One-Pot Reaction of Amidrazones, Phthaloyl Chloride, and Triethyl Amine: Synthesis of 1-(1′,2′,4′-Triazole)-2-Benzoic Acid

Ashraf A. Aly,[a]* Alan B. Brown,[b] and Ahmed M. Shawky[c]

[a]Department of Chemistry, Faculty of Science, Minia University, 61519, El Minia, Egypt
[b]Chemistry Department, Florida Institute of Technology, Melbourne, Florida 32901, USA
[c]Science and Technology Unit (STU), Umm Al-Qura University, Makkah, KSA
*E-mail: ashrafaly63@yahoo.com

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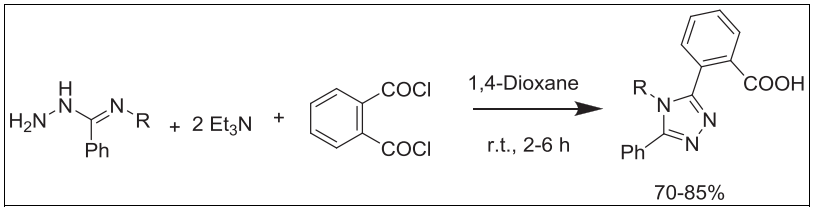

One-pot reaction of equimolar amounts of phthaloyl chloride and *N*-aryl-benzamidrazones in the presence of two equivalents of triethylamine (Et_3N), gave at r.t. 4-aryl-3-(*o*-carboxyphenyl)-5-phenyl-1,2,4-triazoles in good yields. The structure of the obtained products was proved by IR, mass, NMR spectra, and elemental analyses. The mechanism of product formation is discussed.

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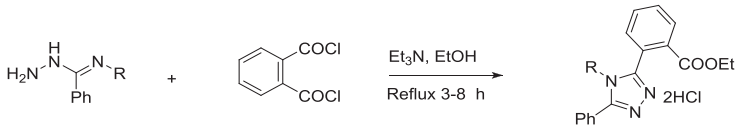
INTRODUCTION

Benzoic acid derivatives are useful agents for experimental studies of both cancer prevention and treatment, as well as for investigation of the mechanism of action of retinoids in the control of cell differentiation [1]. Benzoic acid derivatives have a wide spectrum of biological activities such as antitumor, antimicrobial, antihelmintic, antileishmanial, anticonvulsant, and anti-inflammatory [2,3]. 3,5-Dimethoxy-4-hydroxy-benzoic acid or protocatechuic acid, *p*-hydroxybenzoic acid, vanillic acid, syringic acid, and ferulic acid were tested *in vitro*, and their anti-sickling properties were confirmed [4,5]. It was reported that some benzoic acid derivatives extracted from the rhizomes of the Asian medicinal herb *Anemarrhena asphodeloides* (Asparagaceae) were evaluated against a lab colony of the generalist caterpillar *Spodoptera exigua* (Noctuidae), and low concentrations of others were found to significantly reduce fitness [6]. Aromatic retinoids having a benzoic acid and its 3,5-diaryl-substituted 4,5-dihydroisoxazole analogue function as retinoid receptor panagonists by activating both retinoic acid and retinoid X receptors to induce gene transcription, and thereby provide scaffolds for retinoid drug development [7]. 4-Pyrrol-1-yl benzoic acid hydrazide analogs were evaluated for their preliminary *in vitro* antibacterial activity against some Gram-positive and Gram-negative bacteria, and compounds were screened for antitubercular activity against mycobacterium tuberculosis H37Rv strain by broth dilution assay method [8]. Some of these compounds showed very good antibacterial and antitubercular activities [8].

The importance of free acids compared to its derivatives is related to the principle that the stability of biological systems increases because of their in state of its hydrogen bond formation [9]. In addition, the lipophilicity of free carboxylic group has effect on many biological processes [10]. From pharmacophore and biological scopes, it becomes importance to synthesize free carboxylic benzoic acid derivatives compared to its substituted acidic group [2].

