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Four component reaction of aldehydes, isocyanides, Me_3SiN_3, and aliphatic alcohols catalyzed by indium triflate

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ABSTRACT

In the presence of catalytic amount of indium(III) Lewis acids, the four component reaction of aldehydes, isocyanides, trimethylsilyl azide and aliphatic alcohols smoothly proceeded to give alkoxylated 1*H*-tetrazole products in good yields. In particular, $In(OTf)_3$ and $In(ONf)_3$ showed notably high level of catalytic activity in this reaction.

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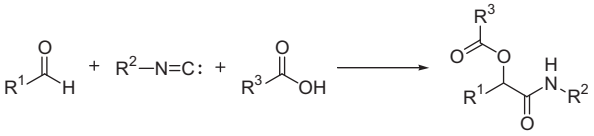
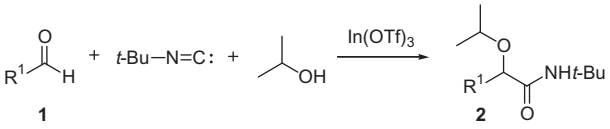
Isocyanide based multi-component reactions (MCRs) are known as powerful strategies to synthesize compounds with structural diversity.[1] One of the most well-known examples of isocyanide based MCRs is the reaction of aldehydes, isocyanides and carboxylic acids (Eq. 1).[2] This reaction, so-called Passerini three component (P3C) reaction, becomes a key methodology to prepare α-acyloxyamides.[3] In general, the replacement of a reaction component in MCRs to a substrate having different reactive functionalities provides a potential synthetic approach toward a new class of compounds, which cannot be obtained by established MCRs.[4] Therefore, recent progress of isocyanide based MCRs using alcoholic component has attracted much attention from synthetic chemists. For example, El Kaim and co-workers reported that, in the presence of nitrophenols instead of carboxylic acids, the reaction of aldehydes with isocyanides gave α-aryloxyamide products in moderate to good yields (arylative P3C reaction).[5] Recently, the successful replacement of the carboxylic acid component with silyl ethers[6] and silanols[7] was also developed. Related to these studies, we reported that indium(III) triflate [$In(OTf)_3$] nicely catalyzes the three component reaction of aldehyde **1**, isocyanide, and free aliphatic alcohol giving rise to α-alkoxyamide product **2** in good yield (direct *O*-alkylative P3C reaction) (Eq. 2).[8] While the classical P3C reaction is often carried out in alcoholic solvents under acidic conditions, the formation of α-alkoxyamides had not been reported for a long time.[9] Our investigation clearly shows that chemically stable, soft, and mild Lewis acids such as $In(OTf)_3$ perform as suitable catalysts to develop new isocyanide based MCRs.[10]





As shown in Figure 1, direct alkylative P3C reaction is initiated by the $In(OTf)_3$-catalyzed carboxonium formation from aldehyde **1** and free aliphatic alcohol. Subsequent nucleophilic attack of isocyanide to the carboxonium ion **A** gives nitrilium intermediate **B**.[11] Since the adduct **C** could not be isolated from the reaction mixture, amide product **2** would then be formed via hydrolysis of **B** or decomposition of **C**.[6a] On the basis of this reaction pathway, we thought that irreversible addition of a fourth reaction component would provide a novel class of products. It is easily expected that the fourth reaction component should have higher reactivity compared to water, but at the same time the reaction of this component with carboxonium intermediate **A** has to be so slow or reversible under the reaction conditions. Keeping these issues in our mind, we adopted azide ion as an acceptable reaction component. Ugi and Meyr reported that the reaction of aldehydes,

