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A VERSATILE AND ONE-POT STRATEGY TO SYNTHESIS OF 1,3,5-TRISUBSTITUTED-1,2,4-TRIAZOLES HAVING THE CYANO SUBSTITUTION

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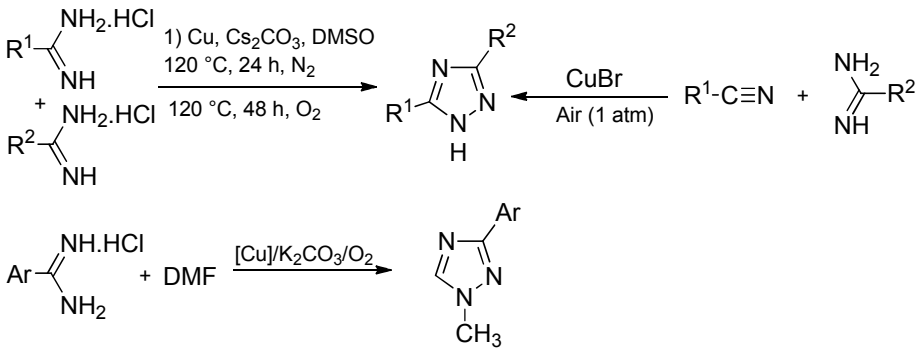
Abstract:
A concise method to synthesize 1,3,5-trisubstituted-triazoles from the 1,3-dipolar cycloaddition between hydrazonoyl chlorides and phthalonitrile in the presence of Et_3N in EtOH is described. This method has the following advantages: starting materials are easily available, the yields are good, it is simple to perform, the reaction conditions are mild, and no metal-catalyst is needed. The structures were confirmed spectroscopically (IR, ^{1}H- and ^{13}C-NMR, and EI-MS) and by elemental analyses. A plausible mechanism for this reaction is proposed.

Key words: Trisubstituted-triazoles, Hydrazonoyl chlorides, Phthalonitrile, 1,3-Dipolar cycloaddition, One-pot synthesis

Introduction

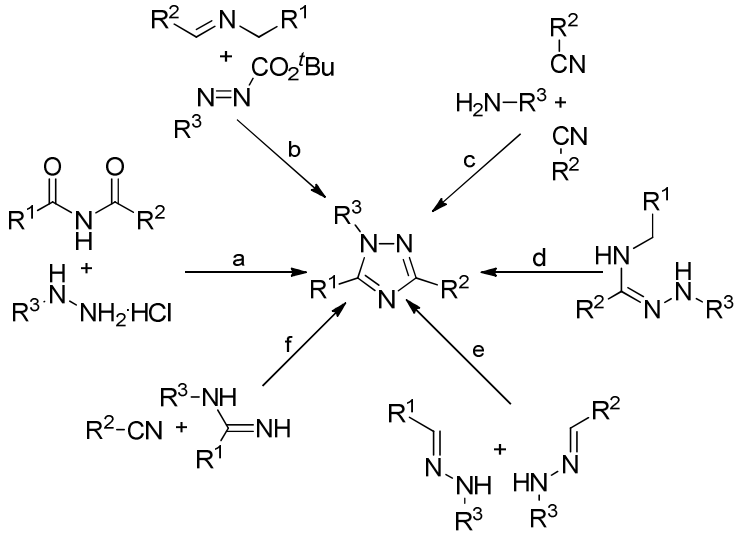
The development of procedures for the synthesis of 1,2,4-triazoles has received much attention recently, due to this class of compounds possessing one of the most important structures among heterocyclic compounds, which are often observed in many natural products,[I-II] agrochemicals,[III] pharmaceuticals,[IV-VI] and functional materials.[VII] 1,2,4-Triazoles have been widely used as anti-inflammatory,[VIII] antifungal,[IX] antibacterial,[X] antianxiety,[XI] and anticancer agents.[XII] On the other hand, 1,2,4-triazole derivatives are good molecular building blocks[XIII] and have gained attention for constructing coordination complexes with remarkable functions like spin crossover behavior.[XIV] Heteroleptic iridium (III) complexes having 1,2,4-triazole moiety provides a higher emission energy with interesting quantum yields for potential application in organic light emitting diodes.[XV]

