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# Reactions of 4-Amino-4,5-Dihydro-1H-1,2,4-Triazol-5-ones and 4-Amino-4H-1,2,4-Triazoles with Some Carboxylic Acid Anhydrides

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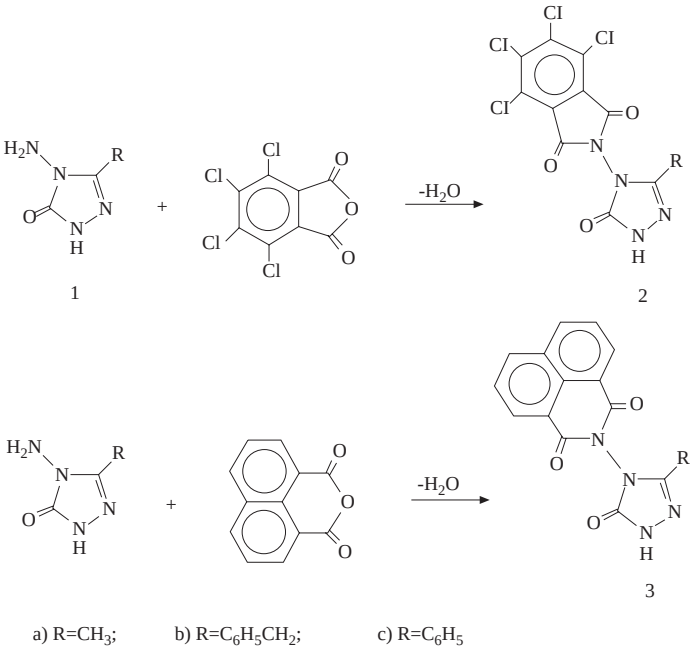
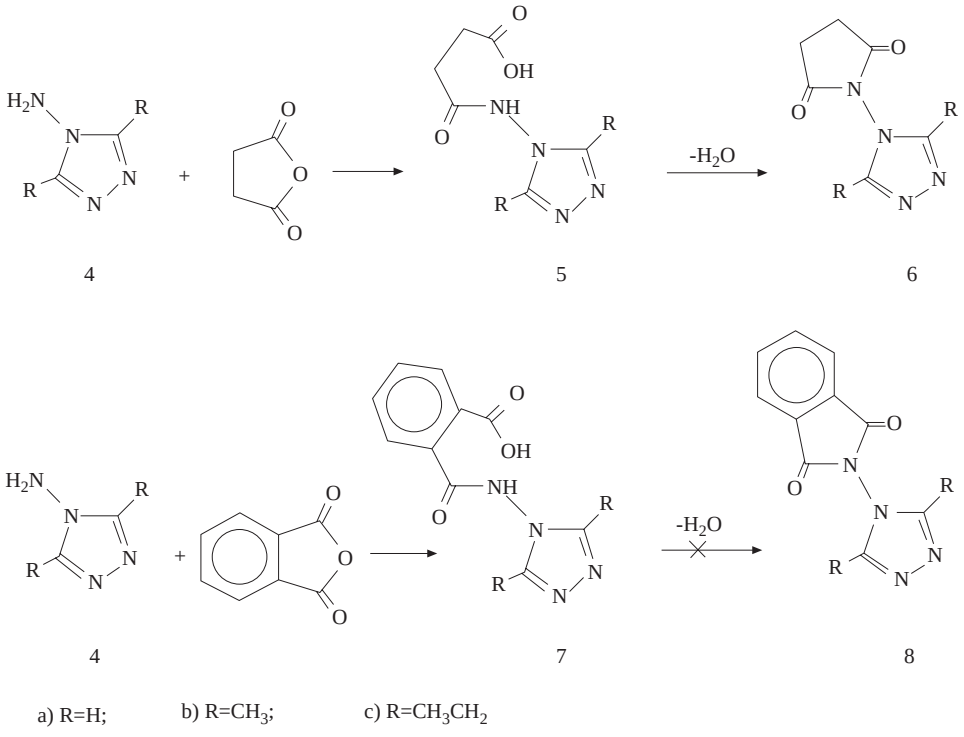
3-Alkyl(Aryl)-4-tetrachlorophthalimido-4,5-dihydro-1H-1,2,4-triazol-5-ones (2) and 3-alkyl(aryl)-4-(1,8-naphthalimido)-4,5-dihydro-1H-1,2,4-triazol-5-ones (3) were synthesized from the reactions of 3-alkyl(aryl)-4-amino-4,5-dihydro-1H-1,2,4-triazol-5-ones (1) with tetrachlorophthalic anhydride and 1,8-naphthalic anhydride, respectively. In addition, the reactions of 4-amino-4H-1,2,4-triazoles (4) with succinic anhydride and phthalic anhydride were studied.