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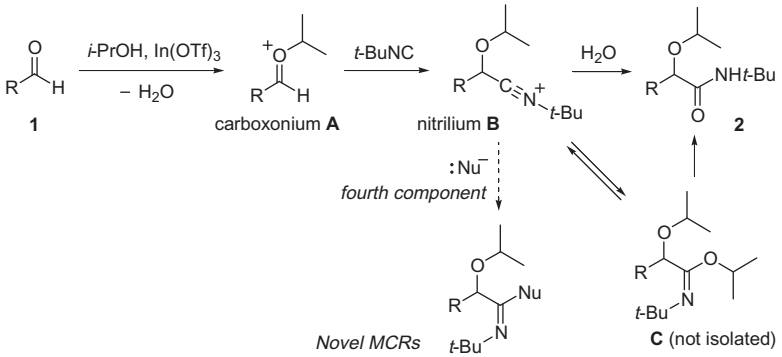


Figure 1. Reaction pathway of direct alkylative P3C reaction and working hypothesis for novel MCRs.

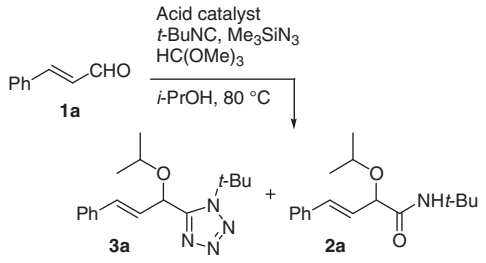
isocyanides, and hydrazoic acid instead of carboxylic acid component gives 1*H*-tetrazoles via irreversible 1,3-dipolar cycloaddition of hydrazoic acid to the nitrilium intermediate.[12–14] We also reported that the aliphatic acetals can be reversibly converted into the corresponding α-azido ethers by treating with trimethylsilyl azide and a catalytic amount of $In(OTf)_3$.[15]

Herein we describe that, in the presence of In(III) Lewis acid catalysts, the reaction of aldehydes, isocyanides, and trimethylsilyl azide in alcoholic solvents smoothly proceeds to give highly substituted 1*H*-tetrazoles as the four component reaction products in good yields. Furthermore, the intramolecular version using mixed acetals as a ω-hydroxy aldehyde equivalent also yielded 1*H*-tetrazole products containing a cyclic ether structure in good to excellent yields.

Initially, we examined the reaction of cinnamaldehyde, *tert*-butyl isocyanide, and trimethylsilyl azide in propan-2-ol as a model reaction. Selected results are shown in Table 1. In the presence of 10 mol % of $In(OTf)_3$, reaction of cinnamaldehyde **1a**, 2 equiv of *tert*-butyl isocyanide, 4 equiv of trimethylsilyl azide, and 1 equiv of trimethyl orthoformate in propan-2-ol produced the amide **2a** as the alkylative P3C product in moderate yield along with a small amount of the desired tetrazole **3a** (entry 1). Interestingly, the yield of **3a** was improved by decreasing the loading of $In(OTf)_3$ (entries 2–4). Indeed, the tetrazole **3a** was obtained in 78% yield by using only 2 mol % of $In(OTf)_3$ and the catalyst loading can be reduced to 1 mol % without the notable decrease in the product yield (entries 3 and 4).[16,17] In these cases, *tert*-butyl isocyanide was added in two parts for effective consumption of aldehyde substrate. When *tert*-butyl isocyanide was added in one portion, poor conversion of aldehydes was observed due to competitive hydrolysis of isocyanide. After further investigations, we found that $In(ONf)_3$ (Nf = n-$C_4F_9SO_2$) shows the similar catalyst activity, but $InCl_3$ results in poor conversion of the starting materials (entries 5 and 6). This result demonstrates that strong Lewis acidity plays a crucial role for the smooth conversion of starting materials. In addition, other metal triflates such as $Al(OTf)_3$, $Sc(OTf)_3$, $Yb(OTf)_3$, and $Bi(OTf)_3$ were not good catalysts for the present reaction (entries 7–10) and the reaction in the absence of any metal triflates resulted in no formation of tetrazole product **3a** (entry 11).[18] Since In(III)-isocyanide complexes favorably dissociated to free isocyanides at high reaction temperature, it is not surprising that In(III) salt works as a suitable Lewis acid catalyst for this reaction system.[19]

