Tetrahedron Letters,Vol.26,No.2,pp 157-160,1985
Printed in Great Britain

0040-4039/85 $3.00 + .00

A FACILE SYNTHESIS OF FUNCTIONALIZED 9,10-ANTHRACENEDIONES VIA TOSYLATE AND TRIFLATE PHENOLIC ACTIVATION

H. D. Hollis Showalter,* Ellen M. Berman, and Judith L. Johnson

Chemistry Department, Warner-Lambert/Parke-Davis Pharmaceutical Research, Ann Arbor, Michigan 48105

Jerry L. Atwood and William E. Hunter

Department of Chemistry, The University of Alabama, University (Tuscaloosa), Alabama 35486

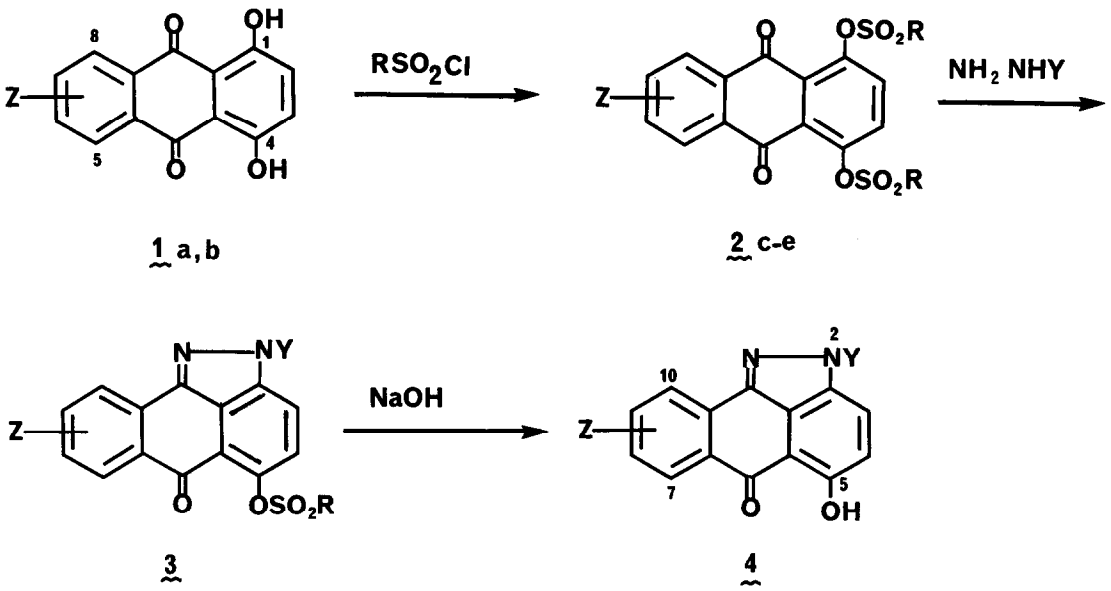
Abstract: Reaction of 1,4-dihydroxy-9,10-anthracenedione bistosylates and bistriflates with a range of common nucleophiles is discussed.

Recently we reported on the synthesis and biological evaluation of a novel class of potent, broad-spectrum anticancer agents, the 5-[(aminoalkyl)-amino]-substituted anthra[1,9-cd]pyrazol-6(2H)-ones (anthrapyrazoles), the initial representatives of chromophore-modified anthracenediones related to the clinical agents ametantrone and mitoxantrone.[1] Traditional approaches to the anthrapyrazole ring system have relied upon the condensation of 1-halo-9,10-anthracenedione precursors with monosubstituted hydrazines. While these reactions generally proceed cleanly and in good yields, their application to complex anthracenedione systems, such as the anthracycline antitumor antibiotics, is precluded because of the stringent conditions required to convert hydroxylated anthracenediones to their corresponding halo derivatives.[2]

This paper describes novel methodology for a convenient transformation of 1,4-dihydroxy-9,10-anthracenediones into functionalized variants by tosylate and triflate phenolic activation. The ready availability of many naturally occurring hydroxylated 9,10-anthracenediones, such as quinizarin (1a), led us to investigate the possibility of nucleophilic displacement of a sulfonate ester by various nucleophiles through an addition-elimination mechanism. The reaction sequence for the synthesis of 5-hydroxyanthrapyrazoles (4) is shown in Scheme I.