Amidrazones are a class of substances with interesting biological properties. They exhibited antibacterial, antifungal [11–14], antitumor [15], and antituberculosis activities [16]. They were also found to be effective herbicides [17], pesticides [18], and insecticides [19]. The interest in amidrazones and their derivatives is not only for their biological relevance but also for their applications as precursors in the synthesis of many heterocyclic compounds [20–22]. Aly *et al.* have a long-running program of synthesis of various heterocycles from amidrazones such as pyrazoles [23,24], pyrimidinethiols [25], 1,2,4-triazepine-6,11-diones [26], triazoles [27], and triazolium salts [28]. Previously, we reacted equimolar amounts of amidrazones **1a–e** and phthaloyl chloride (**2**) in dry ethanol under reflux, catalyzed by a few drops of triethylamine (Et_3N). The reaction gave triazolium dihydrochloride salts **3a–e** (80–95%, Scheme 1) [29]. We found out that ethanol was engaged in the reaction, and the exclusive hydrochloric acid formed triazolium salts **3a–e** (Scheme 1). Therefore,

Scheme 1. Reaction of amidrazones **1a–e** with phthaloyl chloride (**2**) catalyzed by Et_3N. Synthesis of 1,2,4-triazolium salts.



1a-e

a: R = C_6H_5
b: = 4-Me-C_6H_5
c: = 4-MeO-C_6H_5
d: = 4-Cl-C_6H_5
e: = 4-NO_2-C_6H_5

2

3a-e (80-95%)

we here try to overcome the problem of salt formation *via* reaction of two equivalents of Et_3N with equal equivalents of amidrazones **1a–e** and phthaloyl chloride (Scheme 2).

RESULTS AND DISCUSSION

We chose amidrazones **1a–e** having aryl groups with either electron-donating or -withdrawing substituents on the benzene ring, in order to examine their effect on the reaction. Elemental analyses IR, NMR (^1H and ^{13}C), and mass spectra were in agreement with the assigned product structures.

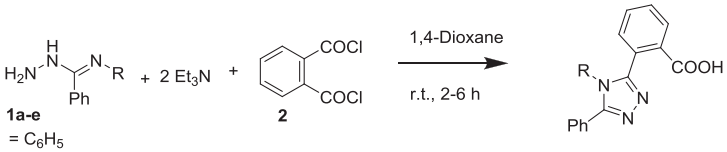
For example, in **4c** (Table 1), the methoxyl protons and carbon are distinctive at δ_H = 3.74 and δ_C = 55.28, respectively. The methoxyl protons give HMBC correlation with a carbon at δ_C = 159.25, assigned as C-*p* (Fig. 1). This carbon also gives HMBC correlation with 2H proton doublets at δ_H = 7.18 and 6.92, which must be H-*o* and H-*m*; based on chemical shift, they are assigned in the order just stated. The attached carbons appear at δ_C = 128.93 (C-*o*) and 114.45 (C-*m*), respectively. Protons H-*m* give HMBC correlation with a carbon at δ_C = 126.91, assigned as C-*i.* H-*o* give HMBC correlation with one or more carbons in the envelope δ_C = 128.02–126.91, which could also be C-*i.* The other distinctive proton resonance is the broad carboxyl signal at δ_H = 13.10. By chemical shift, the carboxyl *carbon* is assigned as the signal at δ_C = 166.99. This carbon gives HMBC correlation with a proton doublet at δ_H = 7.89,

