REACTION OF 1-(1-ALKOXYALKYL)-1H-1,2,4-TRIAZOLE WITH AMIDES

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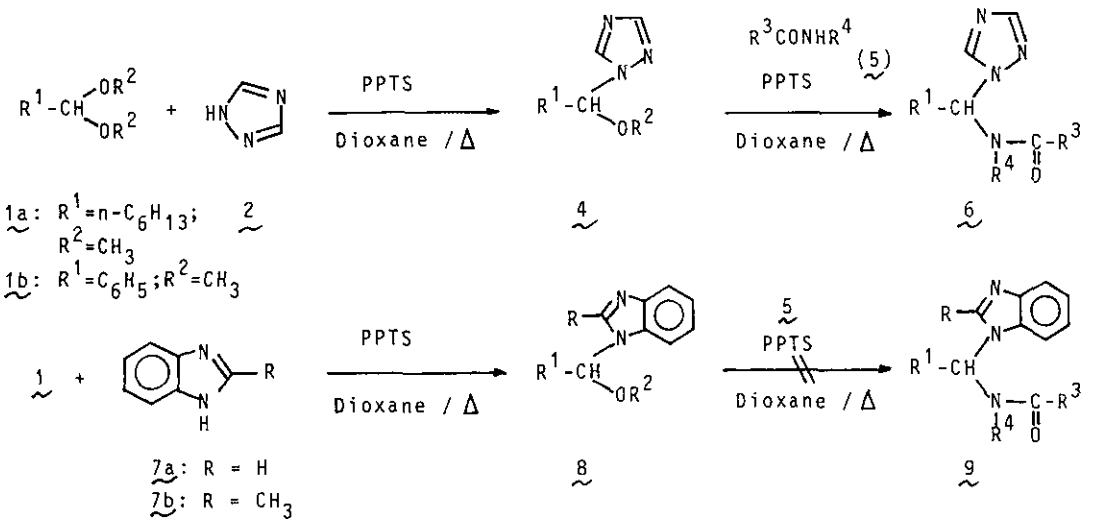
Abstract ----- 1-(1-Alkoxyalkyl)-1H-1,2,4-triazoles (4) were prepared by treating acetals (1) with 1H-1,2,4-triazole (2) in the presence of pyridinium p-toluenesulfonate (3). The alkoxy group of 4 was substituted with $-NR^4COR^3$ group by treating with carboxamides to give various 1-(1-acylaminoalkyl)-1H-1,2,4-triazole (6) in variable yields.

It has been well known that the activity of biologically active compounds sometimes increases by the introduction of an azole nucleus. 1H-1,2,4-Triazole (2) is one of the important azole not only in the drug design but also in exploiting new antieubacterial agents.[1] This paper deals with a new methodology for the introduction of a (1H-1,2,4-triazolyl)methyl moiety into the primary and secondary carboxamides. Substitution reactions of the alkoxy group of triethyl orthoformate with 1H-imidazole and benzimidazole were reported by Curtis[2] and Ooi,[3] respectively. We examined similar substitution reaction of heptanal dimethyl acetal (1a) with 1H-imidazole in refluxing dioxane, but almost no reaction was observed even in the presence of an acidic catalyst such as pyridinium p-toluenesulfonate (3; PPTS).[4] On the other hand, the reactions of the acetal (1a) with 1H-1,2,4-triazole (2) and benzimidazole (7; R=H) in the presence of PPTS in refluxing dioxane proceeded to give 1-(1-ethoxyhexyl)-1H-1,2,4-triazole (4a; 82.9%) and 1-(1-ethoxyhexyl)benzimidazole (8a; 70.4%), respectively. The results of the reactions are summarized in Table I.



Scheme 1

Although the reaction of the aromatic aldehyde acetals with 2 or 7 generally proceeded smoothly comparing with that of the aliphatic aldehyde acetals (entries 2, 4, 8 and 10 in Table I), the cyclic acetal was inactive (entry 5 in Table I). The ketal, only one example, was also reactive (entry 6 in Table I). In N-alkylation of 1H-1,2,4-triazole (2), a mixture of 1- and 4-alkyl-1H-1,2,4-triazoles was generally produced,[5] while in the present reaction the 1-substituted triazole compound (4) was solely obtained.

