Direct Approach to Multi-substituted Pyrroles from 2-Propynylamine and 1,3-Diketone or β-Keto Ester Using $Bi(OTf)_3$ Catalyst

Kimihiro Komeyama,* Motoyoshi Miyagi, and Ken Takaki*
Department of Chemistry and Chemical Engineering, Graduate School of Engineering,
Hiroshima University, 1-4-1 Kagamiyama, Higashi-Hiroshima 739-8527

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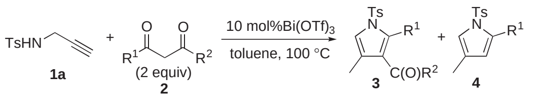
$Bi(OTf)_3$ was found to be a good catalyst for the direct synthesis of multisubstituted pyrroles from the readily accessible 2-propynylamine and activated methylene compounds in which the bismuth played two roles: σ- and π-activations.

New synthetic strategies for multisubstituted pyrroles are of continuous interest due to the ubiquity of this heterocycle in natural products[1] and pharmaceuticals.[2] For their construction, there are a number of classic methods and modified processes, such as the Paal–Knorr,[3] and Hantzsch syntheses.[4] Recently, these methods have been improved and partly altered into cyclizations such as hetero-annulation and cycloisomerization to achieve more complex pyrrole skeletons.[5] However, these methodologies typically require the initial synthesis of the correctly adjusted precursors prior to the cyclization, which makes structural modifications of substituted pyrroles complicate. Therefore, the development of more practical and efficient approaches to the pyrroles from readily available and easily diversified building blocks remains an active research area.[6] In this communication, we report a new direct synthesis of multisubstituted pyrroles from 2-propynylamine and 1,3-diketones and β-keto esters with a bismuth catalyst.[7]

When *N*-tosyl-2-propynylamine (**1a**) was treated with two equivalents of 2,4-pentanedione (**2a**) and $Bi(OTf)_3$ (10 mol %) in toluene at 100 °C for 9 h, the substituted pyrrole **3a** and **4a** were isolated in 74% total yield (**3a**/**4a** = 36/64) (Entry 1, Table 1). The high catalytic performance of the bismuth on the reaction was specific. Thus, any other Lewis acid catalysts like $BF_3\cdot OEt_2$, $AlCl_3$, $Sc(OTf)_3$, $La(OTf)_3$, $Zn(OTf)_2$, and TfOH showed negligible or no catalytic activities. Although complete conversions of **1a** were observed by means of noble metal catalysts, $PdCl_2$ and $PtCl_2$, insoluble white polymeric materials were obtained instead of the pyrrole. In contrast, $Fe(OTf)_{2or3}$, $Ni(OTf)_2$, and $Cu(OTf)_2$ catalysts were slightly effective for the transformation (3–12% yield of **3a** and **4a**). Another bismuth catalysts $Bi(ClO_4)_3$ was moderately active (38% yield), but $Bi(BF_4)_3$ was useless.[8] 1,2-Dichloroethane was suitable solvent as well as toluene, whereas tetrahydrofuran and acetonitrile prevented the reaction.

Next, we investigated the scope and limitation of the $Bi(OTf)_3$-catalyzed reaction of 2-propynylamine **1** with the active methylene compounds **2** (Entries 2–11, Table 1). With optimized conditions in hand,[9] the reaction with 1,3-diphenyl-1,3-propanedione (**2b**) provided the corresponding pyrroles in 64% total yield (**3b**/**4b** = 42/58) as well as with **1a** (Entry 2). Electron-deficient aromatic diketone **2c** was also permitted to participate at the transformation (Entry 3). Notably, electron-rich diketones, **2d** (R = $4\text{-}MeC_6H_4$) and **2e** (R = $4\text{-}MeOC_6H_4$), were mainly converted to the 3-acylpyrroles **3** (Entries 4 and 5).

Table 1. Direct synthesis of pyrroles **3** and **4** from the reaction of 2-propynylamine **1a** and various diketones and β-keto esters **2**

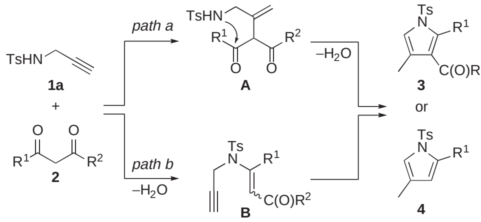


Entry	Ketone **2**			Time/h	Total yield
		R^1	R^2		(**3**/**4**)/%[a]
1	**2a**	Me	Me	9	74 (36/64)
2	**2b**	Ph	Ph	6	64 (42/58)
3	**2c**	$4\text{-}ClC_6H_4$	$4\text{-}ClC_6H_4$	6	57 (45/55)
4	**2d**	$4\text{-}MeC_6H_4$	$4\text{-}MeC_6H_4$	8	67 (54/46)
5	**2e**	$4\text{-}MeOC_6H_4$	$4\text{-}MeOC_6H_4$	6	58 (81/19)
6	**2f**	Me	OEt	6	55 (100/0)
7	**2g**	Ph	OMe	12	41 (100/0)
8	**2h**	Ph	OEt	10	55 (100/0)
9	**2i**	$4\text{-}ClC_6H_4$	OEt	6	34 (100/0)
10	**2j**	$4\text{-}MeC_6H_4$	OEt	12	54 (100/0)
11	**2k**	$2\text{-}MeC_6H_4$	OEt	12	36 (100/0)

[a]Isolated yield.