Table 1

NMR spectroscopic data of **4c.**

^1H NMR (DMSO-d_6)	COSY	Assignment	
13.10 (b; 1H)		CO_2H	
7.89 (d, J = 7.6; 1H)	7.60	H-3′	
7.65 (dd, J = 7.4, 7.0; 1H)		H-*p*′, 5′,6′	
7.60	7.89,		
(“t”, J = 6.9; 2H)	7.43		
7.43 (m; 5H)	7.60	H-*o*′,*m*′,4′	
7.18 (d, J = 8.4; 2H)	6.92	H-*o*	
6.92 (d, J = 8.4; 2H)	7.18	H-*m*	
3.74 (s; 3H)		OCH_3	
^{13}C NMR (DMSO-d_6):	**HSQC:**	**HMBC:**	**Assignment:**
166.99		7.89	C=O
159.25		7.18, 6.92, 3.74	C-*p*
154.99		7.60	C-3,C-5
152.96		7.43	C-2′
131.93	7.60	7.89, 7.60	C-*p*′/5′/6′
131.60	7.65		C-*p*′/5′/6′
130.57			C-*i*′/1′/2′
130.11	7.60		C-*p*′/6′
129.82	7.89		C-3′
129.48	7.43		C-4′
128.93	7.18		C-*o*
128.58	7.43	7.65	C-*o*′/*m*′
128.02		7.18	C-*i*′/1′/2′
127.89	7.43	7.89, 7.43	C-*o*′/*m*′
127.14			C-*i*′/1′/2′
126.91		6.92	C-*i*
114.45	6.92	6.92	C-*m*
55.28	3.74		OCH_3

Scheme 2. Reaction of amidrazones **1a–e** with phthaloyl chloride (**2**) and triethylamine. Synthesis of 1-(1′,2′,4′-triazole)-2-benzoic acid derivatives.



1a-e

a: R = C_6H_5
b: = 4-Me-C_6H_5
c: = 4-MeO-C_6H_5
d: = 4-Cl-C_6H_5
e: = 4-NO_2-C_6H_5

2

4a-e (70-85%)

a; 80%, **b**; 82%, **c**; 85%, **d**; 75%, **e**; 70%

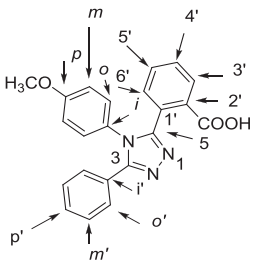


Figure 1. Designations of carbons in compound **4c.**

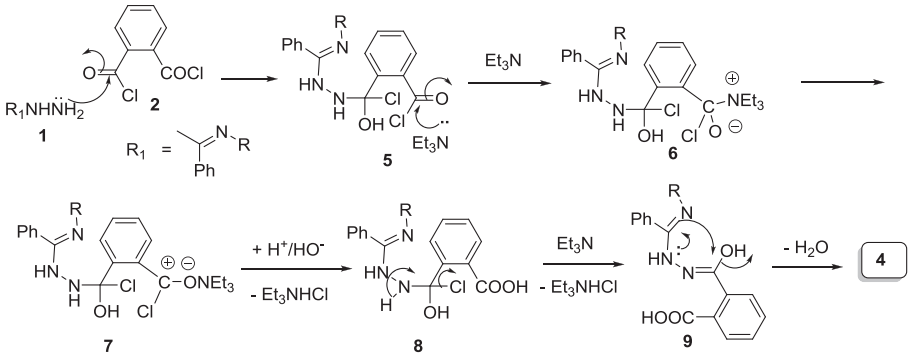
assigned as H-3′; the attached carbon appears at δ_C = 129.82. H-3′ gives COSY correlation with one of the three protons between δ_H = 7.65–7.60, which could be H-4′ or H-5′. At this point assignments become imprecise because of signal overlap. H-4′ and H-5′ should appear as 1H double-doublets, and H-6′ as a doublet; in the phenyl ring, H-*p*′ should appear as a 1H triplet, H-*m*′ as a 2H double-doublet and H-*o*′ as a 2H doublet. The three protons between δ_H = 7.65–7.60 correlate with three different carbon signals, which therefore bear only one proton each and cannot be C-*m*′ or C-*o*′. The attached protons H-*m*′ and H-*o*′ add to 4H, and must appear at δ_H = 7.43; therefore, two of the protons on the carboxyl-bearing ring must appear between δ_H = 7.65–7.60, and the remaining one at δ_H = 7.43. The third proton between δ_H = 7.65–7.60 must be H-*p*′. Three ^{13}C lines give HSQC correlation with the protons at δ_H = 7.43; two of these lines are double-height and must be C-*o*′ and C-*m*′, and the third must be on the carboxyl-bearing ring, and is tentatively assigned as C-4′ based on chemical-shift estimation of its attached proton using CHEMWINDOW. If this is correct, the other two protons between δ_H = 7.65–7.60 must be H-5′ and H-6′. One of the two carbons between δ_C = 131.93–131.60 gives HMBC correlation with H-3′, which C-*p*′ cannot and C-6′ should not, but C-5′ should. The carbons at δ_C = 154.99 and 152.96 should be C-3 and C-5, by chemical-shift estimation; the former gives HMBC correlation with the envelope containing H-*p*′/5′/6′. H-6′ is three bonds from C-3, which is therefore assigned as δ_C = 154.99. The carbon at δ_C = 152.96 gives HMBC correlation with the protons at δ_H = 7.43; this envelope contains H-*o*′, which is three bonds from C-5, and therefore C-5 is assigned as δ_C = 152.96.