## Introduction

In recent years, certain reactions of 4-amino-4,5-dihydro-1H-1,2,4-triazol-5-ones have been reported[1−9]. Moreover, some N,N'-linked biheteroaryl systems have been formed by the reactions of several N-aminoheterocycles, including 4-amino-1,2,4-triazole and 1-aminopyrrole with 1,4-dialdehydes or 1,4-diketones[10−13]. In the present study, 3-alkyl(aryl)-4-amino-4,5-dihydro-1H-1,2,4-triazol-5-ones (1) were treated with tetrachlorophthalic anhydride and 1,8-naphthalic anhydride to give the corresponding 3-alkyl(aryl)-4-tetrachlorophthalimido-4,5-dihydro-1H-1,2,4-triazol-5-ones (2) and 3-alkyl(aryl)-4-(1,8-naphthalimido)-4,5-dihydro-1H-1,2,4-triazol-5-ones (3) with potential biological activity (Scheme 1). Furthermore, the reactions of 4-amino-4H-1,2,4-triazole (4a), 4-amino-3,5-dimethyl-4H-1,2,4-triazole (4b) and 4-amino-3,5-diethyl-4H-1,2,4-triazole (4c) with succinic anhydride and/or phthalic anhydride were also investigated, and type 5, 6 and 7 1,2,4-triazole derivatives with potential biological activity were obtained (Scheme 2).




**Scheme 1.**




**Scheme 2.**

# Experimental

Melting points were determined with a Büchi oil heated melting point apparatus. IR spectra were run by KBr pellets using a Perkin-Elmer 377 spectrophotometer, and UV spectra were measured at between 210 and 350 nm on a Varian spectrophotometer, using 10 mm quartz cells. The $^1$H NMR spectra were obtained on a Varian 60A spectrometer. Combustion analyses were performed on a Carlo Erba 1106 elemental analyzer.

Starting compounds 1, 4b and 4c were synthesized by methods described earlier[2,3,14]. The other necessary chemicals were obtained from Fluka.

**Preparation of 3-alkyl(aryl)-4-tetrachlorophthalimido-4,5-dihydro-1H-1,2,4-triazol-5- ones (2) and 3-alkyl(aryl)-4-(1,8-naphthalimido)-4,5-dihydro-1H-1,2,4-triazol-5-ones (3). General Synthetic Procedure**. - 3-Alkyl(Aryl)-4-amino-4,5-dihydro-1H-1,2,4-triazol-5-one (1) (0.01 mol) was heated with 0.01 mol of tetrachlorophthalic anhydride or 1,8-naphthalic anhydride at high temperatures for 1.5 hr. and cooled. The crude product was crystallized from an appropriate solvent to give compound 2 or 3.

**3-Methyl-4-tetrachlorophthalimido-4,5-dihydro-1H-1,2,4-triazol-5-one (2a).-** Reaction temperature 145-150°C, yield 2.48 g. (65 %), mp. 294°C (acetone/petroleum ether, 1:1); IR(KBr): 3230(NH), 1786, 1736, 1710(C=O), 1600(C=N)cm$^{-1}$; UV(ethanol) $\lambda_{max}(\Sigma)$: 339nm(218), 287.5(846); $^1$H NMR(DMSO-$d_6$): $\delta$ 2.08(s,3H,$CH_3$), 11.72(s,1H,NH); $^1$H NMR(TFA): $\delta$ 2.44(s,3H,$CH_3$).

