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Reaction of 4-Amino-4,5-Dihydro-1*H*-1,2,4-Triazol-5-one with Some Carboxylic Acid Anhydrides and their Antiinflammatory Activity

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Syntheses of a series of 3-alkyl(aryl)-4-tetrachlorophthalimido-4,5-dihydro-1*H*-1,2,4-triazol-5-ones and 3-alkyl(aryl)-4-(1,8-naphthalimido -4,5- dihydro)-1*H*-1,2,4-triazol-5-ones are described. The newly compounds were characterized by spectral and elemental analyses. Some compounds were screened for their antiinflammatory activity. All the compounds carring 1,2,4-triazole moiety showed significant antiinflammatory activity.

Key Words: 1,2,4-Triazolones, Tetrachlorophthalic anhydride, 1,8-Naphthalic anhydride.

INTRODUCTION

The chemistry of heterocyclic compounds continuous to be an explore field in the organic chemistry. The importance of triazole-derivative lies in the field that these have occupied a unique position in heterocyclic chemistry due to their biological activity[1-3]. The syntheses of these heterocyclics have received considerable attention in recent years. In this work, we report the 3-alkyl[aryl]-4- tetrachlorophthalimido-4,5-dihydro-1*H*-1,2,4-triazol-5-ones and 3-alkyl[aryl]-4-[1,8-naphthalimido]-4,5-dihydro-1*H*-1,2,4-triazol-5-ones through the reaction of 3-alkyl[aryl]-4-amino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones[4] with tetrachlorophthalic anhydride[5] and 1,8-naphthalic anhydride[6], respectively.

In views of these observations and in continuation of our earlier work[7-12] on the syntheses of some 1,2,4- and 1,2,3-triazole derivatives, we now report the syntheses of some more triazole derivatives derived from 4-amino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones and their antiinflammatory activity.

EXPERIMENTAL

Melting and boiling points were determined on a Gallen Kamp apparatus in open capillaries and are uncorrected. IR spectra (KBr in cm^{-1}) were recorded on a

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Jasco FT-IR 5300 spectrophotomer and PMR spectra (DMSO-d_6) on an EM 390 spectrometer using TMS as an internal standard (chemical shift in δ ppm). Purity of the compounds was checked by TLC using silica gel G. All compounds showed satisfactory elemental analyses.

3-Alkyl(aryl)-4-amino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (1): An aqueous solution of hydrazine hydrate (0.01 mol) was reacted with corresponding ester ethoxycarbonyl hydrazones (0.01 mol) at 125 ºC for the period of 1.5 h. After cooling the separated 3-alkyl(aryl)-4-amino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**1**) was taken out, dried and used directly for the next step without further purification (yield 72 %).

3-Alkyl(aryl)-4-tetrachlorophthalimido-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (2): General procedure: 3-Alkyl(aryl)-4-amino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**1**) (0.01 mol) was reacted with tetrachlorophthalic anhydride (0.01 mol) at 140-240 ºC for the period of 2.5 h. After cooling the separated crude product was filtered, washed with water and recrystallized from an appropriate solvent to give compound (**2**).

3-Methyl-4-tetrachlorophthalimido-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (2a): It was prepared by using the above method. Reaction takes place at 145-150 ºC and recrystallized from acetone-petroleum ether (1:1), (yield 70 %) m.p. 295 ºC. Anal. calcd. for $C_{11}H_4N_4O_3Cl_4$: C, 35.60; H, 1.66; N, 15.60 %; found: C, 34.34; H, 1.35; N, 15.41 %. IR (KBr, ν_{max}, cm^{-1}): 3231 (N-H), 1785, 1735, 1710 (C=O) and 1601 (C=N); PMR: δ 2.09 (3H, s, CH_3); 3.99 (2H, s, CH_2) and 11.70 ppm (1H of NH, s); MS: m/z 176 (M^+) other peaks were observed at 133, 109, 107, 889, 81 and 53.