In the case of compound **4d**, both mass spectrum and elemental analysis indicated a molecular formula of $C_{21}H_{14}ClN_3O_2$. It is of interest to explain the clear fragmentation patterns appearing in the mass spectrum of **4d**. The following common features of the fragmentation patterns, as for example, the base peak and with the fragment of M + 1 appeared at *m/z* = 375 (32%) and 376 (20%), respectively, indicating the presence of three nitrogen atoms. [27] The IR spectrum of **4d** showed CO—OH stretching at ν_{max} = 2500 cm^{-1}, whereas its carbonyl absorbed at ν_{max} = 1710 cm^{-1}. The carboxylic proton was confirmed by ^{1}H NMR spectrum *via* its appearance at δ_H = 13.40, whilst the carbonyl carbon resonated at δ_C = 168.20. Again the C-3 and C-5 carbons appeared in the expected region at δ_C = 154.20 and 153.60, respectively (see the experimental section).

The mechanism can be explained as because of addition of hydrazine-NH_2 in **1** to the carbonyl of acid chloride **2** leading to intermediate **5** (Scheme 3). That was followed by addition of Et_3N to the carbonyl group to give the salt **6** (Scheme 3). Expected rearrangement would be occurred to **6** to produce the electrophilic carbon in **7**, which because of the presence of water molecule would give the free acid **8** (Scheme 3). Elimination of a second mole of triethyl amine·HCl would give intermediate **9**. Finally, cyclization would proceed via addition of N^3 to the electrophilic carbinol, which would be accompanied by elimination of a water molecule to give **4** (Scheme 3).

It is noteworthy to mention that reaction of two equivalents of both amidrazones and triethyl amine with

Scheme 3. Plausible mechanism for formation of triazole–benzoic acid derivatives **4a–e.**



one equivalent of **2** gave the same mono triazole with the same yield percentages of the products **4a–e**.

CONCLUSION

Our results deal with the second reported reaction of amidrazones with phthaloyl chloride to produce the 2-(1′,2′,4′-triazolo)benzoic acids in good yields. Interestingly, addition of two equivalents of triethyl amine as we can see affects on the bi-acid chloride functions and therefore causes facile elimination of corresponding two equivalents triethyl amine·HCl. Free bases of triazole·2HCl might be obtained via neutralization with NaOH followed by hydrolysis of the ester group, which of course would give low yields compared with the established method. The short time taken and the simplicity to obtain the free triazole moiety give advantage on the previous one. Most indicative is that our previous method gave the ester of benzoic acid, whereas the new one produces directly the triazole derivatives of benzoic group.

EXPERIMENTAL

NMR spectra were measured on a Bruker AV-400 spectrometer (Bruker BioSpin Corp., Billerica, MA) (400 MHz for ^{1}H, 100 MHz for ^{13}C, and 40.55 MHz for ^{15}N) at Florida Institute of Technology, USA. The ^{1}H and ^{13}C chemical shifts are given relative to internal standard TMS = 0. Zones were detected by quenching of indicator fluorescence upon exposure to 254 nm UV light. Elemental analyses were carried in the National Research center, Dokki, Cairo, Egypt. Mass spectrometry was performed by electron impact at 70 eV, with a Finnigan Mat 8430 spectrometer in the National Research center, Dokki, Cairo, Egypt. IR spectra using KBr pellets, were run on a FT-IR (Bruker), Minia University, El-Minia, Egypt. Amidrazones **1a-g** were prepared according to reference [30,31].

