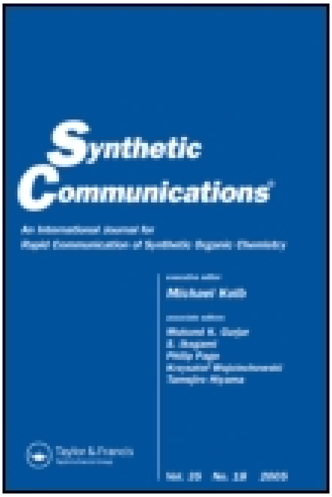

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Novel Process for Synthesis of 1,2,4-Triazoles: Ytterbium Triflate–Catalyzed Cyclization of Hydrazonyl Chlorides with Nitriles

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Abstract: A series of 1,3,5-trisubstituted 1,2,4-triazoles were synthesized via the intermolecular cyclization of hydrazonyl chlorides with nitriles catalyzed by ytterbium triflate [Yb(OTf)$_3$]. The amount of catalysis was discussed and Yb(OTf)$_3$ could be reused without loss of activity.

Keywords: Cyclization, hydrazonyl chlorides, nitriles, triazoles, ytterbium triflate

It is reported that 1,2,4-triazoles have been a topic of research interest because molecules with these structural features have been found to display a wide range of potent biological activities, such as antifungal[1] and antibacterial activities.[2] Because of the important biological properties of 1,2,4-triazole compounds, several kinds of methods have been reported for the preparation of triazoles. Initially most of the 1,2,4-triazoles were synthesized by the reaction of hydrazonyl chlorides with aromatic or aliphatic nitriles in the presence of $AlCl_3$.[3] Synthesis of 1,2,4-triazoles were accomplished by cyclization of 1,2,4-triazene employing oxidizing agents such as Ag_2CO_3,[4,5] H_2O_2/KOH,[6] NaClO, Ca(ClO)$_2$, Dess–Martin periodinane, and Ley's oxidizing agent (TPAP/NMO).[7] However, these methods required more than stoichiometric amounts of reagents and these reagents were difficult to

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handle. Therefore, it is necessary to explore a convenient and environmentally friendly method for the prepatation of 1,2,4-triazoles.

In recent years, Yb(OTf)$_3$ has attracted attention as catalyst for a wide range of reactions in organic synthesis.[8] A catalytic amount of Yb(OTf)$_3$ was enough to complete the reactions in most cases. It was demonstrated that the catalysts were easily recovered after the reaction and could be reused without loss of activity. Until now, there were no reports on the reaction of hydrazonyl chlorides and nitriles catalyzed by Yb(OTf)$_3$. Herein we report the preparation of 1,2,4-triazoles from hydrazonyl chlorides and nitriles in the presence of Yb(OTf)$_3$ (Scheme 1).

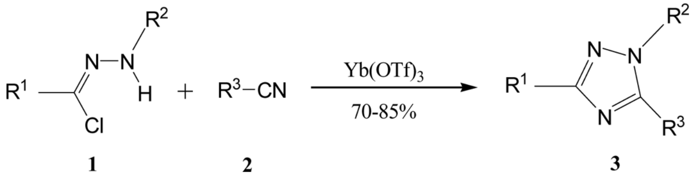
RESULTS AND DISCUSSION

Yb(OTf)$_3$, as a reusable Lewis acid, can catalyze the cyclizations of hydrazonyl chlorides with nitriles in chlorobenzene at reflux (Scheme 1). The results are summarized in Table 1.

As shown in Table 1, the reactions were run well with the catalytic amounts of Yb(OTf)$_3$. The yields were not obviously affected by different amounts of Yb(OTf)$_3$ 0.1 equiv. of catalyst was enough to complete the reaction (entries 2–4) and excessive amounts of Yb(OTf)$_3$ did not increase the yields. We also found that the reactions of aliphatic nitriles with hydrazonyl chlorides were quicker than that of aromatic nitriles (entries 2, 5–8). Furthermore, comparision of the yields (entries 4–7) shows that aliphatic nitriles got better results than aromatic nitriles under similar conditions. Unfortunately, when *p*-nitrobenzonitrile was used as substrate in the same conditions (entry 8), the desired product was not detected even for a long time. On the other hand, by prolonging the reaction time and increasing the reaction temperature, 1,3,4,6-tetraphenyl-1,4-dihydro-1,2,4,5-tetrazine was obtained.