| | | |
|---|---|---|
| Anal. Calcd for $C_{11}H_4N_4O_3Cl_4$ | : | C, 34.59; H, 1.06; N, 14.67 |
| Found | : | C, 34.14; H, 1.05; N, 14.37 |

**3-Benzyl-4-tetrachlorophthalimido-4,5-dihydro-1H-1,2,4-triazol-5-one (2b).-** Reaction temperature 145-150°C, yield 2.76 g. (60 %), mp. 220°C (acetone/petroleum ether, 1:1); IR(KBr): 3190(NH), 1795, 1740, 1688(C=O), 1575(C=N), 730, 696(monosubstituted benzenoid ring)cm$^{-1}$; UV(ethanol) $\lambda_{max}(\Sigma)$: 339nm(500), 226.5(21484); $^1$H NMR (DMSO, $d_6$): $\delta$ 3.90 (S, 2H, $CH_2$), 7.16-7.44 (m, 5H, aromatic H), 12.36 (S, 1H, NH); $^1$H NMR (TFA): $\delta$ 4.20(s,2H,$CH_2$), 7.10-7.50(m,5H, aromatic H).

| | | |
|---|---|---|
| Anal. Calcd for $C_{17}H_8N_4O_3Cl_4$ | : | C, 44.57; H, 1.76; N, 12.23 |
| Found | : | C, 44.33; H, 1.77; N, 11.91 |

**3-Phenyl-4-tetrachlorophthalimido-4,5-dihydro-1H-1,2,4-triazol-5-one (2c).-** Reaction temperature 235-240°C, yield 2.13 g. (48 %), mp. 278°C (benzene); IR(KBr): 3178(NH), 1788, 1740, 1715(C=O), 1575(C=N), 730,678(monosubstituted benzenoid ring)cm$^{-1}$; UV(ethanol) $\lambda_{max}(\sum)$: 340.5nm-(1604), 237.5(31635); $^1$H NMR(DMSO-$d_6$): $\delta$ 7.32 (s,5H,aromatic H), 12.42(s,1H,NH); $^1$H NMR(TFA): $\delta$ 7.80(s,5H,aromatic H).

| | | |
|---|---|---|
| Anal. Calcd for $C_{16}H_6N_4O_3Cl_4$ | : | C, 43.28; H, 1.36; N, 12.62 |
| Found | : | C, 43.05; H, 1.30; N, 12.32 |

**3-Methyl-4-(1,8-naphthalimido)-4,5-dihydro-1H-1,2,4-triazol-5-one (3a).-** Reaction temperature 245-250°C, yield 1.65 g. (53 %), mp. 328°C (acetone); IR(KBr): 3316(NH), 1738, 1696, 1683(C=O), 1578(C=N)cm$^{-1}$; UV(ethanol) $\lambda_{max}(\Sigma)$: 337nm(11493), 230 (24650); $^1$H NMR(DMSO-$d_6$): $\delta$ 2.12(s,3H,$CH_3$), 7.34-7.86(m,2H,aromatic H), 8.10-8.36 (m,4H,aromatic H), 11.60(s,1H,NH); $^1$H NMR(TFA): $\delta$ 2.50(s,3H,$CH_3$), 6.96-8.14(m,2H,aromatic H), 8.40-8.92(m,4H,aromatic H).

| | | |
|---|---|---|
| Anal. Calcd for $C_{15}H_{10}N_4O_3$ | : | C, 61.22; H, 3.43; N, 19.04 |
| Found | : | C, 61.42; H, 3.27; N, 19.13 |

**3-Benzyl-4-(1,8-naphthalimido)-4,5-dihydro-1H-1,2,4-triazol-5-one (3b).-** Reaction temperature 240-245°C, yield 2.26 g. (58 %), mp.250°C (ethanol); IR(KBr): 3170(NH), 1763, 1728, 1703(C=O), 1580(C=N), 765, 697(monosubstitued benzenoid ring)cm$^{-1}$; UV(ethanol) $\lambda_{max}(\Sigma)$: 340nm(14738), 234(25301);

$^1$H NMR(DMSO-$d_6$): $\delta$ 3.80(s,2H,$CH_2$), 6.92(s,5H,aromatic H), 7.50-7.90(m,2H,aromatic H), 8.10-8.45(m, 4H,aromatic H), 11.76(s,1H,NH); $^1$H NMR(TFA): $\delta$ 4.40(s,2H,$CH_2$), 7.36(s,5H,aromatic H), 8.20-8.60(m,2H,-aromatic H), 8.84-9.30(m,4H,aromatic H).