Among various methods to prepare the 1,2,4-triazole skeletons, one particularly straightforward and atom economical process has been the use of transition-metal-catalyzed coupling of amidines with nitriles,[XVI] coupling and aerobic oxidative dehydrogenation of amidines,[XVII] condensation of amidines with a C1 source such as DMF (Scheme 1).[XVIII]



Scheme 1 Previous work for synthesis of 1,2,4-triazoles.

Cyclization reaction of *N*-acylated amide derivatives with various hydrazine hydrochlorides under microwave irradiation give 1,3,5-trisubstituted-1,2,4-triazoles (route a, Scheme 2).[XIX] Highly substituted 1,2,4-triazoles could be obtained from cycloaddition reactions of glycine imines and phenylazocarboxylates (route b, Scheme 2).[XX] 1,3,5-Trisubstituted triazoles are prepared from copper-mediated three-component reaction of one molecule of amine and two molecules of nitriles under microwave assistance (route c, *Scheme 2*).[XXI] Triazenes generated in situ from primary amines and hydrazonyl chlorides cyclized to 1,3,5-trisubstituted-1,2,4-triazoles in the presence of silver carbonate (route d, Scheme 2).[XXII] Punniyamurthy disclosed the efficient formation of 1,3,5-triaryl-1,2,4-triazoles *via* the copper(II)-catalyzed aerobic oxidative of bisarylhydrazones (route e, Scheme 2).[XXIII] Zhang *et al*. reported a copper catalyzed synthesis of trisubstituted 1,2,4-triazoles from amidines and nitriles through a N–H functionalization/N–N bond forming process (route f, Scheme 2).[XXIV] Despite the synthetic efficiency of these reactions, limitations related to formation of undesirable products, need for additive or strong base, the isolation of the activated reactant, expensive reagents, the use of toxic metals and solvents, long reaction times, and sensitivity to steric hindrance of starting materials are evident.



a) pyridine, MW (300 W, 200 °C)
b) i) DBu (1 equiv), ii) MnO_2 (2.5 equiv), iii) CF_3COOH
c) $Cu(OAc)_2$ (1 eq), 120 °C
d) Ag_2CO_3, CH_3CN, rt, 2 h,
e) i) DABCO, dioxane, 60 °C, 30 h. ii) $Cu(OH)_2.H_2O$ (10 mol %), rt, air, 1.5-7 h
f) $Cu(OAc)_2.H_2O$ (10 mol %), 1,10-Phen (0.1 eq), Na_2CO_3 (2 eq) toluene, air, 110 °C

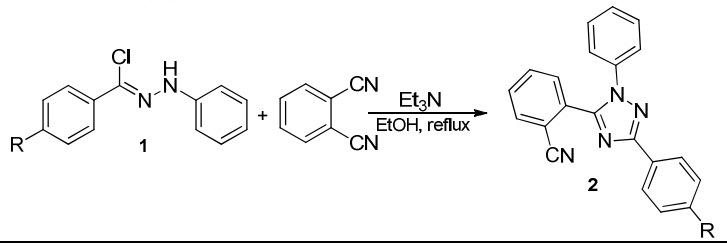
Scheme 2 Previous synthesis of 1,3,5-trisubstituted-1,2,4-triazoles.

