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ORIGINAL ARTICLE

*1st Heterocyclic Update*

# Heterocyclic synthesis using nitrilimines: Part 19. Synthesis of novel 1,3,5-trisubstituted-1,2,4-triazoles

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**KEYWORDS**

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**Abstract** This paper describes the synthesis of a new series of 1,3,5-trisubstituted-1,2,4-triazoles by 1,3-dipolar cycloaddition reaction of *C*-phenyl-aminocarbonyl-*N*-arylnitrilimines with guanidine derivatives. The structures of the newly synthesized compounds were elucidated by spectral methods (IR, $^{1}$H NMR, $^{13}$C NMR and MS spectroscopy) and elemental analysis. The microbial features of the synthesized compounds were studied using well-established methods from the literature.

## 1. Introduction

A literature survey revealed azole derivatives belonging to an important group of heterocyclic compounds that have a long history in pharmaceutical and medicinal chemistry. In particular, triazoles represent a class of heterocyclic compounds with a wide variety of biological activities (Dogan et al., 2005; Amir and Kumar, 2007; Tozkoparan et al., 2007; Ezabadi et al., 2008; Küçükgüzel et al., 2008; Sakac et al., 2009; Sun et al., 2010; Jyothi et al., 2010; Rama et al., 2010). Furthermore, fused heterocyclic compounds containing a 1,2,4-triazole nucleus have a broad spectrum of pharmacological activities, including anti-inflammatory (Husain and Naseer, 2011; Aytac et al., 2009), analgesic (Aytac et al., 2009), ulcerogenic (Amir et al., 2008; Reddy et al., 2010), antimicrobial (Amir et al., 2008; Reddy et al., 2010; Sztanke et al., 2008), anticancer (Sztanke et al., 2008; Badr and Barwa, 2011), antiproliferative and apoptotic properties (Sztanke et al., 2008). The synthesis of compounds whose structure contains 1,2,4-triazole rings has attracted widespread attention. 1,3-Dipolar cycloaddition is one of the most versatile methods for the construction of five-membered heterocycles (Padwa, 1991). Recently, we have described a versatile and efficient one-pot synthesis of dispiroheterocycles containing 1,2,4-triazole moieties utilizing available keto oximes, hydrazones, and hydrazonoyl halides (Dalloul and Abu Samaha, 2010). Considering the promising opportunities that the synthesis of such heterocycles might open with regard to the production of biologically active nitrogen, the present study represents a continuation of our previous work in an attempt to search for and synthesize a biologically active nitrogen heterocycle (Yuksek et al., 1997;

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**Table 1** Physical data, molecular ion peaks and elemental analysis for compounds **5a–j**.

| Cpd. No. | Mol. Formula (MW) | Yield: mg (%) | Mp. ± 2 (°C) | Analysis (%), Calcd./Found | | | $[M^+]$ |
|---|---|---|---|---|---|---|---|
| | | | | C | H | N | |
| **5a** | $C_{15}H_{13}N_5O$<br>(279.30) | 0.0021<br>(76) | 173 | 64.51<br>(64.75) | 4.69<br>(4.80) | 25.07<br>(24.95) | 279 |
| **5b** | $C_{15}H_{12}ClN_5O$<br>(313.75) | 0.0022<br>(72) | 184 | 57.42<br>(57.60) | 3.86<br>(3.70) | 22.32<br>(22.45) | 313/315 |
| **5c** | $C_{15}H_{12}BrN_5O$<br>(358.20) | 0.0028<br>(78) | 163 | 50.30<br>(50.55) | 3.38<br>(3.20) | 19.55<br>(19.65) | 358/360 |
| **5d** | $C_{15}H_{12}FN_5O$<br>(297.29) | 0.0021<br>(73) | 171 | 60.60<br>(60.35) | 4.07<br>(3.90) | 23.56<br>(23.40) | 297/299 |
| **5e** | $C_{16}H_{15}N_5O$<br>(293.33) | 0.0022<br>(75) | 189 | 65.52<br>(65.75) | 5.15<br>(5.00) | 23.88<br>(24.00) | 293 |
| **5f** | $C_{21}H_{17}N_5O$<br>(355.40) | 0.0025<br>(72) | 187 | 70.97<br>(70.75) | 4.82<br>(4.95) | 19.71<br>(19.55) | 355 |
| **5g** | $C_{21}H_{16}ClN_5O$<br>(389.85) | 0.0027<br>(71) | 212 | 64.70<br>(64.50) | 4.14<br>(4.30) | 17.96<br>(18.10) | 389/391 |
| **5h** | $C_{21}H_{16}BrN_5O$<br>(434.30) | 0.003<br>(70) | 193 | 58.08<br>(57.85) | 3.71<br>(3.60) | 16.13<br>(16.30) | 434/436 |
| **5i** | $C_{21}H_{16}FN_5O$<br>(373.39) | 0.0026<br>(69) | 188 | 67.55<br>(67.70) | 4.32<br>(4.20) | 18.76<br>(18.60) | 373/375 |
| **5j** | $C_{22}H_{19}N_5O$<br>(369.43) | 0.0023<br>(63) | 241 | 71.53<br>(71.30) | 5.18<br>(5.00) | 18.96<br>(19.15) | 369 |

Ikizler et al., 2000; Demirbas et al., 2002, 2005; Demirbas and Ugurluoglu, 2004; Bayrak et al., 2009). This paper reports on the synthesis of a series of some new substituted amino-1,2,4-triazoles via the reaction of *C*-phenylaminocarbonyl-*N*-arylnitrilimines with guanidine derivatives, and investigates the spectra of potential biological activities involved in the process.

