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Oxidative Cyclization of 6-Substituted Amino-5-benzylideneamino-1,3-dimethyluracils to 9-Substituted 8-Aryltheophyllines with Thionyl Chloride

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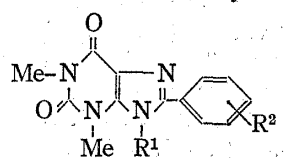
Treatment of 6-substituted amino-5-benzylideneamino-1,3-dimethyluracils with thionyl chloride at 0° for 30 min gave the corresponding 9-substituted 8-aryltheophyllines in 56—98% yields.

Keywords——6-substituted amino-5-benzylideneamino-1,3-dimethyluracils; thionyl chloride; oxidative cyclization; 9-alkyl-8-aryltheophyllines; 8-aryl-9-phenyltheophyllines

Thionyl chloride has recently been shown to be an effective oxidizing agent for the cyclization of 6-amino-5-benzylideneamino-1,3-dimethyluracils to the corresponding 8-aryltheophyllines.[2] The present paper describes an extension of this reaction to the preparation of various 9-substituted 8-aryltheophyllines, which are of particular interest as potential inhibitors of 3′,5′-cyclic AMP phosphodiesterase.[3]

TABLE I. 9-Substituted 8-Aryltheophyllines



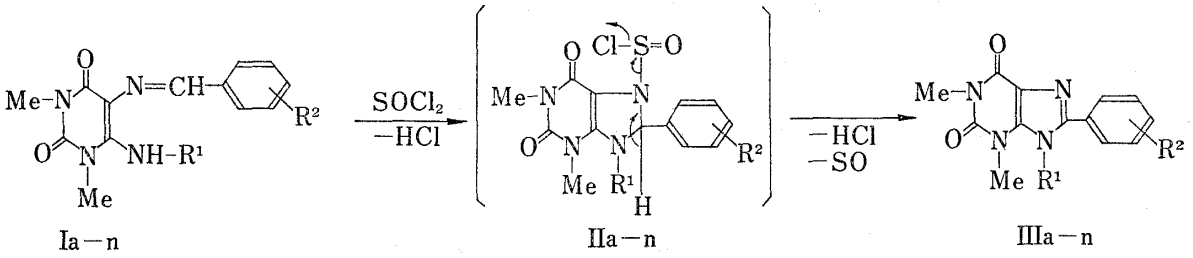
Compd. No.[a]	R^1	R^2	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N	IR (Nujol) cm^{-1} (CO)	
IIIa	Me	H	221—222	85	$C_{14}H_{14}N_4O_2$	62.21	5.22	20.73	62.37	5.42	20.55	1650	1700
IIIb	Me	4-Br	266—268	66	$C_{14}H_{13}BrN_4O_2$	48.13	3.75	16.05	48.10	3.62	16.10	1650	1690
IIIc	Me	4-Cl	227—228	98	$C_{14}H_{13}ClN_4O_2$	55.16	4.30	18.40	55.34	4.30	18.62	1650	1700
IIId	Me	3,4-Cl_2	242—244	60	$C_{14}H_{12}Cl_2N_4O_2$	49.55	3.57	16.53	49.75	3.49	16.69	1645	1700
IIIe	Me	4-Me	255—257	56	$C_{15}H_{16}N_4O_2$	63.36	5.67	19.71	63.60	5.67	19.90	1650	1700
IIIf	Me	4-OMe	242—243	80	$C_{15}H_{16}N_4O_3$	59.99	5.37	18.66	60.12	5.31	18.89	1645	1695
IIIg	Et	H	213—215	70	$C_{15}H_{16}N_4O_2$	63.36	5.67	19.71	63.38	5.71	20.01	1650	1695
IIIh	Et	4-Br	270—272	66	$C_{15}H_{15}BrN_4O_2$	49.58	4.16	15.43	49.39	4.11	15.49	1645	1695
IIIi	Et	4-OMe	231—233	89	$C_{16}H_{18}N_4O_3$	61.13	5.77	17.83	60.84	5.63	17.96	1650	1700
IIIj	Ph	H	275—276	90	$C_{19}H_{16}N_4O_2$	68.66	4.85	16.86	68.72	4.90	16.75	1655	1700
IIIk	Ph	4-Br	>300	97	$C_{19}H_{15}BrN_4O_2$	55.47	3.68	13.63	55.52	3.63	13.68	1645	1695
IIIl	Ph	4-Cl	288—291	96	$C_{19}H_{15}ClN_4O_2$	62.19	4.12	15.28	62.43	4.00	15.32	1650	1700
IIIm	Ph	4-Me	>300	98	$C_{20}H_{18}N_4O_2$	69.35	5.24	16.18	69.28	5.15	16.08	1650	1700
IIIn	Ph	4-OMe	258—259	97	$C_{20}H_{18}N_4O_3$	66.28	5.01	15.46	66.52	5.01	15.52	1650	1700