To determine the scope of this four component synthesis, we conducted the reactions of several aldehydes under the optimized conditions (Table 2). In the presence of 2.0 mol % of $In(OTf)_3$, the reaction of crotonaldehyde **1b**, *tert*-butyl isocyanide, and trimethylsilyl azide afforded tetrazole **3b** in 61% yield (entry 1). Likewise, tetrazole **3c** was obtained in 49% yield by the reaction of hex-2-enal **1c** (entry 2). Aromatic aldehydes such as benzaldehyde **1d**, 4-substituted benzaldehyde derivatives **1e**–**1f**, and 2-naphthaldehyde **1g** were the nice reaction components to give the corresponding tetrazoles **3d**–**3g** in good yields (entries 3–6).[20] This reaction could be applied to not only *tert*-butyl isocyanide but also secondary and primary alkyl isocyanides. For example, the reaction of cinnamaldehyde **1a** with isopropyl isocyanide in propan-2-ol afforded the 1-isopropyl-1*H*-tetrazole **3i** in 68% yield under similar conditions (entry 8). In addition, the reactions with cyclohexyl isocyanide and with benzyl isocyanide gave the corresponding tetrazoles **3j** and **3k** in good yields, respectively (entries 9 and 10). In contrast, the reaction with less nucleophilic 2,6-dichlorophenyl isocyanide resulted in selective formation of the corresponding amide in moderate yield. We also examined the reactions in several alcoholic solvents. By the reactions in secondary alcohols such as cyclopentanol and cyclohexanol, the corresponding products **3m** and **3n** were obtained in 61% and 60% yields, respectively (entries 11 and 12). The structure of cyclopentyloxy derivative **3m** was also confirmed by an X-ray crystallographic analysis (Fig. 2). Likewise, the reactions in primary alcohols such as ethanol, propanol, and 2-methylpropan-1-ol smoothly gave the tetrazole products **3o**–**3q** in good yields in each case (entries 13–15).

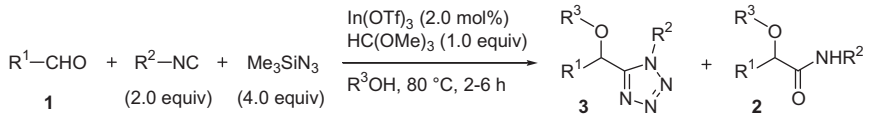
Table 1
Survey of effective acid catalysts[a]



Entry	Acid catalyst (mol%)	Yield[b] **3a** (%)	**2a** (%)
1	$In(OTf)_3$ (10)	18	40
2	$In(OTf)_3$ (5.0)	49	30
3	$In(OTf)_3$ (2.0)	78	15
4	$In(OTf)_3$ (1.0)	77	12
5	$In(OTf)_3$ (2.0)	72	10
6	$InCl_3$ (2.0)	57	<5
7	$Al(OTf)_3$ (2.0)	34	<5
8	$Sc(OTf)_3$ (2.0)	51	<5
9	$Yb(OTf)_3$ (2.0)	55	<5
10	$Bi(OTf)_3$ (2.0)	37	<5
11	None	0	0

[a] Reaction conditions: **1a** (1.5 mmol), *t*-BuNC (2.0 equiv), Me_3SiN_3 (4.0 equiv), $HC(OMe)_3$ (1.0 equiv), *i*-PrOH (6.0 mL), 80 °C, 2–5 h. *t*-BuNC was added in two portions.
[b] Isolated yield.

Table 2
Four component synthesis of 1*H*-tetrazoles[a]



