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SYNTHESIS OF QUINOLINE AND BENZO[b]THIOPHENE DERIVATIVES BY RING ANNELATION OF PYRIDINES AND THIOPHENES

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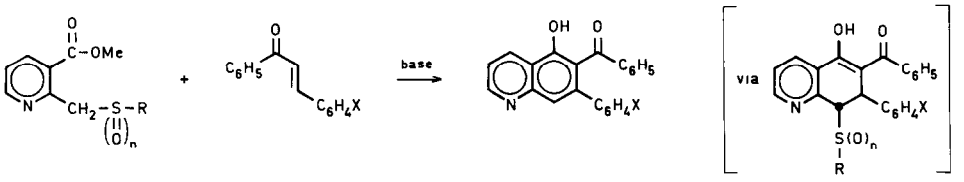
Selected ortho-disubstituted pyridines and thiophenes react with Michael acceptors to give functionalized quinolines or benzo[b]thiophenes, respectively.

Existing methodology for annelating pyridines to quinolines is extremely scarce, as was emphasized quite recently by Ghera *et al.*[1] Attempts of these authors to reduce this gap prompt us to report our own efforts to achieve the same goal. A similar situation exists for benzothiophenes: methods for constructing the thiophene ring to benzenes are available in variety but again the reverse approach, *i.e.* annelation of thiophenes, is hardly investigated.[2]

Scheme I (R=p-tolyl)[3]



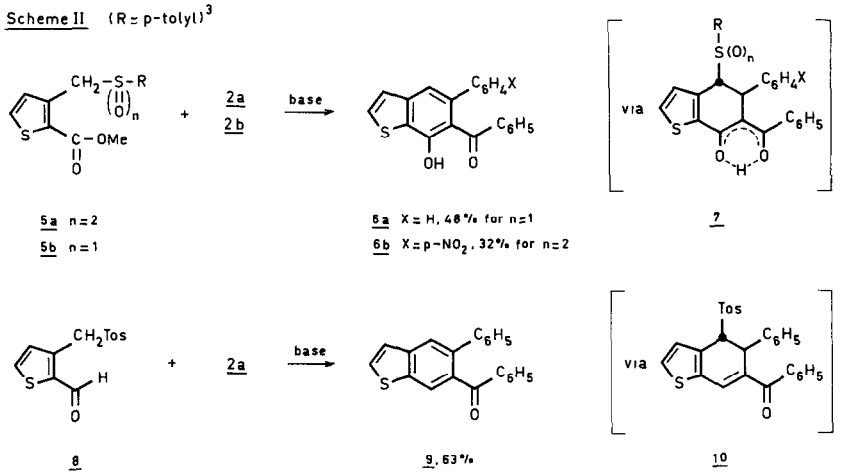
1a n=2 1b n=1 | 2a X=H 2b X=p-NO_2 | 3a X=H, 72% for n=1 3b X=p-NO_2 20% for n=2 | 4a X=H, 59% for n=2 4b X=p-NO_2 n=2

The basis of our approach is the reaction of conjugated systems of the Michael acceptor type with pyridines — or thiophenes — carrying vicinal substituents that provide a nucleophilic as well as an electrophilic center alpha to the heterocyclic ring. Schemes I and II give characteristic examples in some detail. To be synthetically effective, substituents and conditions should preferably be chosen so that the three individual reaction steps (Michael addition, ring closure, and elimination) take place concomitantly in one operation. We find this possible indeed. Also, the new method of ring annelation allows substitution patterns in quinolines and benzothiophenes that are not easily obtained otherwise.

Several substituents are conceivable to stabilize the negative charge in the conjugate bases of methylpyridines, or methylthiophenes, required for the Michael addition. Previous work in our group[4] and by Hauser and Rhee[5] on the synthesis of naphthalenes has shown that sulfonyl and sulfinyl substituents are especially useful for this purpose; they frequently lead to aromatized products by base-induced or thermal 1,2-elimination processes, respectively.[6] We, thus, have prepared and investigated methyl 2-tosylmethylnicotinate (1a), methyl 3-tosylmethylthiophene-2-carboxylate (5a), the corresponding sulfoxides 1b and 5b, and 3-tosylmethylthiophene-2-carboxaldehyde (8).[3,7]

Reaction of the pyridine sulfoxide 1b with chalcone (2a) and *t*-BuOK (2.5 equiv.) in 1,2-dimethoxyethane (DME) for 24 h at 20°C resulted in 6-benzoyl-5-hydroxy-7-phenylquinoline (3a, 72% yield, mp 134.5-135.5°C). Although no intermediates were obtained, the reaction is postulated to proceed by Michael addition of the conjugate base of 1b to 2a to give an enolate, which by intramolecular acylation gives 4, followed by a (thermal *cis*) elimination of *p*-toluenesulfenic acid to 3a. An analogous series of steps is assumed in the conversion of the thiophene sulfoxide 5b to 6a (48% yield, mp 135-137.5°C, Scheme II).