Reaction of amidrazones 1a–e with phthaloyl chloride (2). A mixture of compounds **1a–e** (1 mmol) with **2** (0.202 g, 1 mmol) in absolute 1,4-dioxane (30 mL) containing 2 mmol of Et_3N, was stirred at r.t. for 2–6 h. The products formed were filtered off, and the precipitates were washed with water (200 mL) and then with 10 mL of ethanol. The products **4a–e** were then dried and recrystallized from the stated solvents.

2-(4″,5″-Diphenyl-4H-1′,2′,4′-triazol-3-yl)benzoic acid (4a). Yellow crystals (ethanol), yield 0.27 g (80%), mp 180–2°C. IR (KBr) (ν_{max}, cm^{-1}): 3060 (w, Ar—CH), 2508 (m, CO-acid), 1710 (s, CO-acid), 1618 (s, C=N), 1550 (s, C=C). ^{1}H NMR (400 MHz, DMSO-*d6*): δ_H = 13.30 (bs, 1H, COOH), 7.80–7.76 (dd, 2H, Ar—H), 7.60–7.56 (dd, 2H, Ar—H), 7.40–7.30 (m, 5H, Ar—H), 7.20–7.16 (dd, 2H, Ar—H), 6.80–6.74 (m, 3H, Ar—H); ^{13}C NMR (100 MHz, DMSO-d_6):δ_C = 167.00 (CO-acid), 154.25 (C-3), 153.90 (C-5), 152.90 (C-2′), 131.90 (C-1′), 131.60, 130.50 (Ar—C), 130.11 (Ar—2C—CH-3′/4′), 129.82, 128.93 (Ar—CH), 128.58, 128.02 (Ph—2CH-*o*), 127.75, 127.14 (Ph—2CH-*m*), 126.91 (Ph′—CH-*p*), 124.45 (Ph—CH-*p*). MS (70 eV, EI, %), *m/z* = 341 ($M^+_{\cdot}$ 22), 313 (100), 296 (28), 220 (18), 144 (32). Calcd for $C_{21}H_{15}N_3O_2$ (341.12): C, 73.89; H, 4.43; N, 12.31. Found: C, 73.70: H, 4.60: N, 12.40.

2–4′-(4″-Methylphenyl)-5-phenyl-4H-1′,2′,4′-triazol-3′-yl)benzoic acid (4b). Yellow crystals (methanol), yield 0.29 g (82%), mp 170–172°C. IR (KBr) (ν_{max}, cm^{-1}): 3100–3030 (w, Ar—CH), 2980–2890 (m, Aliph-CH), 2560 (s, CO-acid), 1708 (s, CO-acid), 1620 (s, C=N), 1560 (s, C=C). ^{1}H NMR (400 MHz, DMSO-*d6*): δ_H = 13.10 (bs, 1H, COOH), 7.60–7.56 (dd, 2H, Ar—H, *J* = 8.0, 1.0 Hz)), 7.50–7.40 (m, 4H, Ar—H), 7.10–6.90 (m, 3H, Ar—H), 6.80–6.60 (m, 4H, Ar—H), 2.30 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 167.10 (CO-acid), 154.15 (C-3), 153.90 (C-5), 152.65 (C-2′), 132.00 (*p*-tolyl-C), 131.60 (C-1′), 130.70, 130.50 (Ar—C), 130.10 (Ar—CH-3′/4′), 129.60, 128.60 (Ar—CH), 128.20, 127.90 (Ph—2CH-*o*), 127.10 (Ph—2CH-*m*), 126.60 (Ph′—CH-*p*), 122.60 (Ph—2CH-*m*), 22.40 (CH_3—Ar). MS (70 eV, EI, %), *m/z* = 335 (M^+, 20), 320 (18), 292 (100), 216 (14), 140 (24), 76 (40). Calcd for $C_{22}H_{17}N_3O_2$ (355.13): C, 74.35; H, 4.82; N, 11.82. Found: C, 74.20; H, 4.85; N, 11.75.