Anal. Calcd for $C_{21}H_{14}N_4O_3$ : C, 68.10; H, 3.81; N, 15.13
Found : C, 67.93; H, 3.64; N, 14.85

**3-Phenyl-4-(1,8-naphthalimido)-4,5-dihydro-1H-1,2,4-triazol-5-one (3c).-** Reaction temperature 255-260°C, yield 1.63 g. (43 %), mp.276°C (acetone); IR(KBr): 3197(NH), 1725, 1703, 1687(C=O), 1575(C=N), 766, 692(monosubstituted benzenoid ring)$cm^{-1}$; UV (ethanol) $\lambda_{max}(\Sigma)$: 339nm(13009), -233(31206); $^1$H NMR(DMSO-$d_6$): $\delta$ 7.04-7.44(m,5H,aromatic H) 7.46-7.80(m,5H,aromatic H), 7.75-8.15(m,2H,-aromatic H), 12.16(s,1H,NH); $^1$H NMR(TFA): $\delta$ 7.40-7.70(s,5H,aromatic H), 8.20-8.60(m,2H,aromatic H), 8.40-8.92(m,4H,aromatic H).

Anal. Calcd for $C_{20}H_{12}N_4O_3$ : C, 67.41; H, 3.39; N, 15.72
Found : C, 67.83; H, 3.39; N, 15.45

**Preparation of N-(3,5-dialkyl-4H-1,2,4-triazol-4-yl)-succinic acid monoamides (5), N-(3,5-dialkyl-4H-1,2,4-triazol-4-yl)-succinimides (6) and N-(4H-1,2,4-triazol-4-yl)- or N-(3,5-dialkyl-4H-1,2,4-triazol-4-yl)-phthalic acid monoamides (7). General Synthetic Procedure.-** The corresponding 4H-1,2,4-triazole (4) (0.01 mol) was heated with 0.01 mol of succinic anhydride or phthalic anhydride at high temperatures for 1.5 hr. and cooled. The crude product was crystallized from an appropriate solvent to give compounds 5, 6 or 7.

**N-(3,5-Dimethyl-4H-1,2,4-triazol-4-yl)-succinic acid monoamide (5b).-** Reaction temperature 180-185°C, yield 0.92 g. (43 %), mp. 182°C (ethanol/ethyl acetate 1:3); IR(KBr): 3210, 3150(NH and OH), 1710, 1698(C=O), 1540(C=N)$cm^{-1}$; UV(ethanol) $\lambda_{max}(\Sigma)$: 213nm(520); $^1$H NMR (DMSO-$d_6$): $\delta$ 2.10(s,6H,2$CH_3$), 2.50(s,4H,2$CH_2$), 11.10(s,1H,OH); $^1$H NMR(TFA): $\delta$ 2.74(s,6H,2$CH_3$), 3.02(s,4H,2$CH_2$).

Anal. Calcd for $C_8H_{12}N_4O_3$ : C, 45.28; H, 5.70; N, 26.40
Found : C, 45.02; H, 5.74; N, 26.47

**N-(3,5-Diethyl-4H-1,2,4-triazol-4-yl)-succinic acid monoamide (5c).-** Reaction temperature 185-190°C, yield 1.16 g. (48 %), mp.157°C (ethanol/ethyl acetate 1:3); IR(KBr): 3225, 3130(NH and OH), 1702, 1675(C=O), 1515(C=N)$cm^{-1}$; UV(ethanol) $\lambda_{max}(\Sigma)$: 215nm(280); $^1$H NMR(DMSO-$d_6$): $\delta$ 1.16(t,6H,2$CH_3$), 2.46(q,4H,2$CH_2$), 2.56(s,4H,2$CH_2$), 11.16(s,1H,OH); $^1$H NMR(TFA): $\delta$ 1.52(t,6H,2$CH_3$), 3.00(q,4H,2$CH_2$), 3.10(s,4H,2$CH_2$).