3-Benzyl-4-tetrachlorophthalimido-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (2b): It was prepared by using the above method. Reaction takes place at 145-150 ºC and recrystallized from acetone-petroleum ether (1:1), (yield 62 %) m.p. 220 ºC. Anal. calcd. for $C_{17}H_8N_4O_3Cl_4$: C, 44.56; H, 1.86; N, 12.33 %; found: C, 44.23; H, 1.76; N, 11.99 %. IR (KBr, ν_{max}, cm^{-1}): 3192 (N-H), 1794, 1739, 1689 (C=O), 15.72 (C=N) and 731, 695 (monosustituted benzenoid ring); PMR: δ 3.92 (2H, s, CH_2); 7.16-7.45 (5H, m, aromatic-H) and 12.30 ppm (1H of NH, s); MS: m/z 185 (M^+) other peaks were observed at 159, 139, 121, 106, 88, 79 and 49.

3-Phenyl-4-tetrachlorophthalimido-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (2c): It was prepared by using the above method. Reaction takes place at 235-240 ºC and recrystallized from benzene, (yield 52 %) m.p. 278 ºC. Anal. calcd. for $C_{16}H_6N_4O_3Cl_4$: C, 43.30; H, 1.46; N, 12.63 %; found: C, 43.07; H, 1.35; N, 12.52 %. IR (KBr, ν_{max}, cm^{-1}): 3179 (N-H), 1789, 1740, 1717 (C=O), 1576 (C=N) and 730, 679 (monosustituted benzenoid ring); PMR: δ 7.30 (5H, m, aromatic-H) and 12.42 ppm (1H of NH, s); MS: m/z 187 (M^+) other peaks were observed at 148, 139, 122, 104, 89, 76, 69 and 47.

3-Alkyl(aryl)-4-(1,8-naphthalimido)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (3): General procedure: 3-Alkyl(aryl)-4-amino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones

(**1**) (0.01mol) was reacted with 1,8-naphthalic anhydride (0.01 mol) at 230-260 ºC for the period of 2.3 h. After cooling the separated crude product was filtered, washed with water and recrystallized from an appropriate solvent to give compound **3**.

3-Methyl-4-(1,8-naphthalimido)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (3a): It was prepared by using the above method. Reaction takes place at 240-250 ºC and recrystallized from acetone, (yield 55 %), m.p. 325 ºC. Anal. calcd. for $C_{15}H_{10}N_4O_3$: C, 61.32; H, 3.42; N, 19.03 %; found: C, 61.44; H, 3.31; N, 19.15 %. IR (KBr, ν_{max}, cm^{-1}): 3315 (N-H), 1738, 1695, 1685 (C=O) and 1579 (C=N); PMR: δ 2.22 (3H, s, CH_3), 7.35-7.85 (2H, m, aromatic-H stretching) and 11.62 ppm (1H of NH, s); MS: m/z 196 (M^+) other peaks were observed at 188, 136, 132, 108, 86, 59 and 46.

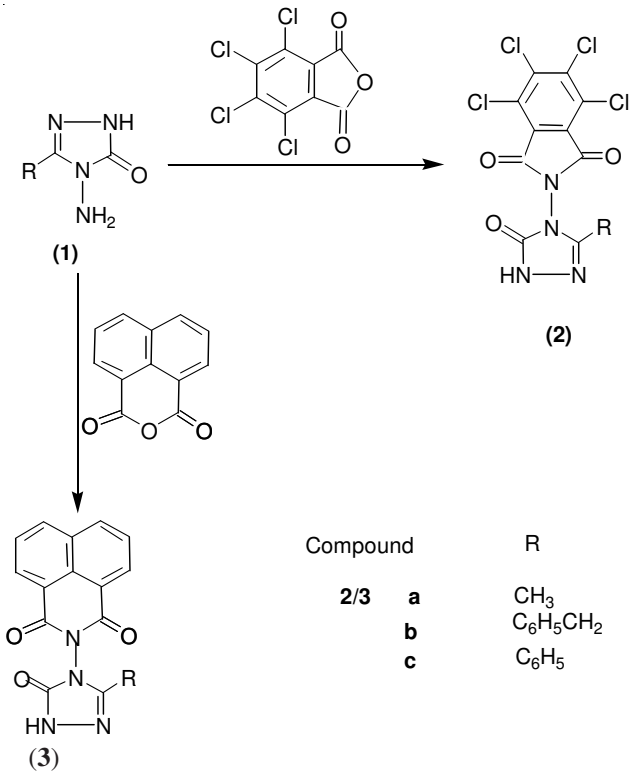
3-Benzyl-4-(1,8-naphthalimido)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (3b): It was prepared by using the above method. Reaction takes place at 240-245 ºC and recrystallized from ethanol, (yield 59 %), m.p. 250 ºC. Anal. calcd. for $C_{21}H_{14}N_4O_3$: C, 68.05; H, 3.85; N, 15.15 %; found: C, 67.99; H, 3.62; N, 14.88 %. IR (KBr, ν_{max}, cm^{-1}): 3172 (N-H), 1765, 1728, 1705 (C=O), 1581 (C=N) and 765, 696 (monosustituted benzenoid ring); PMR: δ 3.81 (2H, s, CH_2), 6.90 (5H, s, aromatic-H stretching) 7.52-7.92 (2H, m, aromatic-H); 8.10-8.46 (4H, m, aromatic-H) and 11.75 ppm (1H of NH, s); MS: m/z 201 (M^+) other peaks were observed at 167, 156, 139, 109, 88, 68 and 51.

