-$CH_3OC_6H_4$–	*t*-Butyl	**4e**	71
6	4-FC_6H_4–	4-$CH_3OC_6H_4$–	4-$CH_3OC_6H_4$–	**4f**	65
7	4-FC_6H_4–	4-$CH_3OC_6H_4$–	2,3-Dihydrobenzodioxine	**4g**	63
8	4-FC_6H_4–	4-$CH_3OC_6H_4$–	2-(2,4-Dimethylpentyl)	**4h**	59
9	4-FC_6H_4–	4-$CH_3OC_6H_4$–	2-Pentyl	**4i**	71
10	4-FC_6H_4–	4-$(CH_3)_3CC_6H_4$–	2-Pentyl	**4j**	65
11	4-FC_6H_4–	2-$(CH_3)_3CC_6H_4$–	2-Pentyl	**4k**	63
12	4-FC_6H_4–	4-$CF_3OC_6H_4$–	2-Pentyl	**4l**	69
13	4-FC_6H_4–	2-$CF_3OC_6H_4$–	2-Pentyl	**4m**	67
14	4-FC_6H_4–	4-BrC_6H_4–	2-Pentyl	**4n**	59
15	4-FC_6H_4–	2-BrC_6H_4–	2-Pentyl	**4o**	56
16	4-FC_6H_4–	3-$CF_3C_6H_4$–	2-Pentyl	**4p**	64
17	4-FC_6H_4–	4-FC_6H_4–	2-Pentyl	**4q**	58
18	4-FC_6H_4–	4-$(CH_3)_2CHC_6H_4$–	2-Pentyl	**4r**	67
19	4-FC_6H_4–	2-CH_3-4-$NO_2C_6H_3$–	2-Pentyl	**4s**	59
20	C_6H_5–	4-$CH_3OC_6H_4$–	2-Pentyl	**4t**	62
21	$(CH_3)_2CHCH_2$–	4-$CH_3OC_6H_4$–	2-Pentyl	**4u**	65
22	4-$NO_2C_6H_4$–	4-$CH_3OC_6H_4$–	2-Pentyl	**4v**	52
23	$C_6H_5C_2H_4$–	4-$CH_3OC_6H_4$–	2-Pentyl	**4w**	55
24	2-Benzofuran	4-$CH_3OC_6H_4$–	2-Pentyl	**4x**	58
25	4-$CH_3OC_6H_4$–	4-$CH_3OC_6H_4$–	2-Pentyl	**4y**	62

Table 3
Synthesis of α-amino amidines



1 2 3 4 5

Entry	R_1	R_2	R_3	**4**, Yield%	**5**, Yield%
1	C_6H_5–	4-$CH_3OC_6H_4$–	*t*-Butyl	(**4a**) 20	(**5a**) 60
2	C_6H_5–	4-$(CH_3)_3CC_6H_4$–	*t*-Butyl	(**4.2**) 13	(**5.2**) 56
3	C_6H_5–	4-Br-C_6H_4–	*t*-Butyl	(**4.3**) 17	(**5.3**) 28
4	C_6H_5–	3-Br-C_6H_4–	*t*-Butyl	(**4.4**) 23	(**5.4**) 25
5	C_6H_5–	4-$NO_2C_6H_4$–	*t*-Butyl	(**4.5**) 9	(**5.5**) 7
6	4-FC_6H_4–	4-$CH_3OC_6H_4$–	*n*-Butyl	(**4b**) 16	(**5b**) 57
7	4-FC_6H_4–	4-$CH_3OC_6H_4$–	2-Pentyl	(**4i**) 18	(**5i**) 57
8	C_6H_4–	4-$CH_3OC_6H_4$–	2-Pentyl	(**4t**) 17	(**5t**) 59
9	$C_6H_5CH_2CH_2$–	4-$CH_3OC_6H_4$–	*t*-Butyl	(**4.9**) 20	(**5.9**) 62

nucleophile (path A) generating compound **4** as the major product. However, when 2 equiv of amine is used, the concentration of amine is higher and the amine molecule competes with the water molecule for the nucleophilic addition reaction (path B). In this case, if the nucleophilicity of the amine is high, such as *p*-anisidine, we obtain compound **5** as the major product (Scheme 2).[14] However, if the nucleophilicity of the amine is low, such as *p*-nitro aniline, we obtain compound **4** as the major product even with excess amine.