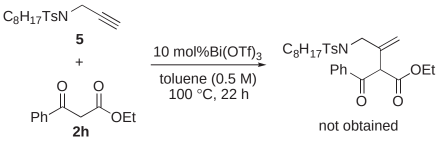
The present reaction could be applied to various β-keto esters (Entries 6–11). It is noteworthy that the reaction with β-keto esters afforded 3-acylpyrroles **3** only, albeit with slightly lower conversions to the product in comparison with the diketone. Unfortunately, the alternation of the terminal proton of the alkyne **1** with aryl and alkyl groups caused the substitution reaction of the TsNH moiety of **1** by the methylene compound **2**, exclusively. Additionally, when the protecting group on nitrogen was replaced to benzyl and H, no reaction was observed.

We envisioned two possible processes of the present reaction as illustrated in Scheme 1. In path a, the addition of the methylene compound **2** to the alkyne part of **1** would provide the intermediate **A**, whose amine and ketone functions would intramolecularly condensed to afford the pyrroles **3** and/or **4**, and H_2O. However, it seems less likely, because the C–C bond formation did not proceed in a similar reaction of **5** with **2h** under the present reaction conditions (eq 1). Another plausible process (path b), involves the formation of 3-aza-1,5-enyne **B** from the amine **1** and the methylene compound **2**,[10] which is followed

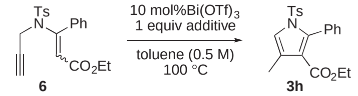


Scheme 1.

by the enyne-cycloisomerization and the subsequent olefinic isomerization to yield the desired pyrroles.[11] Evidence to support definitely the latter process was obtained in eq 2. When azaenyne (*E*)-**6**, independently prepared, was treated with $Bi(OTf)_3$ catalyst in the presence of one equivalent of water for 5 h at 100 °C, the product **3h** was obtained in 80% yield. It was noteworthy that the presence of water and the stereochemistry of **6** drastically affected the present reaction. Thus, the product yield decreased under anhydrous conditions and in the reaction of azaenyne (*Z*)-**6**.



(1)



(2)

E/*Z* ratio of **6**	Additive	Time / h	Yield / %
100/0	H_2O	5	80
100/0	none	17	37
67/33	H_2O	10	61
0/100	H_2O	22	21

Based on these results, we proposed the reaction mechanism in Scheme 2. In the initial step (i), the bismuth catalyst would act as a Lewis acid for the enamine formation to provide the metalated 3-aza-1,5-enyne **B**. In contrast, π-acidity of the same catalyst would accelerate the cycloisomerization of the enyne unit of **B** to give the zwitterion intermediate **C** (ii), which could spontaneously deprotonate or deacylate to liberate the two types of products and the catalyst (iii). In this step, the deprotonation could occur in the case of β-keto ester due to instability of $^{+}C(O)OR$. About effect of water, it might induce other pyrrole route via *N*,*O*-acetal **D**.

In conclusion, we have demonstrated a new method for the direct synthesis of multisubstituted pyrroles from simple 2-propynylamine and various 1,3-diketones or β-keto esters by the bismuth catalyst. The transformation depended on the presence of water generated in the initial step. Moreover, the stereochemistry of the 3-aza-1,5-enyne intermediate influenced the reaction efficiency, i.e., the E isomer was more active than the Z isomer.

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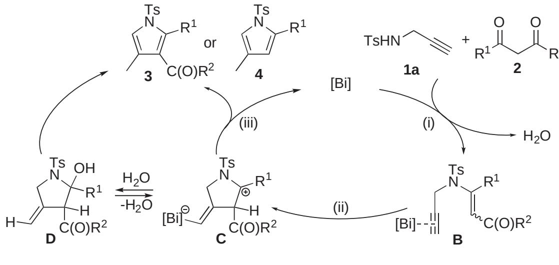

Scheme 2. Plausible reaction mechanism.

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8 $Bi(ClO_4)_3$ and $Bi(BF_4)_3$ were prepared in situ from the reaction of $BiCl_3$ and 3 equivalent of $AgClO_4$ and $AgBF_4$ at room temperature for 1 h, respectively. Detail on the catalyst screening was summarized in Table S1 (see Supporting Information).[12]

9 General procedure for synthesis of **3a** and **4a** catalyzed by $Bi(OTf)_3$: 2,4-Pentanedione (**2a**) (51.5 mg, 0.51 mmol) was added to a solution of *N*-tosyl-2-propynylamine (**1a**) (52.4 mg, 0.25 mmol) and $Bi(OTf)_3$ (16 mg, 24 µmol, 10 mol %) in anhydrous toluene (0.5 mL), and the reaction vial was sealed. After stirring at 100 °C for 9 h, the mixture was cooled to ambient temperature, passed through a short silica-gel column, and concentrated to leave the reddish black residue. Purification of the residue by column chromatography on silica gel (hexane/ethyl acetate = 20/1) gave pyrroles **3a** and **4a** as a yellow solid (Mp.: 85.0–86.0 °C, 20 mg, 27%) and a yellow oil (29 mg, 47%), respectively.

10 Bismuth-catalyzed formation of enamines from amines and ketones. See: A. R. Khosropour, M. M. Khodaei, M. Kookhazadeh, *Tetrahedron Lett.* **2004**, *45*, 1725.

11 Under the silver/gold catalyst system or microwave conditions, 3-hetero-1,5-enynes undergo the 2-propynyl-Claisen rearrangement to give the allene intermediate, which followed by sequent cyclization to afford the pyrrole skeleton different from the present products. See: Refs. 5a and 6b.

12 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

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