In addition, we investigated the recycling of Yb(OTf)$_3$. It was found that the reaction proceeded smoothly with recovered Yb(OTf)$_3$ and gave good yields of the corresponding products. The results are summarized in Table 2.

In summary, in the presence of catalytic amount of Yb(OTf)$_3$, hydrazonyl chlorides can react with nitriles to obtain the corresponding 1,2,4-triazoles in good yields. Ten percent mol of ytterbium triflate is enough to complete the reaction, and it can be recovered and reused easily.



Scheme 1.

Table 1. Preparation of triazoles catalyzed by $Yb(OTf)_3$[a]

Entry	$Yb(OTf)_3$ (equiv.)	Time (h)	R^1	R^2	R^3	Product	Yield (%)[b]
1	None	4	C_6H_5	C_6H_5	CH_3	**3a**	ND[c]
2	0.1	4	C_6H_5	C_6H_5	CH_3	**3a**	82
3	0.5	4	C_6H_5	C_6H_5	CH_3	**3a**	85
4	1.0	4	C_6H_5	C_6H_5	CH_3	**3a**	84
5	0.1	4	C_6H_5	C_6H_5	$H_5C_2OOCCH_2$	**3b**	80
6	0.1	6	C_6H_5	C_6H_5	C_6H_5	**3c**	72
7	0.1	6	C_6H_5	C_6H_5	p-$H_3COC_6H_4$	**3d**	70
8	0.1	10	C_6H_5	C_6H_5	p-$O_2NC_6H_4$	—	ND[c]
9	0.1	4	C_6H_5	p-$O_2NC_6H_4$	CH_3	**3e**	80
10	0.1	6	C_6H_5	p-$O_2NC_6H_4$	C_6H_5	**3f**	70
11	0.1	4	C_6H_5	p-$O_2NC_6H_4$	$H_5C_2OOCCH_2$	**3g**	80
12	0.1	4	p-$H_3CC_6H_4$	C_6H_5	CH_3	**3h**	83

[a] The reaction were carried out using 1.2 equiv. of nitriles and 1 equiv. of hydrazonyl chlorides.

[b] Isolated yields based on hydrazonyl chlorides.

[c] Not detected.

Table 2. Catalyst recovery and its catalytic activity[a] using N-phenylbenzhydrazonyl chloride and acetonitrile

Use	Reaction time/h	Yield/%	Cat. recovered/%
1st	4	82	95
2nd	4	81	94
3rd	4	80	93
4th	4	80	94

[a] Recovered catalyst.

EXPERIMENTAL

^{1}H NMR spectra was recorded on a Varian-400 MHz instrument using $CDCl_3$ as the solvent with TMS as an internal standard. IR spectra was recorded on a AVATAR-370 Infrared Spectrophotometer. MS spectra was determined on a Thermo Finnigan LCQ-Advantage (ESI) instrument. Melting points were determined on a Digital Melting Point Apparatus WRS-1B and are uncorrected. Microanalysis was carried out on a Carlo-Erba 1106 instrument. All reactions were carried out under a dry nitrogen atmosphere. Hydrazonyl chlorides were synthesized by the literature procedure;[9] $Yb(OTf)_3$ was prepared from ytterbium oxide and trifluoromethanesulfonic acid in water according to the literature.[10] All reagents used are commercial available.

General Procedure for the Preparation of 1,3,5-Trisubstituted 1,2,4-Triazoles

Nitrile (2.4 mmol), $Yb(OTf)_3$ (0.2 mmol), hydrazonyl chloride (2 mmol), and dry chlorobenzene (10 mL) were subsequently added into a dry three-neck flask under nitrogen atmosphere. The reaction mixture was refluxed for 4 h and turned dark, then the mixture was washed with water (10 mL), the organic layer was isolated, and the aqueous layer was extracted by ethyl acetate (10 mL 3). $Yb(OTf)_3$ can be recovered by removing the water and can then be reused after recrystallization from CH_3CN/CH_2Cl_2. The combined organic layer was dried by anhydrous $MgSO_4$, filtered, and concentrated in vacuo, which was purified by preparative TLC (ethyl acetate–petroleum ether = 3:1) to obtain the product.

3a: Mp 92–93°C (Lit.[3], 95–96°C); IR (cm^{-1}) 1633, 1599, 1516, 1500, 1469, 1356, 1456, 1444, 1115; ^{1}H NMR ($CDCl_3$) ppm δ: 2.56 (3H, s, CH_3), 7.40–7.52 (8H, m, ArH), 8.14–8.16 (2H, m, ArH); MS (ESI) m/z: 236.2 ($M^+ + 1$).