Results and Discussion

Hence, developing a green approach to synthesize 1,3,5-trisubstituted-1,2,4-triazoles under mild conditions without the need of a strong base, additives or metal-catalysts is still meaningful. In continuation of our project on applying aryl hydrazonoyl chloride in synthesis of *N*-heterocyclic compounds, herein, we report a simple and efficient strategy to unsymmetrically 1,3,5-trisubstituted 1,2,4-triazoles from phthalonitrile and aryl hydrazonoyl chlorides. The phthalonitrile was chosen based on this factor that cyano functional groups are able to change to other functional groups.[XXV-XXVI] Our study commenced with cyclization reaction between phthalonitrile and phenyl hydrazonoyl chloride (**1a**) in the presence of different bases and in various solvents to search for the optimized conditions. Treatment of these substances in the presence of Et_3N in EtOH afforded the expected product **2a** in 74 % yield.

With the established optimal conditions, the scope of this one-pot reaction was examined by applying different hydrazonoyl chlorides (Table 1). The try for converting both cyano groups of phthalonitrile to triazoles was unsuccessful, probably due to hindrance effects. Also benzonitrile did not yield the product in this condition.

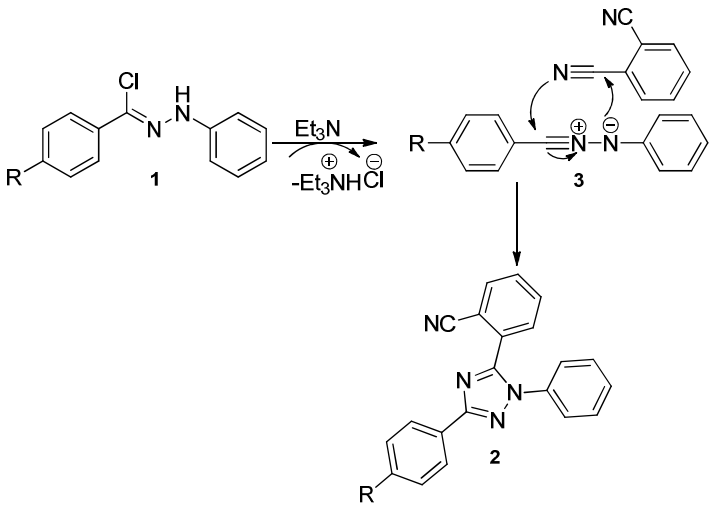
Table 1 Synthetic results of 1,3,5-trisubstituted 1,2,4-triazoles **2**



Entry	R	Product	Yield (%)
1	H	**2a**	74
2	Br	**2b**	57
3	Cl	**2c**	76
4	F	**2d**	73
5	Me	**2e**	68
6	OMe	**2f**	60

The structures of the resultant products **2** have been confirmed by IR, ^{1}H NMR, and ^{13}C NMR spectral analysis. In the IR spectrum of **2e** absorption bands at 2228 (C≡N) and 1650 (C=N) cm^{-1} are the most significant stretching frequencies. In ^{1}H NMR spectrum of **2e** a singlet at δ = 2.42 ppm is related to CH_3 group. A multiplet at δ = 7.34-7.41 ppm is ascribed to phenyl group. Other aromatic hydrogen atoms were appeared as three doublets at δ = 7.29, 7.73, and 8.14 ppm and a multiplet at δ = 7.53-7.66 ppm. Observation of 18 distinct signals in the ^{1}H-decoupled ^{13}C NMR spectrum of **2e** is in agreement with the proposed structure.

On the basis of our results, we propose the mechanism shown in Scheme 3. The nitrile imine **3** generated *in situ* by treating hydrazonoyl chloride **1** with Et_3N reacted with phthalonitrile *via* 1,3-dipolar cycloaddition reaction to furnish 1,3,5-trisubstituted-1,2,4-triazoles **2**.



Scheme 3 Mechanistic rationalization for the formation of **2**

Conclusion

In conclusion, we have disclosed a mild and efficient synthesis of 1,3,5-trisubstituted-1,2,4-triazoles. The protocol uses readily available hydrazonoyl chloride, phthalonitrile and Et_3N as starting materials. Additionally, in comparison with pervious methods, this reaction includes some important aspects like simple operation, absence of transition metal catalysts and strong bases or acids, the use of EtOH as reaction medium, and short reaction time.

