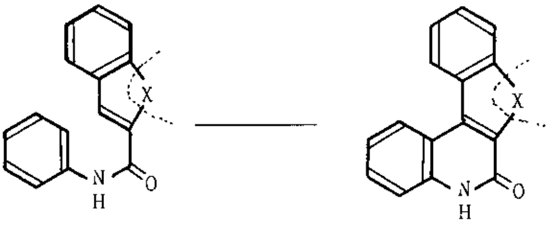
HETEROCYCLES, Vol.12, No.4, 1979

A FACILE SYNTHESIS OF 4-PHENYLCARBOSTYRILS AND 4-PHENYLISOCARBOSTYRIL INVOLVING PHOTOCYCLIZATION OF BENZO[b]THIOPHENE-2-CARBOXANILIDES AND 2-BENZOYLAMINO-3-CHLOROBENZO[b]THIOPHENE

Shinzo Kano, Toshihiko Ozaki, and Satoshi Hibino
Tokyo College of Pharmacy, 1432-1 Horinouchi, Hachioji,
Tokyo 192-03, Japan

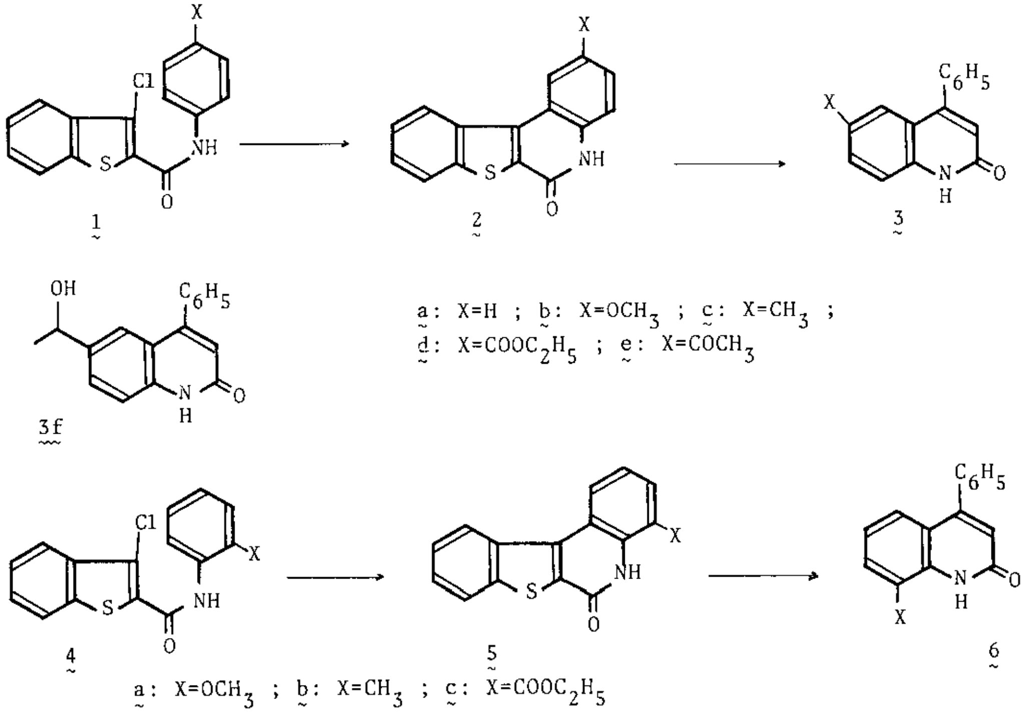
Abstract —— Photocyclization of 3-chlorobenzo[b]thiophene-2-carboxanilide afforded 1-benzothiophene[2,3-c]quinolin-6-one, which upon desulfurization gave 4-phenylcarbostyril (3a). In this way, 4-phenyl-6-substituted-carbostyrils (3b), (3c), (3d) and (3f) and 8-substituted analogues (6a), (6b) and (6c) were also obtained. This approach to 4-phenylcarbostyrils was applied to a synthesis of 4-phenylisocarbostyril (12) through photocyclization of 2-benzoylamino-3-chlorobenzo[b]thiophene.