3b: Mp 46–47°C (Lit.[3], 47°C); IR (cm^{-1}) 1746, 1599, 1500, 1446, 1397, 1370, 1335, 1260, 1197, 1097, 1027; ^{1}H NMR ($CDCl_3$) ppm δ:

1.27(3H, t, CH_3), 3.95 (2H, s, CH_2), 4.20–4.26 (2H, q, CH_2), 7.40–7.46 (6H, m, ArH), 7.51–7.55 (2H, m, ArH), 8.12–8.15 (2H, m, ArH); MS (ESI) *m/z*: 308.2 ($M^+ + 1$).

3c: Mp 102–103°C (Lit.[3], 103–104°C); IR (cm^{-1}) 1594, 1516, 1498, 1480, 1461, 1446, 1378; ^{1}H NMR ($CDCl_3$) ppm δ: 7.34–7.56 (11H, m, ArH), 7.62 (2H, m, ArH), 8.24–8.26 (2H, m, ArH); MS (ESI) *m/z*: 298.3 ($M^+ + 1$).

3d: Mp 105–106°C (Lit.[11], 105–106°C); IR (cm^{-1}) 1607, 1595, 1576, 1459, 1461, 1440, 1388; ^{1}H NMR ($CDCl_3$) ppm δ: 3.80 (3H, s, CH_3O), 6.94 (2H, m, ArH), 7.40–7.58 (10H, m, ArH), 8.22 (2H, m, ArH); MS (ESI) *m/z*: 328.3 ($M^+ + 1$).

3e: Mp 140–142°C (Lit.[6], 140–142°C); IR (cm^{-1}) 1633, 1599, 1516, 1499, 1469, 1444, 1342, 1115; ^{1}H NMR ($CDCl_3$) ppm δ: 2.71 (3H, s, CH_3), 7.46 (2H, d, J = 6.4, ArH), 7.59–7.63 (1H, m, ArH), 7.81 (2H, d, J = 8.6 Hz, ArH), 8.15 (2H, d, J = 6.4 Hz, ArH), 8.42 (2H, d, J = 8.6 Hz, ArH); MS (ESI) *m/z*: 281.1 ($M^+ + 1$).

3f: Mp 160–162°C (Lit.[6], 160–162°C); IR (cm^{-1}) 1595, 1517, 1480, 1461, 1446, 1379, 1338; ^{1}H NMR ($CDCl_3$) ppm δ: 7.42–7.53 (6H, m, ArH), 7.53 (2H, m, ArH), 7.57–7.62 (2H, m, ArH), 8.21 (2H, m, ArH), 8.22–8.25 (2H, m, ArH); MS (ESI) *m/z*: 343.2 ($M^+ + 1$).

3g: Mp 113–115°C; IR (cm^{-1}) 1736, 1612, 1597, 1469, 1528, 1500, 1447, 1345, 1212, 1174, 1112, 1026; 855,724; ^{1}H NMR ($CDCl_3$) ppm δ: 1.33 (3H, t, J = 7.2 Hz, CH_3), 4.11 (2H, s, CH_2), 4.28 (2H, q, J = 7.2 Hz, CH_2), 7.53–7.55 (3H, m, ArH), 7.92 (2H, q, J = 8.6 Hz, ArH), 8.21–8.23 (2H, q, ArH), 8.49 (2H, q, J = 8.6 Hz, ArH); MS (ESI) *m/z*: 353.1 ($M^+ + 1$); Anal. calcd. for $C_{18}H_{16}N_4O_4$: C, 61.36; H, 4.58; N, 15.90; found, C, 61.39; H, 4.53; N, 15.82.

3h: Mp 102–103°C (Lit.[12], 103–104°C); IR (cm^{-1}) 1599, 1514, 1500, 1455, 1400, 1346, 1112, 1020; ^{1}H NMR ($CDCl_3$) ppm δ: 2.39 (3H, s, CH_3), 2.57 (3H, s, CH_3), 7.25 (2H, d, J = 8.0 Hz, ArH), 7.45–7.52 (5H, m, ArH), 8.03 (2H, d, J = 8.0 Hz, ArH); MS (ESI) *m/z*: 250.2 ($M^+ + 1$).

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