Experimental Section

General

Elemental analyses for C, H and N were performed using a *Heraeus CHN–O–Rapid* analyzer. Mass spectra were recorded on a *FINNIGAN-MATT 8430* mass spectrometer operating at an ionization potential of 70 eV. ^{1}H-NMR (300 MHz) and ^{13}C-NMR (75 MHz) spectra in $CDCl_3$ were obtained using *Bruker DRX-300 AVANCE* spectrometers. IR spectra were recorded as KBr pellets on a *NICOLET FT-IR 100* spectrometer; absorbencies are reported in cm^{-1}.

General procedure for the synthesis of 2a-f

A mixture of phthalonitrile (1 mmol), hydrazonoyl chloride **1** (1 mmol) and Et_3N (1 mmol) in EtOH (2 mL) was refluxed. Upon completion (1 h), monitored by TLC, the solvent was removed and the residue purified by column chromatography (hexane/EtOAc, 1:6) to afford the pure product **2a-f**.

2-(1,3-Diphenyl-1*H*-1,2,4-triazol-5-yl)benzonitrile (2a):

White powder; yield: 0.24 g, (74%); mp 111-113 °C. IR (KBr): 3064 (C-H), 2228 (CN), 1648 (C=N), 1598, 1488, and 1466 (Ar), 1340 and 1096 (C-N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.21-7.52 (m, 5 H, 5 × CH of Ph) 7.54-7.88 (m, 6 H, 6 × CH of Ar), 8.10-8.32 (m, 3 H, 3 × CH of Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 113.1 (C_{ipso}-CN), 116.6 (CN), 124.7 (2 × CH of Ph), 128.1 (2 × CH_{meta} of Ph), 128.6 (CH_{para} of Ph), 128.9 (2 × CH_{meta} of Ph), 129.1 (CH_{para} of Ph), 129.5 (2 × CH_{ortho} of Ph), 130.7 (CH of Ar), 131.2 (CH of Ar), 131.4 (C_{ipso}–C^3), 132.9 (CH of Ar), 133.9 (CH of Ar), 135.7 (C_{ipso}–C^5), 137.1 (C_{ipso}-N), 151.3 (C^5), 161.4 (C^3). Anal. Calcd. for $C_{21}H_{14}N_4$ (322.37): C, 78.24; H, 4.38; N, 17.38. Found: C, 78.30; H, 4.42; N, 17.29.

2-[3-(4-Bromophenyl)-1-phenyl-1*H*-1,2,4-triazol-5-yl]benzonitrile (2b):

White powder; yield: 0.23 g (57%); mp 107-109 °C. IR (KBr): 3063 (C-H), 2227 (CN), 1644 (C=N), 1596, 489, and 1463 (Ar), 1338 (C-N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35-7.36 (m, 2 H, 2 × CH of Ph), 7.40-7.43 (m, 3 H, 3 × CH of Ph), 7.55-7.67 (m, 3 H, 3 × CH of

Ar), 7.73-7.77 (m, 2 H, 2 × CH of Ar), 7.83 (d, $^3J_{HH}$ = 5.5 Hz, 1 H, CH of Ar), 8.12 (d, $^3J_{HH}$ = 8.2 Hz, 2 H, 2 × CH of Ar). ^{3}C NMR (75 MHz, $CDCl_3$): δ = 113.2 (C_{ipso}-CN), 116.8 (CN), 124.1 (C_{ipso}-Br), 124.7 (2 × CH_{ortho} of Ph), 128.4 (2 × CH_{meta} of Ph), 129.2 (CH_{para} of Ph), 129.4 (C_{ipso}–C^3), 129.6 (2 × CH of Ar), 130.7 (CH of Ar), 131.1 (CH of Ar), 131.8 (C_{ipso}–C^5), 132.0 (2 × CH of Ar), 132.9 (CH of Ar), 134.0 (CH of Ar), 137.4 (C_{ipso}-N), 151.5 (C^5), 161.7 (C^3). Anal. Calcd. for $C_{21}H_{13}BrN_4$ (401.26): C, 62.86; H, 3.27; N, 13.96. Found: C, 62.95; H, 3.21; N, 14.04.