The reaction of quinizarin with p-toluenesulfonyl chloride occurred smoothly in the presence of Hunig's base to form bistosylate 2c in 95% yield.[3] Condensation of 2c with 2-(hydroxyethyl)hydrazine in DMF at room temperature afforded a 79% yield of 5-(tosyloxy)anthrapyrazole 3 (Table I, entry 1). The additions of other monosubstituted hydrazines to 2c proceeded similarily and are listed in Table I (entries 2,3) along with 5-hydroxy-anthrapyrazoles (4) derived from hydrolysis of 3 (1 equiv 10N NaOH/3:2 95%

SCHEME I

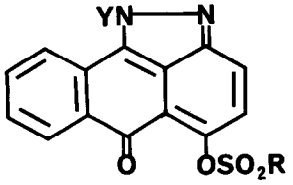


Series: (a) Z=H. (b) Z=5-OCH_3. (c) Z=H; R=$C_6H_4CH_3$. (d) Z=5-OCH_3; R=$C_6H_4CH_3$. (e) Z=H; R=CF_3.

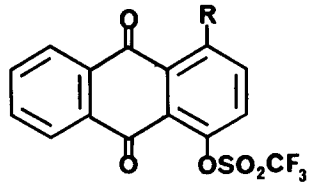
EtOH:p-dioxane/25°C).[4] 1,4-Bis(tosyloxy)-5-methoxy-9,10-anthracenedione (2d, mp 167-170°C), derived from 5-methoxyquinizarin (1b)[5], reacted more sluggishly because of the deactivating effect of the methoxy substituent and afforded a 40% yield of a ~ 4:1 mixture of C-7 and C-10 methoxyanthrapyrazoles, respectively, (entry 4).

The possibility exists that hydrazine addition could afford one of two regioisomers, viz. 3 or structure 5. Confirmation that monoalkyl hydrazine addition gave a single regioisomer with the side chain orientation as shown in 3 was provided by single-crystal X-ray analysis (Table I, entry 1).[6]

We also explored the chemistry of bistriflate 2e which was synthesized by standard techniques. Treatment of 2e with hydrazines was examined in several solvents including DMF, CH_3CN, CH_2Cl_2 and lower alcohols. Yields ranged from 13-46%. Better yields and reaction reproducibility were realized utilizing THF as solvent (Table I, entries 5-7). Additionally, we reacted 2e with a range of common hard and soft nucleophiles. Soft nucleophiles (amines, thiols) gave excellent yields of monosubstituted products 6a-c. Reaction with hard nucleophiles [n-Bu_4NN_3, NaCN, KF, $NaCH(CO_2CH_3)_2$] in a variety of solvents led either to complex mixtures or rapid desulfonation to phenol precursors.



5



6

a: R=$NHCH_2Ph$ (86%; mp 190-191°C)
b: R=$NHCH_2CH_2NMe_2$ (92%; mp 138-139°C)
c: R=SPh (89%; mp 168-170°C)

TABLE I

$$2 \xrightarrow{NH_2NHY} 3 \xrightarrow{OH^-} 4$$

Entry	Quinone 2	Anthrapyrazole 3			% Isolated Yield; mp °C	Hydrolysis Product 4 (% Isolated Yield; mp °C)
		Z	R	Y		
1	2c	H	$C_6H_4CH_3$	CH_2CH_2OH	79; 184-186	45; 180-181
2	2c	H	$C_6H_4CH_3$	$CH_2CH_2NEt_2$	82; 93-94	69; 259-263 (d) (HCl)
3	2c	H	$C_6H_4CH_3$	$CH_2CH_2NHCH_2CH_2OH$	64; 164-167	56; 268-270 (d) (HCl)
4	2d	7-OCH_3	$C_6H_4CH_3$	$CH_2CH_2NEt_2$	33; 138-140	-
		10-OCH_3	$C_6H_4CH_3$	$CH_2CH_2NEt_2$	7; 131-134	-
5	2e	H	CF_3	CH_3	76; 169-170	-
6	2e	H	CF_3	$CH_2CH_2NEt_2$	62; 129-131	-
7	2e	H	CF_3	$CH_2CH_2NHCH_2CH_2OH$	55; 166-168	-