Interestingly, *p*-toluenesulfonic acid (*p*TSA) yielded no product using the same reaction conditions. This is likely due to instability of the sulfonate version of intermediate **11** (Scheme 2). PTSIA has rarely been used in organic synthesis as a catalyst. This work suggests that *p*-toluenesulfinic acid may be useful in many other reactions that require an acid catalyst.

In summary, we have developed a mild and efficient method (the *p*TSIA-catalyzed three-component Ugi-type reaction) to generate α-amino amides and amidines. Product **4** is formed in good yield with readily available substrates and catalyst. When 2 equiv of *p*-anisidine is used, compound **5** is obtained in good yield. The broad scope of the reaction is operational simplicity, practicability, and mild reaction conditions rendering it an attractive approach for the generation of different α-amino amides and α-amino amidines. Further studies are in progress to use the functionalized amino amides for the synthesis of natural and unnatural amino acids.

Acknowledgments

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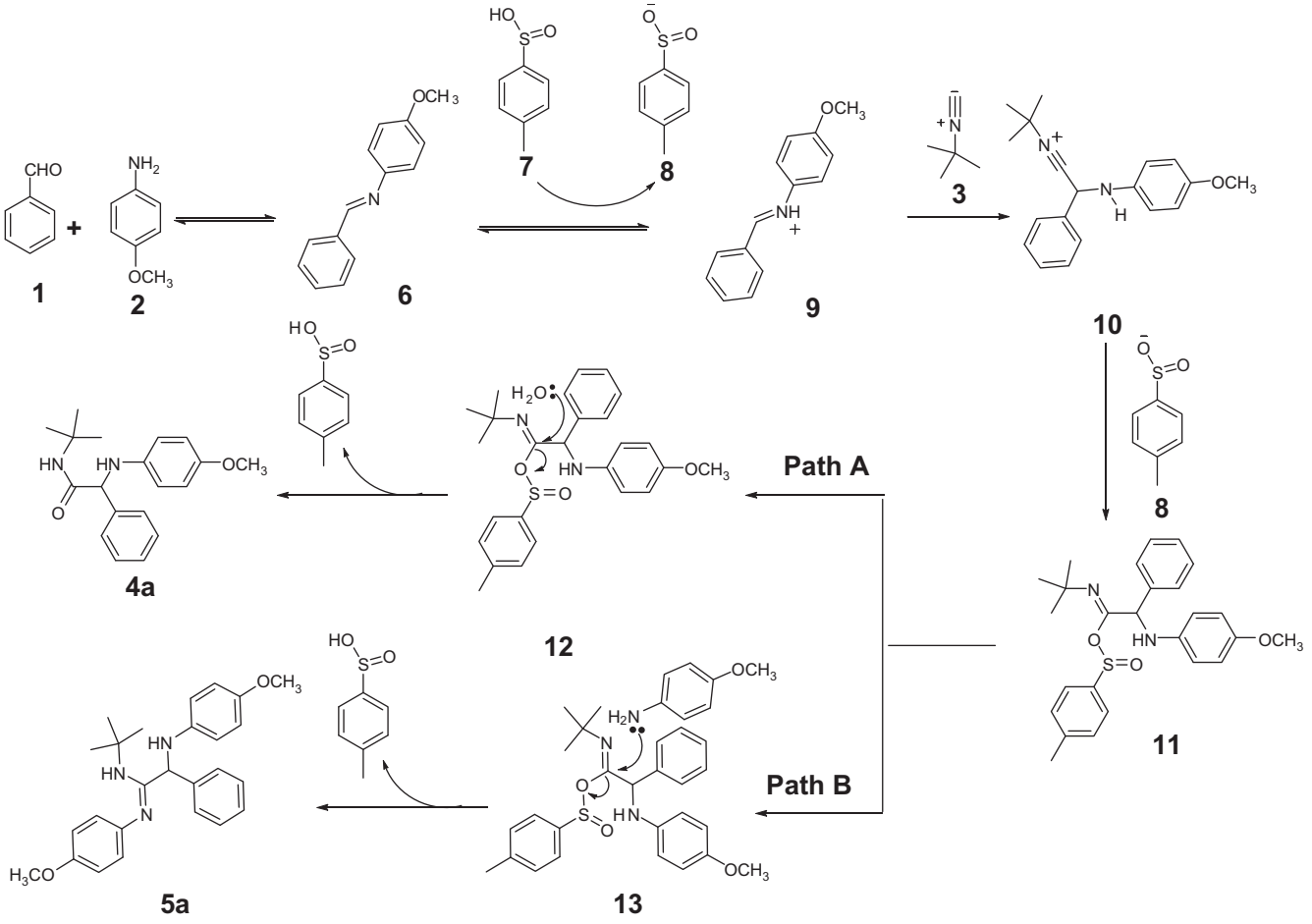

