

Direct Passerini Reaction of Aldehydes, Isocyanides, and Aliphatic Alcohols Catalyzed by Bismuth (III) Triflate

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Abstract

Bismuth (III) triflate was found to be effective Lewis acid catalyst for direct alkylative Passerini reaction of aldehydes, isocyanides, and aliphatic alcohols. In the present reaction, α -unsaturated and aromatic aldehydes used as substrates produced the corresponding α -alkoxy amide products in good yield.

Keywords: Passerini reaction, Lewis acid catalyst, α -alkoxy amide, Bismuth (III) triflate

1. Introduction

Multicomponent reactions (MCRs), due to their productivity, simple procedures, significant advantages over conventional linear-type syntheses, and facile execution, are one of the best tools in combinatorial chemistry (Zhu, J. et. al 2005, Dömling, A. et. al 2000). Therefore, the design of novel MCRs has attracted great attention from research groups working in medicinal chemistry, drug discovery, and materials science. Isocyanide-based multicomponent reactions are used extensively in target oriented and diversity oriented organic synthesis (Dömling, A., 2006). The most widely known and best characterized isocyanide-based multicomponent reaction is the Passerini three-component reaction (P-3CR). In the Passerini 3CR, an isocyanide, a carboxylic acid, and either an aldehyde or a ketone react with one another to yield an α -acyloxycarboxamide (Dömling, A. et. al 2006). But the use of phenol or aliphatic alcohol derivatives instead of a carboxylic acid component has not been realized until recently. *O*-arylate Passerini-type reaction (El Kaim, L. et. al 2006, El Kaim, L. et. al 2007) was reported by the using *O*-nitrophenol derivatives in 2006, which have a more acidic proton compared to aliphatic alcohols. On the other hand, Chatani and co-workers (Tobisu, M. et. al 2007, Yoshioka, S. et. al 2005) reported that the reaction of benzaldehyde, isocyanide, and silyl-protected aliphatic alcohol can be catalyzed by triflic acid to give α -alkoxy amides in moderate yield. But the direct Passerini reaction using aliphatic alcohol derivatives instead of carboxylic acid components are still unsolved and the corresponding researches are less found. Yanai group have reported that direct alkylative Passerini reaction of aldehydes, isocyanides, and free aliphatic alcohols catalyzed by Indium triflate

(Yanai, H. et. al 2009). Therefore, the development of direct Passerini three-component type reaction of aldehydes, isocyanides, and aliphatic alcohols is still very necessary.

Bismuth (III) triflate is known as mild, soft, chemically stable Lewis acid, and used widely for condensation (Matsushita, Y. et. al 2005, Yadav, J. S. et. al 2006), addition (Ollevier, T. et. al 2009, Ollevier, T. et. al 2007), rearrangement (Ollevier, T. et. al 2006, Ollevier, T. et. al 2008) and multicomponent reactions (Ollevier, T. et. al 2003, Ollevier, T. 2006) as an effective catalyst in organic synthesis. In the present study, we were interested in the application of bismuth (III) triflate Lewis acid to the direct P-3CR of aldehydes, isocyanides, and aliphatic alcohols at reflux in THF providing to the corresponding α -alkoxy amide products (Figure 1).

To explore the effective Bismuth (III) triflate for direct O-alkylative P-3CR reaction and optimize the reaction condition, our initial attempts to examine the reaction of benzaldehyde, *tert*-butyl isocyanide and 2-propanol in THF with Bi(OTf)₃ as catalyst. In the presence of 20 mol % Bi(OTf)₃, the reaction of benzaldehyde with 1.0 molar equiv of *tert*-butyl isocyanide and 2-propanol at reflux for 10 h gave alkylative Passerini product in 40 % yield, and the product yield improved to 53% when *tert*-butyl isocyanide was added to 2.0 molar equiv. Moreover, the stepwise addition of *tert*-butyl isocyanide in reaction mixture dramatically increased the product yield. For example, in the presence of 20 mol % of Bi(OTf)₃, benzaldehyde was reacted with 1.0 molar equiv of *tert*-butyl isocyanide at reflux for 10 h, then further treatment by additional 1.0 molar equiv of *tert*-butylisocyanide in THF gave the corresponding product at reflux for 10 h in 75% yield.

Secondly, we checked the reaction with various aldehydes under the optimized conditions, the results exhibited the reactions with aromatic or α,β -unsaturated aldehydes to give alkylative Passerini product in good yield, such as, the reaction of cinnamaldehyde, *tert*-butyl isocyanide, and 2-propanol was nicely catalyzed by 20 mol % of Bi(OTf)₃ to give the corresponding α -isopropoxy alkylative amides 10 h in 82% yield. Under the same conditions, 2-naphthaldehyde and 2-furaldehyde gave Passerini products **4g** and **4h** in 73 and 78% yield, respectively. Unfortunately, with aliphatic aldehydes, the yield of O-alkylated products was not so good. For example, the reaction of cyclopentylaldehyde, *n*-propylaldehyde with *tert*-butyl isocyanide and 2-propanol, and produced the desired product **4i** and **4j** only in 50% and 44% yield.