3-Phenyl-4-(1,8-naphthalimido)-4,5-dihydro-1H-1,2,4-triazol-5-ones (3c): It was prepared by using the above method. Reaction takes place at 250-260 ºC and recrystallized from acetone, (yield 45 %), m.p. 275 ºC. Anal. calcd. for $C_{20}H_{12}N_4O_3$: C, 67.40; H, 3.41; N, 15.75 %; found: C, 67.85; H, 3.41; N, 15.55 %. IR (KBr, ν_{max}, cm^{-1}): 3196 (N-H), 1725, 1705, 1686 (C=O), 1576 (C=N) and 765, 691 (monosustituted benzenoid ring); PMR: δ 7.0-7.45 (5H, m, aromatic-H), 7.45-7.82 (5H, s, aromatic-H stretching) 7.77-8.17 (2H, m, aromatic-H) and 12.15 ppm (1H of NH, s); MS: m/z 203 (M^+) other peaks were observed at 169, 147, 126, 107, 91, 79, 57and 47.

Antiinflammatory activity: Antiinflammatory activities of all the six compounds were measured using formal in induced rat find paw edema technique[13]. Male albino rats were injected with 0.1 mL of a 1 % carageenan solution in saline in to sub planter region of the left find paw. The paw was marked with ink at the level of the lateral molecules and immersed in mercury up to this mark the paw volume was measured before and 1, 2, 3, 4 and 5 h after the injection of carageenan by mercury displacement method plethysmographically. The edema volume was determined and expressed as percentage swellings, compared with initial find paw volume of each rat. Ibuprofen was used as reference standard. The screening results revealed that showed significant antiinflammatory activity which was comparable with ibuprofen[14] (Table-1).

RESULTS AND DISCUSSION

In present work, compound 3-alkyl(aryl)-4-amino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**1**) required as starting material were treated with tetrachlorophthalic anhydride and 1,8-naphthalic anhydride at relevant temperature and pressure to obtained the corresponding 3-alkyl(aryl)-4-tetrachlorophthalimido-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**2**) and 3-alkyl(aryl)-4-(1,8-naphthalimido)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**3**), respectively (**Scheme-I**).



Scheme-I

TABLE-1
EVALUATION OF ANTIINFLAMMATORY ACTIVITY OF THE COMPOUNDS

Compd.	Substituent (R)	Percentage inhibition at the end of		
		1 h	3 h	5 h
2a	CH_3	46.92	51.80	54.11
2b	$C_6H_5CH_2$	48.92	52.60	57.21
2c	C_6H_5	61.38	67.09	64.22
3a	CH_3	62.33	68.09	64.33
3b	$C_6H_5CH_2$	56.33	58.37	51.19
3c	C_6H_5	47.88	52.61	55.21
Ibuprofen (standard)		64.06	68.10	72.62

All compounds containing 1,2,4-triazole moiety showed significant antiinflammatory activity. The structures of all the compounds are confirmed by IR, PMR and MS spectral data (experimental part).

Conclusion

In conclusion, a group of 1,2,4-triazole derivatives were synthesized and characterized. All these compounds containing 1,2,4-triazole moiety is more active and plays a prominent role in antiinflammatory activity. The structure of all the compounds are confirmed by IR, PMR and MS spectral data and are further supported by correct elemental analysis.

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