a) All compounds were recrystallized from ethanol.

1) Location: *35, Shinanomachi, Shinjuku-ku, Tokyo 160, Japan.*
2) K. Senga, K. Shimizu, and S. Nishigaki, *Chem. Pharm. Bull.* (Tokyo), **25**, 495 (1977).
3) Although a wide variety of theophylline derivatives have been examined for their ability to inhibit this enzyme, none of theophyllines possessing a substituent at position 9 have been investigated: M.S. Amer and W.E. Kreighbaum, *J. Pharm. Sci.*, **64**, 1 (1975).

Stirring of the appropriate 6-alkylamino-5-benzylideneamino-1,3-dimethyluracils (Ia—i)[4] with excess thionyl chloride at 0° for 30 min, followed by concentration of the reaction mixture and subsequent trituration of the residue with aqueous ammonia gave the corresponding 9-alkyl-8-aryltheophyllines (IIIa—i)[4] in 56—98% yields. Analogous treatment of the 6-anilino-5-benzylideneamino-1,3-dimethyluracils (Ij—n)[4] with thionyl chloride yielded the respective 8-aryl-9-phenyltheophyllines (IIIj—n)[4] in 90—98% yields (Table I).

As depicted in the Chart 1, the oxidative cyclization of Ia—n to IIIa—n with thionyl chloride presumably proceeds by the initial formation of the N-sulfinyl chloride intermediates (IIa—n) and subsequent elimination of hydrogen chloride and sulfur monoxide. A similar mechanism has been proposed in the reaction of 5-benzylideneamino-1,3-dimethylbarbituric acids with thionyl chloride leading to 2-aryl-5,7-dimethyloxazolo[5,4-*d*]pyrimidine-4,6(5H, 7H)-diones.[5] It should be noted that the cyclization of Ia—n to IIIa—n could be achieved under more milder conditions than that of 6-amino-5-benzylideneamino-1,3-dimethyluracils to 8-aryltheophyllines.[2,6]



Ia—n IIa—n IIIa—n

Chart 1

Experimental[7]

9-Substituted 8-Aryltheophyllines (IIIa—n). General Procedure——A mixture of the appropriate 6-substituted amino-5-benzylideneamino-1,3-dimethyluracils (Ia—n)[4] (0.0001 mol) and thionyl chloride (2 ml) was stirred at 0° for 30 min. The reaction mixture was concentrated *in vacuo* at room temperature and the residue was triturated with 5% aqueous ammonia (10 ml). The insoluble solid was filtered and recrystallized to give the corresponding pure products IIIa—n, which were identical with the authentic samples.[4]

4) F. Yoneda, M. Higuchi, K. Mori, K. Senga, Y. Kanamori, K. Shimizu, and S. Nishigaki, *Chem. Pharm. Bull.* (Tokyo), **26**, 2905 (1978).
5) K. Senga, J. Sato, and S. Nishigaki, *Chem. Pharm. Bull.* (Tokyo), **26**, 765 (1978).
6) Treatment of 6-amino-5-benzylideneamino-1,3-dimethyluracils with thionyl chloride at 0° for 30 min resulted in the quantitative recovery of the starting materials.
7) Melting points were taken on a Yanagimoto micro-melting point apparatus and are uncorrected. Identity of compounds was confirmed by comparison of infrared spectra (Nujol mulls) with a Japan Spectroscopic Co. Ltd., Model IR-E spectrophotometer.