Next, we examined the reactivity of the alkoxyl group of 4 and 8, and it was found that the alkoxyl group could be replaced by a $-NR^4COR^3$ moiety when the substrates (4 and 8) were treated with primary and secondary amides in refluxing dioxane in the presence of PPTS. For example, treatment of two equivalents of 4a with banzamide (5a) in the presence of PPTS in dioxane at 100 ℃ gave crystalline 1-(1-benzoylaminoheptyl)-1H-1,2,4-triazole (6f) in 46.8 yield. But similar treatment of the benzimidazole derivative (8a) with benzamide (5a) did not afford any substitution product. The results are listed in Table II, which indicates that the 1-alkoxy-1-arylmethyltriazole such as 4b reacted more smoothly with the primary amides (5a~d; R^4 = H; entry 1 ~ 4) and 2-pyrrolidone (5e; $R^4 \neq$ H; entry 5) while the 1-alkoxyalkyltriazole (4a) did not react with 2-pyrrolidone (entry 11). Entries 3, 4, 8, 9 and 10 in Table II are examples in an application of the present methodology to the chemical modification of the practically useful drugs.

Table I. Reaction of Acetals with 1H-1,2,4-Triazole (2) and Benzimidazole (7)

Entry	1 R^1	R^2	Azole	Product[c] (bp or mp; ℃)	Yield (%)	^{1}H-Nmr (in $CDCl_3$) (δ ppm)
1	1a	CH_3	2	4a (bp_3 110)	82.9	0.74-1.50(m,11H),1.84-2.26(m,2H),3.30(s,3H), 5.30(t,J=11Hz,1H),7.79(s,1H),8.23(s,1H)
2	1b	CH_3	2	4b (bp_3 150)	87.8	3.51(s,3H),6.38(s,1H),7.40(s,5H),7.99 (s,1H), 8.11(s,1H)
3	1c	C_2H_5	2	4c (bp_2 175)	57.0	1.25(t,J=7Hz,3H),3.48-3.77(q,J=7Hz,2H),6.03-6.09(m,1H),6.23-6.48(m,1H),6.74-6.94(m,1H), 7.16-7.47(m,5H),7.98(s,1H),8.30(s,1H)
4	1d	C_2H_5	2	4d (bp_2 160)	36.3	1.35(t,J=6Hz,3H),3.73(q,J=6Hz,2H),6.58(s,1H), 7.53-8.33(m,6H)
5	1e[a]	$-C_2H_4-$	2	(no reaction)	----	
6	1f[b]		2	4f (bp_3 125)	64.6	1.50-2.50(m,10H),3.07(s,3H),7.97,8.30(s each, 1H each)
7	1a	CH_3	7a	8a (bp_3 150)	70.4	0.85(br t,J=5Hz,3H),1.08-1.38(m,8H),2.02-2.17(m,2H),3.22(s,3H),5.30(t,J=6Hz,1H),7.22-7.89(m,4H),7.99(s,1H)
8	1g	C_2H_5	7b	8b (mp 81-84)	84.9	1.27(t,J=7Hz,3H),2.54(s,3H),3.41-3.73(q,J=7Hz, 2H),6.62(s,1H),7.09-7.77(m,9H)
9	1h	C_2H_5	7a	8c (bp_3 135)	59.5	1.22(t,J=7Hz,3H),1.84(d,J=6Hz,3H),3.20-3.67 (m,J=7Hz,2H),5.70(q,J=6Hz,1H),7.23-7.97(m, 4H),8.07(s,1H)
10	1i	C_2H_5	7a	8d[d] (mp 123-125)	53.5	1.28(t,J=7Hz,3H),3.51-3.95(q,J=7Hz,3H),3.87(s, 6H).6.66(s,1H),7.01-7.87(m,6H),7.86(s,1H)

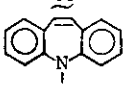
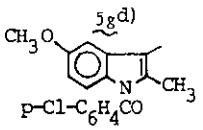
a) Ethyleneglycol acetal was used.

b) Cyclohexanone dimethyl ketal was used.

c) Satisfied hrms data were obtained (entries 1 - 9).

d) Anal. for $C_{18}H_{19}N_2BrO_3$ Calcd (Found): C, 55.26 (55.23); H, 4.89 (4.96); 7.16 (7.15).