Entry	1	R^1	R^2	R^3		Yield[b] (%)		
1	**1b**	CH=CHMe	*t*-Bu	*i*-Pr	**3b**	61	**2b**	6
2	**1c**	CH=CH*n*-C_3H_7	*t*-Bu	*i*-Pr	**3c**	49	**2c**	3
3[c]	**1d**	Ph	*t*-Bu	*i*-Pr	**3d**	70	**2d**	7
4[c]	**1e**	4-$MeOC_6H_4$	*t*-Bu	*i*-Pr	**3e**	62	**2e**	3
5[c]	**1f**	4-MeC_6H_4	*t*-Bu	*i*-Pr	**3f**	74	**2f**	8
6[c]	**1g**	2-Naphthyl	*t*-Bu	*i*-Pr	**3g**	72	**2g**	7
7	**1a**	CH=CHPh	CMe_2CH_2*t*-Bu	*i*-Pr	**3h**	45	**2h**	Trace
8	**1a**	CH=CHPh	*i*-Pr	*i*-Pr	**3i**	68	**2i**	Trace
9	**1a**	CH=CHPh	*c*-Hex	*i*-Pr	**3j**	64	**2j**	3
10	**1a**	CH=CHPh	Bn	*i*-Pr	**3k**	60	**2k**	5
11[d]	**1a**	CH=CHPh	*t*-Bu	*c*-C_5H_9	**3m**	61	**2m**	4
12[d]	**1a**	CH=CHPh	*t*-Bu	*c*-C_6H_{11}	**3n**	60	**2n**	5
13[d]	**1a**	CH=CHPh	*t*-Bu	Et	**3o**	64	**2o**	Trace
14[d]	**1a**	CH=CHPh	*t*-Bu	*n*-Pr	**3p**	58	**2p**	Trace
15[d]	**1a**	CH=CHPh	*t*-Bu	*i*-Bu	**3q**	63	**2q**	Trace

[a] Isocyanides were added in two portions.
[b] Isolated yield.
[c] 2.5 mol % of $In(OTf)_3$ and 4.0 equiv of *t*-BuNC were used.
[d] 6.0 mol % of $In(OTf)_3$ was used.

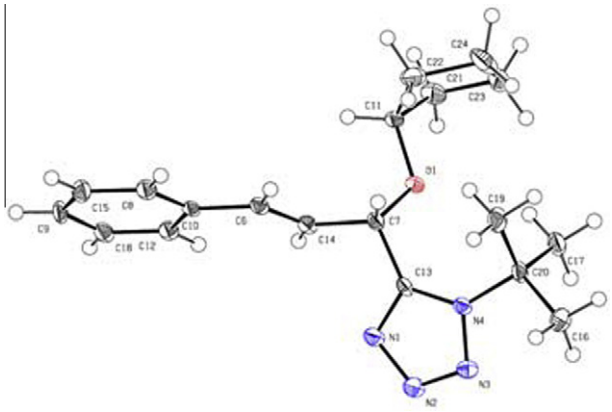
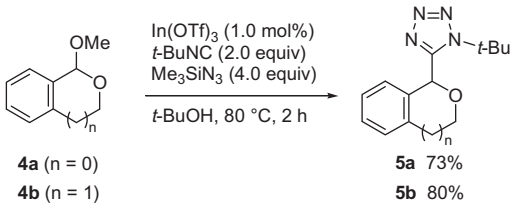


Figure 2. ORTEP drawing from X-ray crystallography of **3m**.



Scheme 1. Intramolecular type reaction of cyclic acetals.

As shown in Scheme 1, intramolecular version of this reaction also successfully proceeded. For example, the reaction of mixed acetal **4a**, *tert*-butyl isocyanide, and trimethylsilyl azide was nicely catalyzed by 1.0 mol % of $In(OTf)_3$ to give the desired tetrazole **5a** in 73% yield. In this case, it should be noted that the addition of orthoformate was not required and the corresponding amide product was not obtained. Under the same conditions, six-membered product **5b** was obtained in 80% yield from **4b**.