Scheme 2. Plausible reaction mechanism

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13. *General experimental procedure for the synthesis of **4**:* To a solution of aldehyde 1 (1 mmol) in methanol, amine **2** (1 mmol), isocyanide **3** (1 mmol), and catalyst *p*TSIA (20 mol %) were added into a flask. Then the reaction mixture was stirred for 12–24 h at rt (monitored by TLC and LCMS until no further increase in the ratio of the desired product vs starting materials). After completion of reaction the solvent was removed under vacuum to get a crude residue. The crude residue was purified by silica gel column chromatography using (10–30%) ethylacetate–hexane to get the pure product **4**.
*Example **4a**:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.29 (m, 5H), 6.84–6.73 (m, 2H), 6.68 (s, 1H), 6.63–6.54 (m, 2H), 4.52 (s, 1H), 4.18 (s, 1H), 3.75 (s, 3H), 1.32 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 153.2, 140.9, 139.4, 129.1, 128.4, 127.3, 115.1, 114.8, 65.8, 55.7, 51.0, 28.6. HRMS-ESI $(M+1)^+$: *m*/*z* calcd for $C_{19}H_{25}N_2O_2$ 313.19105, found 313.19083.
14. *General experimental procedure for the synthesis of **5**:* To a solution of aldehyde **1** (1 mmol) in methanol, amine **2** (2 mmol), isocyanide **3** (1 mmol), and *p*TSIA (20 mol %) were added into a flask. Then the reaction mixture was stirred for 12–24 h at rt (monitored by TLC and LCMS until no further increase in the ratio of the desired product vs starting materials). After the completion of reaction the solvent was removed under vacuum to get a crude residue. The crude residue was purified by silica gel column chromatography using (10–30%) ethylacetate–hexane to get the pure product **5**.
*Example **5a**:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.21 (m, 3H), 7.15 (dd, J = 6.5, 2.9 Hz, 2H), 6.88–6.77 (m, 2H), 6.68–6.54 (m, 4H), 6.46–6.32 (m, 2H), 6.00 (s, 1H), 4.86 (s, 1H), 3.77 (s, 3H), 3.71 (s, 3H), 3.51 (s,1H), 1.46 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.8, 154.4, 153.2, 144.0, 141.3, 140.1, 128.7, 128.1, 128.0, 122.9, 114.9, 114.7, 113.9, 60.5, 55.7, 55.5, 50.8, 28.4. HRMS-ESI $(M+1)^+$: *m*/*z* calcd for $C_{26}H_{32}N_3O_2$ 418.24890, found 418.24861. The detailed information on X-ray analysis of compound **5a** will be reported in *Acta Crystallogr. E*.