Finally, we examined the reaction with various alcohols instead of 2-propanol, and this reaction also proceeded in secondary or primary alcohol. Under the same conditions, the reaction in cyclopentanol and cyclohexanol gave **4k** and **4l** in 72% and 67% yield, respectively. In general, the reactivity of primary alcohol such as *n*-butanol (**4m**) and *n*-propanol (**4n**) was lower than that of several secondary alcohols.

2. Experimental

In a typical procedure, a mixture of Bi(OTf)₃ (0.4 mmol, 20 mol %), aliphatic alcohol (2.0 mmol) in THF (30 ml), *t*-BuNC (2.0 mmol, 1.0 equiv) and aldehyde (2.0 mmol) were added. After being stirred at reflux for 10 h, the reaction mixture was treated by additional *t*-BuNC (2.0 mmol, 1.0 equiv) in THF (20 ml), and then stirred at reflux for 10 h. The resultant mixture was concentrated under reduced pressure and purified by column chromatography on silica gel and gave the corresponding direct alkylative Passerini products.

N-*tert*-Butyl-2-isopropoxy-2-phenylacetamide (**4a**) as a white crystal. Mp. 58.5~60.0 °C (57.5~59.0 °C^[8]); ¹H NMR (400 MHz, CDCl₃) δ 1.07 (3H, d, J = 6.2 Hz), 1.16 (3H, d, J = 6.2 Hz), 1.29 (9H, s), 3.61 (1H, J = 6.1 Hz), 4.59 (1H, s), 6.62 (1H, brs, -NH), 7.18-7.30 (3H, m), 7.33-7.38 (2H, m); ¹³C NMR (100 MHz, CDCl₃) δ 22.3 and 22.9, 29.6, 51.3, 72.0, 81.1, 125.9, 127.4, 127.8, 139.1, 171.2; ESI-MS *m/z* 272([M+Na]⁺, 100%); Anal. Calcd for C₁₅H₂₃NO₂: C, 72.26; H, 9.29; N, 5.63. Found: C, 72.29; H, 9.20; N, 5.58.

N-*tert*-Butyl-2-(2-furyl)-2-isopropoxyacetamide (**4h**) ¹H NMR (400 MHz, CDCl₃) δ 1.18 (3H, d, J = 6.2 Hz), 1.23 (3H, d, J = 6.2 Hz), 1.42 (9H, s), 3.72 (1H, J = 6.2 Hz), 4.75 (1H, s), 6.28-6.34 (2H, m), 6.68 (1H, brs, NH), 7.33-7.37 (1H, m); ¹³C NMR (100 MHz, CDCl₃) δ 22.1, 22.8, 29.2, 51.8, 72.0, 73.8, 110.1, 110.8, 143.2, 151.8, 169.0; ESI-MS *m/z*: 262 ([M+H]⁺, 100%); Anal. Calcd for C₁₃H₂₁NO₃: C, 65.26; H, 8.85; N, 5.86. Found: C, 65.12; H, 8.91; N, 5.96.

3. Conclusion

In conclusion, we have developed a new and efficient method for the direct Passerini alkylative reaction of aldehydes, isocyanides, and aliphatic alcohols using aliphatic alcohols instead of a carboxylic acid component. In the present reaction, α -unsaturated and aromatic aldehydes used as nice substrates produced the corresponding α -alkoxy amide products in good yield. The present reaction is a highly useful method to construct the chemical library of α -alkoxy amide derivatives.

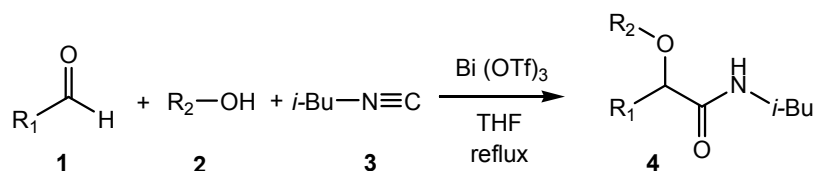
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Table 1. P-3CR of Aldehydes, Isocyanides, and Aliphatic Alcohols Catalyzed by Bi(OTf)₃

Product ^a	R ₁	R ₂	Yield (%) ^b
4a	Ph	<i>i</i> -Pr	75
4b	<i>p</i> -MeOPh	<i>i</i> -Pr	69
4c	<i>p</i> -BrPh	<i>i</i> -Pr	76
4d	<i>p</i> -MePh	<i>i</i> -Pr	72
4e	propenyl	<i>i</i> -Pr	78
4f	styryl	<i>i</i> -Pr	82
4g	2-naphthyl	<i>i</i> -Pr	73
4h	2-furyl	<i>i</i> -Pr	78
4i	cyclopentyl	<i>i</i> -Pr	50
4j	<i>n</i> -propyl	<i>i</i> -Pr	44
4k	Ph	cyclopentyl	72
4l	Ph	cyclohexyl	67
4m	Ph	<i>n</i> -butyl	38
4n	Ph	<i>n</i> -propyl	32

^aAll known compounds were characterized by comparing their spectral data with those reported; ^bIsolated yields

Figure 1. P-3CR of Aldehydes, Isocyanides, and Aliphatic Alcohols Catalyzed by Bi(OTf)₃