2-[3-(4-Chlorophenyl)-1-phenyl-1*H*-1,2,4-triazol-5-yl]benzonitrile (2c):

White powder; yield: 0.27 g (76%); mp 136-138 °C. IR (KBr): 3086 (C-H), 2238 (CN), 1577 and 1468 (Ar), 1348, 1224, and 1140 (C-N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34-7.41 (m, 5 H, 5 × CH of Ph), 7.48 (d, $^3J_{HH}$ = 7.4 Hz, 2 H, 2 × CH of Ar), 7.57-7.67 (m, 3 H, 3 × CH of Ar), 7.75 (d, $^3J_{HH}$ = 7.6 Hz, 1 H, CH of Ar), 8.26 (d, $^3J_{HH}$ = 7.4 Hz, 2 H, 2 × CH of Ar). ^{3}C NMR (75 MHz, $CDCl_3$): δ = 113.2 (C_{ipso}-CN), 116.8 (CN), 124.8 (2 × CH_{ortho} of Ph), 126.8 (2 × CH of Ar), 128.8 (2 × CH_{meta} of Ph), 129.0 (CH_{para} of Ph), 129.6 (2 × CH of Ar), 129.8 (CH of Ar), 130.4 (C_{ipso}-C^3), 130.6 (CH of Ar), 131.2 (CH of Ar), 132.1 (C_{ipso} –C^5), 132.9 (C_{ipso}-Cl), 134.0 (CH of Ar), 137.5 (C_{ipso}-N), 151.4 (C^5), 162.6 (C^3). Anal. Calcd. for $C_{21}H_{13}ClN_4$ (356.81): C, 70.69; H, 3.67; N, 15.70. Found C, 70.74; H, 3.60; N, 15.66.

2-[3-(4-Fluorophenyl)-1-phenyl-1*H*-1,2,4-triazol-5-yl]benzonitrile (2d):

White powder; yield: 0.25 g (73%); mp 98-100 °C. IR (KBr): 3074 (C-H), 2229 (CN), 1645 (C=N), 1600 and 1488 (Ar), 1338 and 1216 (C-N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.15 (t, ^3J = 8.7 Hz, 2 H, 2 × CH of Ar), 7.33-7.42 (m, 5 H, 5 × CH of Ph), 7.55-7.67 (m, 3 H, 3 × CH of Ar), 7.76 (d, $^3J_{HH}$ = 5.7 Hz, 1 H, CH of Ar), 8.22 (dd, $^3J_{HH}$ = 8.5 Hz, $^4J_{HF}$ = 5.6 Hz, 2 H, 2 × CH of Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 113.2 (C_{ipso}-CN), 115.8 (2 × CH, d, $^2J_{CF}$ = 21.7 Hz, 2 CH of Ar) 116.8 (CN), 124.7 (2 × CH_{ortho} of Ph), 126.7 (C_{ipso}–C^3, d, $^4J_{CF}$ = 3.1 Hz), 128.8 (2 × CH of Ar, $^3J_{CF}$ = 8.4 Hz), 129.1 (CH_{para} of Ph), 129.6 (2 × CH_{meta} of Ph), 130.7 (CH of Ar), 131.1 (CH of Ar), 131.9 (C_{ipso}–C^5), 132.9 (CH of Ar), 134.0 (CH of Ar), 137.4 (C_{ipso}-N), 151.5 (C^5), 161.7 (C^3), 163.3 (C_{ipso}-F, d, $^1J_{CF}$ = 250.1 Hz). Anal. Calcd. for $C_{21}H_{13}FN_4$ (340.36): C, 74.11; H, 3.85; N, 16.46. Found: C, 74.06; H, 3.76; N, 16.53.