Photocyclization of α,β-unsaturated anilides giving 4-substituted 3,4-dihydrocarbostyrils was reported by Ogata[1] and Chapman[2,3] and this reaction was extended to the synthesis of a wide range of hardly accessible heterocycles by substituting a heterocylic ring such as pyridine, pyrimidine, pyrazine, imidazole for phenyl of the anilides[4]. Most of these reaction proceeded in moderate yield. However, photocyclization of the cinnamic acid anilide resulted in failure[1,5]. Photocyclization of anilides of the appropriate heteroaromatic acids[6] possessing a styrene moiety, such as benzo[b]thiophene can be applied to a synthesis of 4-phenylcarbostyrils, if X can be removed after cyclization. (Scheme 1). By this method, 4-phenylcarbostyrils can be easily obtained. Upon consideration of this design for 4-phenylcarbostyrils, sulfur was picked as one of most suitable atom for X, since sulfur is easily removable[7] after cyclization. From these points of view, we investigated the synthesis of 4-phenylcarbostyrils by an application of photocyclization of 3-chlorobenzo[b]thiophene-2-carboxanilides. These results were described in this paper.



Scheme 1

Irradiation of 3-chlorobenzo[b]thiophene-2-carboxanilide (1a)[8] in acetone, prepared by condensation of 3-chlorobenzo[b]thiophene-2-carbonyl chloride[9] with aniline in benzene in the presence of triethylamine, afforded 1-benzothiophene-[2,3-c]quinolin-6-one (2a)[8,10,11,12] in 70 % yield. Desulfurization of 2a with Raney Ni gave 4-phenylcarbostyril (3a)[13] in 65 % yield. This approach to 3a was applied to the preparation of 4-phenyl-6-substituted-carbostyrils. The amide (1b), (1c), (1d) and (1e) were prepared as in the formation of 1a. On irradiation of these amides (1b-1e) the corresponding 2-substituted 1-benzothiophene-[2,3-c]quinolin-6-ones (2b), (2c), (2d) and (2e) were obtained. Desulfurization of (2b), (2c) and (2d) gave 6-methoxy-4-phenylcarbostyril (3b), 6-methyl-4-



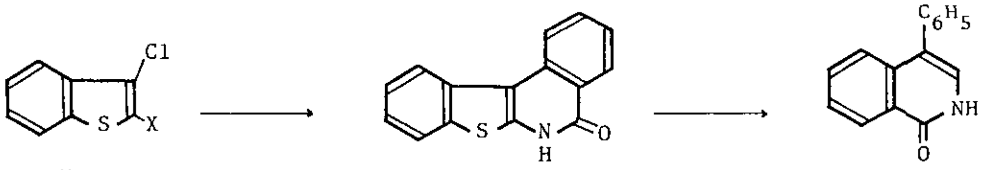
a: X=H ; b: X=OCH_3 ; c: X=CH_3 ;
d: X=$COOC_2H_5$; e: X=$COCH_3$

a: X=OCH_3 ; b: X=CH_3 ; c: X=$COOC_2H_5$

Scheme 2

phenylcarbostyril (3c) and ethyl 4-phenylcarbostyril-6-carboxylate (3d) in good yield, respectively. In the case of 2e, reduction of acetyl group occurred during desulfurization affording 6-(α-hydroxy)ethyl-4-phenylcarbostyril (3f) in 15 % yield. Furthermore, in a similar fashion, photocyclization of the anilides (4a), (4b) and (4c) was also examined to yield the corresponding 4-substituted 1-benzothiophene[2,3-c]quinolin-6-ones (5a), (5b) and (5c), respectively. Desulfurization of (5a-5c) afforded the corresponding 4-phenyl-8-substituted-carbostyrils (6a), (6b) and (6c), respectively. Physical character and yields of these products are listed in the Table 1. Thus, photocyclization of benzo[b]-thiophene-2-carboxanilides followed by desulfurization of the photo-products was shown to be a unique method for the approach to a variety of 4-phenylcarbostyrils with varying yields. (Scheme 2).

Finally, this synthetic design of carbostyrils was applied to the synthesis of 4-phenylisocarbostyril. Condensation of 2-amino-3-chlorobenzo[b]thiophen (7), derived from 3-chlorobenzo[b]thiophene (8)[14] (8 ⟶ 9 ⟶ 7), and benzoyl chloride yielded the amide (10), which was subjected to photocyclization in benzene. The photo-product (11; 25 %), mp >290 °C, was treated with Raney Ni in ethanol under reflux to give 4-phenylisocarbostyril (12)[15] in 80 % yield. Thus, the ease of synthesis of the amides and the photo-products makes this approach to 4-phenylcarbostyrils and 4-phenylisocarbostyril an attractive synthetic design.