The synthesis of 2c,e and general methods for the synthesis of anthrapyrazoles 3 are as follows:

1,4-Bis-(p-toluenesulfonyloxy)-9,10-anthracenedione (2c): A stirred suspension of 48 g (0.2 mole) of quinizarin (1a), 76.6 ml (0.44 mole) of i-Pr_2NEt, 82 g (0.43 mole) of p-toluenesulfonyl chloride, and 500 ml of CH_3CN was heated at reflux for 3 hr. The mixture was diluted with 200 ml of $CHCl_3$, refluxed for an additional 1 hr, then cooled to 25°C. Filtration of the slurry gave 98 g (90%) of the dried product; mp 224-227°C. Processing of the mother liquor left 5.6 g (5%) of additional product; mp 221-226°C.

1,4-Bis-(trifluoromethanesulfonyloxy)-9,10-anthracenedione (2e): A carefully maintained 5-10°C suspension of 14.4 g (60 mmole) of quinizarin, 24 ml (138 mmole) of i-Pr_2NEt, 733 mg (6 mmole) of DMAP, and 180 ml of dry CH_2Cl_2 was treated dropwise with 13.1 ml (123 mole) of TfCl. After 30 min at 5°C, the mixture was concentrated to a solid that was triturated from 2-PrOH to give 29.4 g (97%) of the dried product; mp 179-181°C.

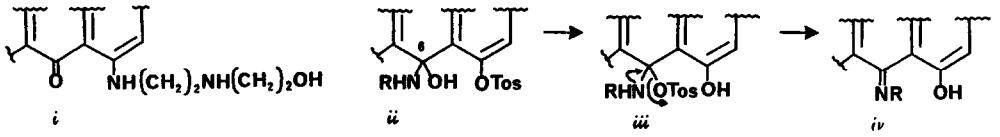
Procedure for Synthesis of Anthrapyrazoles 3: (a) From bistosylate 2c - An ice-cold suspension of 2c, 1.5 equiv of i-Pr_2NEt, and DMF was treated dropwise with 3.5 equiv of the hydrazine in DMF. The mixture was maintained at

25°C until completion of the reaction as judged by TLC (1-4 hr). The DMF was removed in vacuo and the residue triturated from 2-PrOH to give the product. Crystallization from CH_3CN gave an analytical sample. (b) From bistriflate 2e - Reaction of 2e with various hydrazines (and nucleophilic precursors to 6a-c) was carried out as described for 2c except that THF was used as solvent.

We believe that the activation of anthraquinone peri-phenolic functionality as outlined in this paper will have broad application in the synthesis of novel anthracenedione and anthracycline anticancer agents. Further efforts toward these applications are being pursued in our laboratories.[7]

References and Notes

1. Showalter, H.D.H.; Johnson, J.L.; Werbel, L.M.; Leopold, W.R.; Jackson, R.C.; Elslager, E.F. J. Med. Chem. 1984, 27, 253.
2. Bayer, O. "Methoden der Organischen Chemie," Houben-Weyl, 4th Edit., Vol. 7, Pt. 3, p 119, G. Thieme Verlag, Stuttgart, 1979.
3. All new compounds showed microanalytical and spectroscopic properties consistent with their assigned structures.
4. Reaction of 3 (Table I, entry 3) with 5-10 equiv. of 2-(2-aminoethylamino)ethanol in pyridine at 70°C or DMF at 50°C gave a 3:2 mixture, respectively, of i, derived from C-5 tosylate displacement, and iv, derived from C-6 carbonyl attack followed by the rearrangement shown.



i *ii* *iii* *iv*

5. Krohn, K.; Tolkiehn, K. Chem. Ber. 1979, 112, 3453.
6. Inquiries on the X-ray analysis should be directed to JLA. Supplementary data are available on request according to instructions outlined in Tet. Lett. 1983, 24, 5154.
7. While we were preparing this manuscript, there was a report on the utilization of bistosylate 2c to synthesize unsymmetrical 1,4-diamino-9,10-anthracenediones. See Zielske, A.G. "Abstracts of Papers;" 188th National Meeting of the American Chemical Society, Philadelphia, PA, August 26-31, 1984; Abstr MEDI 56.

(Received in USA 1 October 1984)