Table II. Reaction of 1-(1-Alkoxymethyl)-1H-1,2,4-triazole (4) with Amide (5)

Entry	4		5		Product 6 (Recryst. Solv.)[e]	Yield	^{1}H-Nmr (in $CDCl_3$)
	R^1	R^2	R^3	R^4	(bp or mp; ℃)	(%)	(δ ppm)
1	4b		5a		6a ($AcOC_2H_5$)	73.0	7.17-7.93(m,12H),7.97(s,1H),8.38
	C_6H_5	CH_3	C_6H_5	H	(mp176-177)		s,1H)
2	4b		5b		6b (C_6H_6)	84.9	6.46(d,J=15.5Hz,1H),7.21-7.58(m,
	C_6H_5	CH_3	ω-styryl	H	(mp164-165)		12H(1H→D_2O exchngd.)),7.70(d,J=
							15.5Hz,1H),7.96(s,1H),8.35(s,1H)
3	4b		5c[a]		6c ($AcOC_2H_5$)	97.8	1.41(t,J=7Hz,3H),4.17(q,J=7Hz,2H),
	C_6H_5	CH_3	2-$C_2H_5OC_6H_4$-	H	(mp127-128)		6.87-7.64(m,9H),7.98(s,1H),8.42
							(s,1H),8.11-8.25(m,1H),9.25(br,1H)
4	4b		5d[b]		6d ($CHCl_3$-CCl_4)	21.4	7.26-7.66(m,7H),7.90(br,1H),7.98
	C_6H_5	CH_3	3-pyridyl	H	(mp139-141)		(s,1H),8.08-8.23(m,1H),8.39(s,1H),
							8.69-8.77(m,1H),9.03-9.07(m,1H)
5	4b		5e		6e (isopropyl ether)	46.2	1.80-2.21(m,2H),2.38-2.59(m,2H),
	C_6H_5	CH_3	(2-pyrrolidone)		(mp107-108)		3.19-3.81(m,2H),7.08-7.56(m,5H),
							7.59(s,1H),8.04(s,1H),8.29(s,1H)
6	4a		5a		6f (CCl_4)	46.8	0.73-0.99(t,J=7Hz,3H),1.12-1.44(m,
	n-C_6H_{13}	CH_3	C_6H_5	H	(mp93.5-94.5)		8H),2.05-2.32(m,2H),6.23-6.53(m,
							1H),7.15(s,1H),7.20-7.82(m,5H),
							7.95(s,1H),8.36(s,1H)
7	4a		5b		6g (CCl_4)	39.1	0.68-0.97(t,J=7Hz,3H),0.98-1.38(m,
	n-C_6H_{13}	CH_3	ω-styryl	H	(mp120-121)		8H),2.01-2.24(m,2H),6.16-6.47(m,
							1H),6.36(d,J=16Hz,1H),7.99(s,1H),
							8.36(s,1H)
8	4a		5c[a]		6h (n-hexane)	78.2	0.74-0.95(t,J=7Hz,3H),1.07-1.49(m,
	n-C_6H_{13}	CH_3	2-$C_2H_5OC_6H_4$-	H	(mp62-63)		8H),1.55(t,J=7Hz,3H),2.06-2.23(m,
							2H),4.06-4.23(m,2H),6.34-6.44(m,
							1H),6.87-8.91(br,1H)
9	4a		5f[c]		6i (c-hexane)	57.6	0.71-0.95(t,J=7Hz,3H),1.02-1.38(m,
	n-C_6H_{13}	CH_3			(mp119-120)		8H),1.64-2.08(m,2H),5.00(br,1H),
							5.82-6.13(m,1H),6.85(s,2H),7.15-
							7.57(m,8H),7.89(s,1H),8.18(s,1H)
10	4a		5g[d]		6j (CCl_4)	35.2	0.72-0.93(t,J=7Hz,3H),0.96-1.33(m,
	n-C_6H_{13}	CH_3			(mp184.5-188)		8H),1.83-2.05(m,2H),2.29(s,3H),
							3.60(s,2H),3.77(s,3H),5.90-6.25
							(m, 1H),6.28-6.50(br,1H),6.72-6.85
							(m,3H),7.39-7.71(m,4H),7.86(s,1H),
							8.23(s,1H)
11	4a		5e		(no reaction)	---	
	n-C_6H_{13}	CH_3	(2-pyrrolidone)				

a) Ethenzamide (an analgetic-antipyretic drug); b) Pyrazinamide (an antitubercular drug);
c) Carbamazepine (an antipiletic drug); d) A carboxamide of indomethacin (an anti-inflammatory);
e) Analytical data are listed in the experimental section.

Stability in variuos pH solution of 6h as a model compound was examined by use of hplc. Although 70% of the compound (6h) applied was decomposed into heptanal and the parent drug ethenzamide (5c) after several hours by treating with dil. HCl at 37 ℃, the model compound (6h) was almost recovered upon treatment with a pH 4 buffer solution as well as dil. NaOH at 37 ℃.

Recently, chemical modification of drugs on the bases of the medicinal chemistry has become very important in development of new and more potent drugs,[6] so the present methodology may provide a new chemical modification procedure for the amide drugs possessing acidic NH.