7: X=NH_2
8: X=H
9: X=NO_2
10: X=$NHCOC_6H_5$

11

12

Scheme 3

Table 1. Synthesis of 4-phenylcarbostyrils (**3** and **6**) through desulfurization of 1-benzothiophene[2,3-c]quinolin-6-ones (**2** and **5**)

Amide	Photo-product			4-Phenylcarbostyril			
		Yield (%)	mp °C		Yield (%)	mp °C	NMR Spectra: ppm
1a	**2a**	70	>290 (EtOH)	**3a**	65	265-266 (benzene)	(CD_3OD) 6.57 (s, 1H), 7.40-8.0 (m, 9H)
1b	**2b**	35	>290 (EtOH)	**3b**	70	255-256 (benzene)	(CD_3OD) 3.70 (s, 3H), 6.53 (s, 1H), 6.83-8.23 (m, 8H)
1c	**2c**	40	>290 (EtOH)	**3c**	99	241-242 (benzene)	(CD_3OD) 2.33 (s, 3H), 6.67 (s, 1H), 7.15-8.15 (m, 8H)
1d	**2d**	98	>290 (EtOH)	**3d**	99	294-295 (EtOH)	($CDCl_3$-d_6-acetone) 1.30 (t, J=8 Hz, 3H), 4.27 (q, J=8 Hz, 2H), 6.45 (s, 1H), 7.17-8.33 (m, 8H)
1e	**2e**	80	>290 (EtOH)	**3f**	15	224-225 (MeOH)	(CD_3OD) 1.42 (d, J=6 Hz, 3H), 4.82 (q, J=6 Hz, 1H), 6.55 (s, 1H), 7.37-8.03 (m, 8H)
4a	**5a**	35	>290 (EtOH)	**6a**	55	186-188 (benzene)	($CDCl_3$) 3.98 (s, 3H), 6.57 (s, 1H), 6.83-7.77 (m, 8H)
4b	**5b**	90	>290 (EtOH)	**6b**	80	222-223 (benzene)	($CDCl_3$) 2.58 (s, 3H), 6.58 (s, 1H), 7.18-7.72 (m, 8H)
4c	**5c**	75	224-225 (EtOH)	**6c**	80	139-140 (benzene-EtOH)	($CDCl_3$) 1.45 (t, J=7 Hz, 3H), 4.45 (q, J=7 Hz, 2H), 6.60 (s, 1H), 6.90-8.42 (m, 8H)

References

1. Y. Ogata, K. Takagi, and I. Ishino, *J. Org. Chem.*, **36**, 3975 (1971).
2. O. L. Chapman and W. R. Adams, *J. Amer. Chem. Soc.*, **90**, 2333 (1968).
3. P. G. Cleveland and O. L. Chapman, *Chem. Commun.*, **1967**, 1064.
4. M. Ogata and H. Matsumoto, *Chem. Pharm. Bull.*, **20**, 2264 (1972).
5. Also in our investigations, only the starting material was recovered. Photo reaction was carried out by the use of 300 W high pressure mercury lamp, Halos PIH-300 instrument.
6. E. Winterfeldt and H. J. Altmann, *Angew. Chem.*, **80**, 486 (1968).
7. A. I. Meyers, 'Heterocycles in Organic Synthesis, 3', p 269, John Wiley & Sons, New York (1974).
8. M. Terashima, K. Seki, K. Itoh, and Y. Kanaoka, 'Abstracts of Papers, 97th Annual Meeting, Pharmaceutical Society of Japan, Tokyo, Apr.5-7, 1977, Part II ', p 56.
9. W. B. Wright, Jr. and H. Brabander, *J. Heterocyclic Chem.*, **8**, 711 (1971).
10. Y. Kanaoka, K. Itoh, Y. Hatanaka, J. L. Flippen, I. L. Karle, and B. Witkop, *J. Org. Chem.*, **40**, 3001 (1975).
11. M. Terashima, K. Seki, K. Itoh, and Y. Kanaoka, *Heterocycles*, **8**, 421 (1977).
12. Y. Kanaoka, K. Itoh, and Y. Hatanaka, *Heterocycles*, **3**, 1106 (1975).
13. E. Ritchie, *J. Proc. Roy. Soc.*, **80**, 33 (1946).
14. S. Nakagawa, J. Okumura, F. Sakai, H. Hoshi, and T. Naito, *Tetrahedron Lett.*, **1970**, 3719.
15. E. F. M. Stepheson, *J. Chem. Soc.*, **1956**, 2557.

Received, 5th January, 1979