## 2. Experimental

### 2.1. Material and instruments

Melting points were taken in open capillary tubes on Gallenkamp apparatus and were uncorrected. Infrared spectra were obtained by means of a Pye Unicam SP-3000 infrared spectrophotometer using a KBr disk technique. The $^1H$ NMR and $^{13}C$ NMR spectra were measured on a Bruker AM 300 MHz spectrometer at room temperature in $CDCl_3$ or DMSO-$d_6$ solution using tetramethylsilane (TMS) as the internal reference. Chemical shifts were recorded as $\delta$ values in parts per million (ppm) downfield from internal TMS. Electron impact (EI) mass spectra were run on a Shimadzu GCMS-QP1000 EX spectrometer at 70 eV. Elemental analyses were performed at Cairo University, Egypt, and the results agreed with the calculated values within experimental errors. The hydrazonoyl halides **1**(Frohberg et al., 2002) were prepared according to well-established procedures in the literature. Guanidine and diphenylguanidine hydrochloride, tetrahydrofuran (THF), and triethylamine were purchased from Avocado Research Chemicals, England, and used without further purification.

### 2.2. Synthesis of 1,3,5-trisubstituted-1,2,4-triazoles (**5a–j**)

To a stirred solution of the hydrazonoyl halides (10 mmol) in THF (50 mL) was added a solution of guanidine hydrochloride derivatives (15 mmol) in methanol (30 ml). To the resulting reaction mixture, cooled in an ice-salt bath (−5–0 °C), was dropwise added triethylamine (50 mmol). After addition was complete, stirring was continued for 1 h at 0 °C, and then at room temperature over night. The solvent was removed under reduced pressure, and the residue was washed with water (50 mL) to remove triethylammonium salt. The resulting crude solid product was collected and recrystallized from methanol or ethanol to give the desired good yields of the products **5a–j**. The physical and analytical data of the title compounds are given in Table 1.

#### 2.2.1. 5-Amino-3-carbanlino-1-phenyl-1,2,4-triazole (**5a**)

IR ($\nu$/cm$^{-1}$): 3430, 3428, 3352 ($NH_2$ and NH), 1660 (C=O), 1622, 1618 (C=N); $^1H$ NMR ($\delta$/ppm): 9.20 (s, 1H, NH amide), 8.23 (s, 2H, $NH_2$), 7.60–7.10 (m, 10H, Ar-H); $^{13}C$ NMR ($\delta$/ppm): 161.7 (C=O), 152.2, 150.8 (C=N), 140.9, 136.9, 129.6, 129.2, 128.7, 127.2, 125.2, 119.7 (C=C, Ar).

#### 2.2.2. 5-Amino-3-carbanlino-1-(4-chlorophenyl)-1,2,4-triazole (**5b**)

IR ($\nu$/cm$^{-1}$): 3426, 3424, 3351 ($NH_2$ and NH), 1665 (C=O), 1625, 1621 (C=N); $^1H$ NMR ($\delta$/ppm): 9.20 (s, 1H, NH amide), 8.31 (s, 2H, $NH_2$), 7.89 (d, $J$ = 8.6 Hz, 2H, Ar-H), 7.90–7.21 (m, 5H, Ar-H), 7.44 (d, $J$ = 8.6 Hz, 2H, Ar-H); $^{13}C$ NMR ($\delta$/ppm): 161.9 (C=O), 153.5, 151.3 (C=N), 140.5, 138.8, 136.4, 132.5, 129.3, 129.1, 126.2, 116.2 (C=C, Ar).

#### 2.2.3. 5-Amino-1-(4-bromophenyl)-3-carbanlino-1,2,4-triazole (**5c**)

IR ($\nu$/cm$^{-1}$): 3434, 3431, 3348 ($NH_2$ and NH), 1663 (C=O), 1620, 1616 (C=N); $^1H$ NMR ($\delta$/ppm): 9.20 (s, 1H, NH amide), 8.30 (s, 2H, $NH_2$), 7.84 (d, $J$ = 8.3 Hz, 2H, Ar-H), 7.74–7.16 (m, 5H, Ar-H) 7.50 (d, $J$ = 8.3 Hz, 2H, Ar-H); $^{13}C$ NMR ($\delta$/ppm): 161.7 (C=O), 152.4, 150.9 (C=N), 140.3, 137.5, 131.2, 128.7, 126.6, 124.5, 120.8, 118.5 (C=C, Ar).