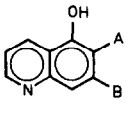
Scheme II (R = p-tolyl)[3]



Under conditions comparable to the reaction of 1b, the pyridine sulfone 1a and chalcone (2a) gave the dihydro derivative 4a (59% yield, mp 170-172.5°C)[8] rather than the quinoline 3a. Apparently the acidic OH in 4a prevents a base-induced elimination of *p*-toluenesulfinic acid (TosH), despite the expected gain in resonance energy.[9] On the other hand 1a and 4-nitrochalcone (2b) give the fully aromatized quinoline 3b (20% yield, mp 165-165.5°C), presumably because the increased acidity of C(7)-H in intermediate 4b facilitates the elimination of TosH.

A comparable situation exists in the thiophene series. 7-Hydroxybenzo[b]thiophene derivatives

TABLE. Functionalized Quinolines, Benzo[b]thiophenes and Dihydroderivatives Synthesized from 1, 5 or 8 using Substrates other than Chalcone and 4-Nitrochalcone (*cf.* Schemes I and II).



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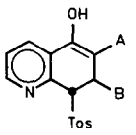

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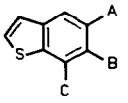

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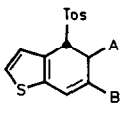

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Compd	A	B	C	Yield (%)	Mp (°C)	From, and	Conditions
11a	COOMe	COOMe	-	46	114-116	1b, diMe maleate	*a*
11a	COOMe	COOMe	-	14	114-116	1a, diMe maleate	*a*
12a	COOMe	COOMe	-	48	170-172	1a, diMe maleate	*b*
12b	COOMe	Me	-	40	165-166.5	1a, Me crotonate	*c*
12c	COOMe	Ph	-	30	182.5-184.5	1a, Me cinnamate	*a*
13a	COOMe	COOMe	OH	52	114-115.5	5a, diMe maleate	*d*
13a	COOMe	COOMe	OH	45	114-115.5	5a, diMe fumarate	*c*
13b	Ph	COOMe	OH	43	148-149	5b, Me cinnamate	*a*
13c	COOH	COOH	H	68	240-260 (d)	8, diMe maleate	*e*
13d	Bz	Bz	H	34	146-147	8, *trans*-1,2-diBz-ethene	*f*
13e	CH_2-CH_2-$C(Me)_2$-CO		H	60	119-120	8, 6,6-diMe-2-cyclohexenone	*g*
14a	COOMe	COOMe	OH	30	152-154	5a, diMe fumarate	*b*
14b	Ph	COOMe	OH	29	169-171	5a, Me cinnamate	*a*
14c	Me	COOH	H	55	140-150 (d)	8, Me crotonate	*h*

Conditions: *a*: 2.5 equiv. *t*-BuOK, DME, 20°C, 24-27 h; *b*: 2.5 equiv. NaOMe, DMSO, 20°C, 24-27 h; *c*: 4 equiv. *t*-BuOK, DME, 20°C, 24 h; *d*: 4 equiv. NaOMe, DME, 20°C, 24 h and 60°C, 4 h; *e*: 4 equiv. *t*-BuOK, DME, 65°C, 2 h; *f*: 4 equiv. *t*-BuOK, DME, 65°C, 2 h and 20°C, 40 h; *g*: 2.5 equiv. *t*-BuOK, DME, -20°C, 1 h and 20°C, 3 h and 50°C, 20 min; *h*: 2 equiv. *t*-BuOK, DME, 20°C, 48 h.

6a and 6b (mp 180-182°C) were obtained from chalcone (2a) and the sulfoxide 5b, and from 4-nitrochalcone (2b) and the sulfone 5a, respectively, whereas the tosyl substituted dihydro derivative 7 (X = H, n = 2, mp 176.5-177.5°C)[10] was formed in 74% yield from 5a and 2a.

3-Tosylmethylthiophene-2-carboxaldehyde (8) gave benzo[b]thiophene 9 (mp 125-126°C) with chalcone (2a). In contrast to the reaction of 5a, ring closure to the aldehyde group of 8 involves elimination of the aldehyde oxygen to give intermediate 10. In the absence of an acidic OH (as in 4) elimination of TosH from 10 occurred spontaneously with *t*-BuOK [with NaOMe compound 10 (mp 184-184.5°C) was isolated in 55% yield].