EXPERIMENTAL

General Procedure for the Synthesis of 1-(1-Alkoxymethyl)-1H-1,2,4-triazole (4; Entry 2 in Table I as a Representative ----- A mixture of benzaldehyde dimethyl acetal (1b; 7.5 ml, 50 mmol), 1H-1,2,4-triazole (2; 4.14 g, 60 mmol), PPTS (3; 50 mg) and dry dioxane (50 ml) was refluxed at 100 ℃ for 3 h under a nitrogen atmosphere. Ethyl acetate (50 ml) and 10% K_2CO_3 (5 ml) were added to the reaction mixture, and the organic layer was shaken with sat. NaCl and dried over Na_2SO_4. Removal of the solvent gave an oily residue (4b), which was purified by vacuum distillation. Yield, 8.29 g (87.8 %). bp_3 150 ℃ (Kugel-Rohr). Ir ($CHCl_3$): 1500 cm^{-1} (>C=C<). ^{1}H-Nmr (80 MHz in $CDCl_3$) δ ppm: 3.51 (s, 3H, $-OCH_3$), 6.38 (s, 1H, >CHOCH$_3$), 7.40 (s, 5H, C_6H_5), 7.99 and 8.11 (s each, 1H each, 3- and 5-positions of triazole). Ms m/z: 121 (base peak), 189 (M^+). Hrms (M^+; m/z): Calcd for $C_{10}H_{11}N_3O$, 189.0901: Found, 189.0962.

General Procedure for the Synthesis of 1-(1-Alkoxymethyl)benzimidazole (7; Entry 8 as a Representative) ----- A mixture of benzaldehyde diethyl acetal (1g; 7.5 ml, 50 mmol), 2-methylbenzimidazole (7b; 7.92 g, 60 mmol), PPTS (50 mg) and dry dioxane (50 ml) was refluxed at 100 ℃ for 5 h under a nitrogen atmosphere. Ethyl acetate (50 ml) and 10% K_2CO_3 (5 ml) were added to the reaction mixture, and the organic phase was washed with sat. NaCl, and dried over Na_2SO_4. Removal of the solvent gave an crystalline residue, which was purified by silica gel column chromatography (AcOEt as a solvent) and finally by recrystallization from n-hexane to give colorless needles. mp 81 - 84 ℃. Yield, 11.29 g (84.9 %). Ir ($CHCl_3$): 1450 cm^{-1} (>C=C<). ^{1}H-

Nmr (80 MHz in $CDCl_3$) δ ppm: 1.27 (t, J = 7 Hz, 3H, $-OCH_2\underline{C}H_3$), 2.54 (s, 3H, $C-\underline{C}H_3$), 3.41 - 3.73 (m, 2H, $-OCH_2\underline{C}H_3$), 6.62 (s, 1H, $ArC\underline{H}OEt$), 7.09 - 7.77 (m, 9H, $Ar\underline{H}$). Ms m/z: 135 (base peak), 266 (M^+). Hrms (M^+; m/z): Calcd for $C_{17}H_{18}N_2O$, 266.1418: Found, 266.1442.

General Procedure for the Synthesis of 1-(1-Acylaminoalkyl)-1H-1,2,4-triazole (6; entry 3 in Table II as a Representative) ----- A mixture of 4b (7.56 g, 40 mmol), ethenzamide (5c, 3.30 g, 20 mmol), PPTS (3; 10 mg), dry benzene (15 ml) and dry dioxane (80 ml) was refluxed for 2 h at 100 ℃ under a nitrogen atmosphere. Ethyl acetate (50 ml) and 10 % K_2CO_3 were added to the reaction mixture, and the organic layer was washed with sat. NaCl and dried over Na_2SO_4. The crystalline residue (6c), obtained by evaporation of the solution, was purified by recrystallization from ethyl acetate - n-hexane to give colorless needles. mp 127 - 128 ℃. Yield, 6.30 g (97.8 %). Ir ($CHCl_3$): 1665 cm^{-1} (C=O). ^{1}H-Nmr (80 MHz in $CDCl_3$) δ ppm: 1.41 (t, J = 7 Hz, 3H, $-OCH_2\underline{C}H_3$), 4.17 (q, J = 7 Hz, 2H, $-OC\underline{H}_2CH_3$), 6.87 - 7.64 (m, 9H, $C_6\underline{H}_3$, $C_6\underline{H}_5$ and $C_6H_5C\underline{H}$-), 7.98 and 8.42 (s each, 1H each, 3- and 5-positions of triazole), 8.11 - 8.25 (m, 1H, 6-position of ethenzamide moiety), 9.10 - 9.40 (br, 1H, N$\underline{H}$). Anal. Calcd for $C_{18}H_{18}N_4O_2$: C, 67.07; H, 5.63; N, 17.38. Found: C, 67.14; H, 5.40; N, 17.38.