2–4′-(4″-Methoxyphenyl)-5-phenyl-4H-1′,2′,4′-triazol-3′-yl) benzoic acid (4c). Yellow crystals ($CHCl_3$/Cyclohexane), yield: 0.32 g (85%), mp 196–8°C. IR (KBr) (ν_{max}, cm^{-1}): 3080 (w, Ar—CH), 2950–2830 (w, Aliph-CH), 2510 (m, CO-OH, st), 1708 (s, CO-acid), 1620 (s, C=N), 1560 (s, C=C). NMR (DMSO-d_6): Table 1. MS (70 eV, EI, %), *m/z* = 371 (M^+, 22), 356 (18), 341 (42), 267 (100), 191 (22), 77 (32). Calcd for $C_{22}H_{17}N_3O_3$ (371.13): C, 71.15; H, 4.61; N, 11.31. Found: C, 71.00; H, 4.51; N, 11.20.

2–4′-(4″-Chlorophenyl)-5-phenyl-4H-1′,2′,4′-triazol-3′-yl)benzoic acid (4d). Pale yellow crystals (methanol), yield: 0.28 g (75%), mp 110–2°C. IR (KBr) (ν_{max}, cm^{-1}): 3110–3020 (w, Ar—CH), 2500 (m, CO—OH, st), 1710 (s, CO-acid), 1615 (s, C=N), 1560 (s, C=C). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 13.40 (bs, 1H, COOH), 7.60–7.40 (m, 5H, Ar—H), 7.30–7.20 (m, 4H, Ar—H), 6.82–6.66 (m, 4H, Ar—H). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 168.20 (CO-acid), 154.20 (C-3), 153.60 (C-5), 152.80 (C-2′), 131.40 (C-1′), 130.60, 130.10 (Ar—C), 130.30 (Ar—CH-3′/4′), 128.70 (Ar—C—Cl), 128.40, 128.00 (Ar—CH), 127.60, 127.20 (Ph—2CH-*o*), 126.80, 126.60 (Ph—2CH-*m*), 124.20 (Ar—CH-*p*). MS (70 eV, EI, %), m/z = 376 (M + 1, 20), 375 (32), 342 (18), 341 (24), 310 (100), 238 (16), 237 (24), 162 (18), 160 (32), 112 (18), 110 (14), 78 (26). Calcd for

$C_{21}H_{14}ClN_3O_2$ (375.08): C, 67.12; H, 3.76; N, 11.18. Found: C, 67.00; H, 3.60; N, 11.05.

2–4′-(4″-Nitrophenyl)-5-phenyl-4H-1′,2′,4′-triazol-3′-yl)benzoic acid (4e). Yellow crystals (ethanol), yield: 0.27 g (70%), mp 210–2°C. IR (KBr) (ν_{max}, cm^{-1}): 3080–3010 (w, Ar—CH), 2500 (s, CO-acid), 1710 (s, CO-acid), 1622 (s, C═N), 1560 (s, C═C). ^1H NMR (400 MHz, DMSO-d_6): δ_H = 13.30 (bs, 1H, COOH), 8.10–8.06 (dd, 2H, Ar—H, J = 8.0, 1.0 Hz)), 7.60–7.40 (m, 5H, Ar—H), 7.10–6.90 (m, 4H, Ar—H), 6.60–6.56 (dd, 2H, Ar—H, J = 8.0, 1.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 167.10 (CO-acid), 159.10 (C-3), 153.60 (C-5), 152.60 (C-2′), 148.30 (nitro-Ar—C), 131.70 (C-1′), 130.90, 130.60 (Ar—C), 130.30 (Ar—CH-3′/4′), 129.40, 128.80 (Ar—CH), 128.30, 127.60 (Ph—2CH-*o*), 127.00 (Ar—2CH-*m*), 124.40 (Ar—CH-*p*), 118.60 (Ph—2CH-*m*). MS (70 eV, EI, %), *m/z* = 386 (M^+, 22), 358 (34), 340 (16), 292 (100), 236 (100), 160 (26), 77 (42). Calcd for $C_{21}H_{14}N_4O_4$ (386.10): C, 65.28; H, 3.65; N, 14.50. Found: C, 65.10; H, 3.60; N, 14.38.

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