2-[3-(4-Methylphenyl)-1-phenyl-1*H*-1,2,4-triazol-5-yl]benzonitrile (2e):

White powder; yield: 0.23 g (68%); mp 151-153 °C. IR (KBr): 3041 (C-H), 2228 (CN), 1650 (C=N), 1599 and 1487 (Ar), 1341 and 1273 (C-N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.42 (s, 3 H, CH_3), 7.29 (d, $^3J_{HH}$ = 8.0 Hz, 2 H, 2 × CH of Ar), 7.34-7.41 (m, 5 H, 5 × CH of Ph), 7.53-7.66 (m, 3 H, 3 × CH of Ar), 7.73 (d, $^3J_{HH}$ = 7.6 Hz, 1 H, CH of Ar), 8.14 (d, $^3J_{HH}$ = 8.0 Hz, 2 H, 2 × CH of Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6 (CH_3), 113.2 (C_{ipso}-CN), 116.8 (CN), 124.7 (2 × CH_{ortho} of Ph), 126.7 (2 × CH of Ar), 127.6 (C_{ipso} –C^3), 128.9 (CH_{para} of Ph), 129.51 (2 × CH_{meta} of Ar), 129.54 (2 × CH of Ar), 130.5 (CH of Ar), 131.2 (CH of Ar), 132.1 (C_{ipso} –C^5), 132.9 (CH of Ar), 134.0 (CH of Ar), 137.5 (C_{ipso}-N), 139.8 (C_{ipso} –CH_3), 151.3 (C^5), 162.7 (C^3). Anal. Calcd. for $C_{22}H_{16}N_4$ (336.39): C, 78.55; H, 4.79; N, 16.66. Found: C, 78.51; H, 4.86; N, 16.72.

2-[3-(4-Methoxyphenyl)-1-phenyl-1*H*-1,2,4-triazol-5-yl]benzonitrile (2f):

White powder; yield: 0.21 g (60%); mp 141-143 °C, IR (KBr): 3058 (C-H), 2225 (CN), 1620 (C=N), 1606 and 1476 (Ar), 1341 and 1250 (C-N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.88 (s, 3 H, OCH_3), 7.50 (d, $^3J_{HH}$ = 8.7 Hz, 2 H, 2 × CH of Ar), 7.33-7.41 (m, 5 H, 5 × CH of Ph), 7.54-7.64 (m, 3 H, 3 × CH of Ar), 7.75 (d, $^3J_{HH}$ = 7.9 Hz, 1 H, CH of Ar), 8.18 (d, $^3J_{HH}$ = 8.7 Hz, 2 H, 2 × CH of Ar). ^{3}C NMR (75 MHz, $CDCl_3$): δ = 55.5 (OCH_3), 113.2 (C_{ipso}-CN), 114.2 (2 × CH of Ar), 116.8 (CN), 123.1 (C_{ipso}–C^3), 124.7 (2 × CH_{ortho} of Ph), 128.3 (2 × CH_{meta} of Ph), 128.9 (CH_{para} of Ph), 129.5 (2 × CH of Ar), 130.5 (CH of Ar), 131.2 (CH of Ar), 132.2 (C_{ipso}–C^5), 132.9 (CH of Ar), 134.0 (CH of Ar), 137.6 (C_{ipso}-N), 151.2 (C^5), 161.0

(C_{ipso}-OMe), 162.5 (C^3). Anal. Calcd. for $C_{22}H_{16}N_4O$ (352.39): C, 74.98; H, 4.58; N, 15.90. Found: C, 74.91; H, 4.64; N, 19.85.

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