Analytical data of the other compounds (6a, 6b, 6d - 6j) in Table II are listed below.

6a --- Calcd for $C_{16}H_{14}N_4O$: C, 69.05; H, 5.07; N, 20.13. Found: C, 69.18; H, 5.03; N, 20.29.

6b --- Calcd for $C_{18}H_{16}N_4O$: C, 71.04; H, 5.30; N, 18.41. Found: C, 70.94; H, 5.27; N, 18.27.

6d --- Calcd for $C_{15}H_{13}N_5O$: C, 64.51; H, 4.69; N, 25.08. Found: C, 64.62; H, 4.69; N, 25.10.

6e --- Calcd for $C_{13}H_{14}N_4O$: C, 64.45; H, 5.82; N, 23.13. Found: C, 64.66; H, 5.89; N, 23.02.

6f --- Calcd for $C_{16}H_{22}N_4O$: C, 67.10; H, 7.74; N, 19.57. Found: C, 66.98; H, 7.55; N, 19.58.

6g --- Calcd for $C_{18}H_{24}N_4O$: C, 69.20; H, 7.75; N, 17.94. Found: C, 69.40; H, 8.03; N, 17.83.

6h --- Calcd for $C_{18}H_{26}N_4O_2$: C, 65.43; H, 7.93; N, 16.96. Found: C, 65.26; H, 7.91; N, 16.95.

6i --- Calcd for $C_{24}H_{27}N_5O$: C, 71.79; H, 6.78; N, 17.44. Found: C, 72.03; H, 6.79; N, 17.49.

6j --- Calcd for $C_{28}H_{32}ClN_5O_3 \cdot H_2O$: C, 62.27; H, 6.35; N, 12.97. Found: C, 62.74; H, 5.94; N, 13.05.

Stability of the Compound 6h ----- The compound (6h; 100 mg) and naphthalene (60 mg; internal standard) were dissolved in a mixture of acetone (2.0 ml) and aqueous acidic or basic solution (1.0 ml: 0.01N HCl; 2N HCl; pH 4 phosphate buffer solution; 1N NaOH). The mixture was stirred at 37 ℃ and 10 μl of the reaction mixture was treated with 10% K_2CO_3 (0.2 ml) and ether (0.5 ml). The ethereal layer (1 μl) was taken and an amount of the produced ethenzamide (5c) and 6h was determined by hplc according to the internal standard method. Hplc condition: column (Wakosil 5C8; φ4.6 mm × 150 mm); solvent (acetonitrile : H_2O = 1 : 1); column temp. (40 ℃); detector (UV); retention time (ethenzamide 5c 3.0 min; 6h 5.5 min; naphthalene 10.5 min).

1) 0.01 N HCl: % of the produced 5c (20% after 30 min; 30% after 1 h; 35% ater 2 h; 50% after 4 h; 70% after 24 h; 90% after 48 h)
2) 2N HCl : % of the produced 5c (79% after 3 h); % of the unreacted 6h (0% after 3 h)
3) pH 4 phosphate buffer solution: % of the produced 5c (0% after 24 h); % of the unreacted 6h (95% after 24 h)
4) 1N NaOH: % of the produced 5c (0% after 24 h); % of the unreacted 6h (98% after 24 h)

REFERENCES

1) M. Ogata, M. Matsumoto, S. Shimizu, S. Kida, M. Shiro, and K. Tawara, J. Med. Chem., 1987, 30, 1348.
For review: H. Noguchi, Microorganism, 1988, 4, 24.
2) N. J. Curtis and R. S. Brown, J. Org. Chem., 1980, 45, 4038.
3) H. C. Ooi and H. Suschinsky, J. Chem. Soc. Perkin Trans. I, 1982, 2981.
4) D. F. Rane, A. G. Fishman, and R. E. Pike, Synthesis, 1984, 694.
5) M. Miyashita, A. Yoshikoshi, and P. A. Grieco, J. Org. Chem., 1977, 42, 3772.

6) H. Bundgaad, "Design of Prodrugs", 1985, Elsevier Science Publishers (Amsterdam); S. M. Roberts and B. J. Price, "Medicinal Chemistry --- The Role of Organic Chemistry in Drug Research", 1985, Academic Press Inc. (London).

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