As shown in Figure 1, the present reaction would be initiated by $In(OTf)_3$-catalyzed carboxonium formation from aldehyde **1** and free aliphatic alcohol.[21] By subsequent addition of isocyanide to carboxonium ion **A**, nitrilium intermediate **B** is formed. Then, stepwise 1,3-dipolar cycloaddition of hydrazoic acid, which is generated by alcoholysis of trimethylsilyl azide, to nitrilium **B** would yield tetrazole product **3**. Considering the relationship between catalyst loading and tetrazole/amide selectivity, we believe that a small loading of $In(OTf)_3$ plays an important role to inhibit the decomposition of intermediate **C** to amide product **2**. Thus, since the use of relatively large amount of $In(OTf)_3$ results in rapid decomposition of **C** to amide **2**, the yield of tetrazole was improved by decreasing the loading of $In(OTf)_3$. Actually, the reaction of benzaldehyde dimethyl acetal, *tert*-butyl isocyanide, and trimethylsilyl azide in propan-2-ol gave an essentially same result (**3d**, 67% yield; **2d**, 6% yield) compared to the reaction of benzaldehyde (Table 2, entry 3). This fact also supports that amide **2** is competitively formed via the decomposition of intermediate **C**.

In summary, we rationally developed the four component reaction of aldehydes, isocyanides, trimethylsilyl azide, and free aliphatic alcohols. On the basis of this reaction, 1*H*-tetrazoles with structural diversity were easily synthesized. In the protic reaction media, $In(OTf)_3$ and $In(ONf)_3$ worked as suitable catalysts. In addition, the In(III) salts can be used as Lewis acids in the presence of relatively basic isocyanides. These results also suggest that chemically stable, soft, and mild In(III) Lewis acids perform as good catalysts for the isocyanide based MCRs. Further studies on this reaction are in progress in our laboratory.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.04.046.

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16. To a solution of cinnamaldehyde **1a** (198 mg, 1.50 mmol), $HC(OMe)_3$ (237 μL, 1.50 mmol), and $In(OTf)_3$ (17.0 mg, 0.03 mmol, 2 mol%) in propan-1-ol (6.0 mL), *t*-BuNC (165 μL, 1.50 mmol) and Me_3SiN_3 (796 μL, 6.00 mmol) were added at room temperature. After being stirred at 80 °C for 1 h, additional isocyanide (165 μL, 1.50 mmol) was reacted for 1 h at the same temperature. The reaction mixture was directly evaporated and the resulting residue was purified by flash column chromatography on neutral silica gel (hexane/EtOAc = 10:1) to give (*E*)-1-*tert*-butyl-5-(1-isopropoxy-3-phenylallyl)-1*H*-tetrazole **3a** in 78% yield (350.8 mg, 1.17 mmol). Colorless crystals (EtOAc); Mp. 40.0–41.0 °C; IR (KBr) ν 3083, 3028, 2976, 1599, 1496, 1093 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (3H, d, *J* = 6.0 Hz) and 1.23 (3H, d, *J* = 6.0 Hz), 1.79 (9H, s), 3.91 (1H, septet, *J* = 6.0 Hz), 5.68 (1H, d, *J* = 6.7 Hz), 6.57 (1H, dd, *J* = 16.1, 6.7 Hz), 6.65 (1H, d, *J* = 16.1 Hz), 7.25–7.29 (1H, m), 7.30–7.37 (2H, m), 7.43 (2H, d, *J* = 8.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6 and 23.0, 30.1, 62.1, 69.9, 71.5, 126.3, 126.9, 128.5, 128.7, 134.3, 135.6, 154.2; MS (ESI-TOF) *m*/*z* 301 $[M+H]^+$; HRMS calcd for $C_{17}H_{25}N_4O$ $[M+H]^+$, 301.2028; found, 301.2052. Anal. Calcd for $C_{17}H_{24}N_4O$: C, 67.97; H, 8.05; N, 18.65. Found: C, 67.82; H, 8.00; N, 18.50.
17. The use of sodium azide instead of trimethylsilyl azide resulted in the selective formation of amide **2a**. When 2 equiv of trimethylsilyl azide was used, tetrazole **3a** was also obtained in only 52% yield along with the formation of amide **2a** in 21% yield.
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20. Since the reaction of 3-phenylpropanal as an aliphatic aldehyde substrate gave a complex mixture, we could not isolate the desired tetrazole.
21. The addition of trimethyl orthoformate possibly accelerates the formation of carboxonium ion **A**, and at the same time, it inhibits the hydrolysis of nitrilium ion **B**.