Further results of these reaction principles applied to other Michael acceptors are collected in the Table.

The synthesis of starting materials[3] 1, 5 and 8 is outlined only briefly, involving essentially known chemistry. Methyl 2-methylpyridine-3-carboxylate[11] on bromination (NBS) and sulfonylation (TosNa) gave 1a (46% overall yield, mp 106-107°C), whereas sulfenylation (C_7H_7SNa) and oxidation ($NaIO_4$) gave 1b (10% overall yield, mp 73-74.5°C). Similarly, bromination and sulfonylation (60% yield) of methyl 3-methylthiophene-2-carboxylate[12] (bp 94-98°C/11 mm Hg, from 3-methylthiophene via 2-iodo derivative,[13] Grignard derivative, and reaction with dimethyl carbonate) gave 5a (mp 129.5-131.5°C) which upon reduction ($LiEt_3BH$), followed by oxidation (pyridinium dichromate) gave 8 (34% overall yield, mp 142-144°C). Compound 5b (mp 93-96°C) was obtained analogously to 1b in 56% overall yield.

To summarize, we feel that our annelation approach to quinolines is superior to those investigated by Ghera *et al*,[1] however, the synthesis of some of our starting materials deserves improvement for which we may benefit from Ghera's work.

References and Notes

1. E. Ghera, Y.B. David and H. Rapoport, *J. Org. Chem.*, 46, 2059 (1981), and references cited therein.
2. For syntheses of benzothiophenes from benzene derivatives, see: B. Iddon and R.M. Scrowston in *Adv. in Heterocyclic Chem.*, Vol. 11, A.R. Katritzky and A.J. Boulton (Eds.), Academic Press, New York, 1970, p. 206-236. For the alternative approach from thiophene derivatives, see: *ibid.* p. 236-238; C.G.M. Janssen, P.M. van Lier, P. Schipper, L.H.J.G. Simons and E.F. Godefroi, *J. Org. Chem.*, 46, 3159 (1980); M.G. Reinecke and J.G. Newson, *J. Am. Chem. Soc.*, 98, 3021 (1976).
3. These and all further new compounds gave satisfactory elemental microanalyses and consistent spectral data (^1H NMR, IR); yields have not been optimized in most cases.
4. J. Wildeman, P.C. Borgen, H. Pluim, P.H.F.M. Rouwette and A.M. van Leusen, *Tetrahedron Lett.*, 1978, 2213.
5. F.M. Hauser and R.P. Rhee, *J. Org. Chem.*, 43, 178 (1978), and 45, 3061 (1980).
6. The use of cyanide as leaving group in quinone synthesis similar to refs. 4 and 5 has been reported meanwhile: G.A. Kraus and H. Sugimoto, *Tetrahedron Lett.*, 1978, 2263; for otherwise related naphthalene syntheses see: N.J.P. Broom and P.G. Sammes, *J.C.S. Chem. Comm.*, 1978, 162; L. Contreras, C.E. Slemon and D.B. MacLean, *Tetrahedron Lett.*, 1978, 4237.
7. In addition to esters and aldehydes other functional groups are useful as electrophilic centers, for example, cyanides as in 2-cyano-3-*p*-tolylsulfinylmethylthiophene (mp 89-92°C), the corresponding sulfone (mp 162-164°C) and its 3,4-isomer (mp 157-159°C), *cf.* ref. 4. Such reactions are under investigation now, as well as annelations of other heterocyclic nuclei.
8. In 4a the substituents at C(7) and C(8) probably have the *trans* configuration, *cf.* note 10.
9. Compare ref. 4.
10. Methylation (CH_2N_2 or Me_2SO_4) of 7 (X = H, n = 2) gave both OMe derivatives (mp 174.3-176.3°C and mp 233.2-233.6°C). X-ray analysis of the latter compound (Me at the benzoyl oxygen), carried out by Mr. F. van Bolhuis of the Department of Chemical Physics of Groningen University, clearly demonstrates the *trans* position of the substituents at C(4) and C(5), even though the ^1H NMR coupling constant of C(4)-H, C(5)-H is only 1 Hz.
11. Synthesized analogous to ethyl ester as described by: F. Bohlmann and D. Rahtz, *Chem. Ber.*, 90, 2265 (1957); NBS-bromination: J. Hurst and Wibberley, *J. Chem. Soc.*, 1962, 119.
12. R.M. Scrowston and D.C. Shaw, *J.C.S. Perkin I*, 1976, 749.
13. H. Suzuki, T. Iawo and T. Sugiyama, *Bull. Inst. Chem. Res., Kyoto Univ.*, Vol. 52, Nb. 3, 561 (1974).

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