Anal. Calcd for $C_{10}H_{16}N_4O_3$ : C, 49.99; H, 6.71; N, 23.32
Found : C, 50.36; H, 7.00; N, 23.38

**N-(3,5-Diethyl-4H-1,2,4-triazol-4-yl)-succinimide (6c).-** Reaction temperature 220-225°C, yield 1.02 g. (46 %), mp.176°C (acetone/petroleum ether 1:1); IR(KBr): 1780, 1730(C=O), 1525(C=N)$cm^{-1}$; UV(ethanol) $\lambda_{max}(\Sigma)$: 217nm(90); $^1$H NMR(DMSO-$d_6$): $\delta$ 1.16(t,6H,2$CH_3$), 2.50(q,4H,2$CH_2$), 3.00(s,4H,-2$CH_2$); $^1$H NMR(TFA): $\delta$ 1.52(t,6H,2$CH_3$), 2.98(q,4H,2$CH_2$), 3.32(s,4H,2$CH_2$).

Anal. Calcd for $C_{10}H_{16}N_4O_3$ : C, 54.04; H, 6.35; N, 25.21
Found : C, 54.27; H, 6.27; N, 24.93

Heating of compound 5c at high temperatures also afforded the corresponding cyclic compound 6c.

**N-(4H-1,2,4-triazol-4-yl)-phthalic acid monoamide (7a).-** Reaction temperature 180-185°C, yield 1.66 g. (72 %), mp. 263°C (ethanol); IR(KBr): 3110, 3050(NH and OH), 1686, 1673(C=O), 1520(C=N)$cm^{-1}$; UV(ethanol) $\lambda_{max}(\Sigma)$: 280nm(1020), 273(1140), 242(1260); $^1$H NMR(DMSO-$d_6$): $\delta$ 8.88(s,2H,2CH), 12.22(s,1H,OH), 7.70-8.40(m,4H,aromatic H); $^1$H NMR(TFA): $\delta$ 9.34(s,2H,2CH), 7.40-

8.36(m,4H,aromatic H).

Anal. Calcd for $C_{10}H_8N_4O_3$ : C, 51.72; H, 3.47; N, 24.13
Found : C, 51.97; H, 3.57; N, 24.02

**N-(3,5-Dimethyl-4H-1,2,4-triazol-4-yl)-phthalic acid monoamide (7b).-** Reaction temperature 195-200°C, yield 1.92 g. (74%), mp.187°C (water); IR(KBr): 3250, 3118 (NH and OH), 1690, 1665(C=O), 1520(C=N)$cm^{-1}$; UV(ethanol) $\lambda_{max}(\Sigma)$: 276nm(1250), 235(2530); $^1$H NMR(DMSO-$d_6$): $\delta$ 2.32(s,6H,2$CH_3$), 11.52(s,1H,OH), 7.38-7.94(m,4H,aromatic H); $^1$H NMR(TFA): $\delta$ 2.90(s,6H,2$CH_3$), 7.60-8.40(m,4H,aromatic H).

Anal. Calcd for $C_{12}H_{12}N_4O_3$ : C, 55.38; H, 4.65; N, 21.53
Found : C, 54.98; H, 4.72; N, 21.26

## Results and Discussion

In this study, a general method was developed for the synthesis of type 2 and 3 compounds. It is plausible that the formation of compounds 2 and 3 probably occurred via intermediate structures similar to 5 or 7, but we were not able to isolate such an intermediate compound. However, the intermediates 5 and 7 were obtained in the study and the achievement of the ring closure from 5c to give 6c revealed that reactions of this type proceed via intermediate carboxylic acid derivatives. Compounds 7a and 7b were heated at relatively higher temperatures for ring closure, but N-triazolophthalimides 8a and 8b were not obtained because of the decomposition of the starting materials.

The results obtained here are in agreement with those obtained by the reactions of some N-aminoheterocycles with some other carboxylic acid anhydrides.[15,16].

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