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N-(ω-TOSYLOXYALKYL)PHTHALIMIDES AS REACTIVE GENERAL SYNTHONS FOR INTRODUCING ALKYLAMINO GROUPS AND THEIR APPLICATION FOR THE "SELF-PROLIFERATIVE" SYNTHESIS OF OPEN-CHAIN POLYAMINES

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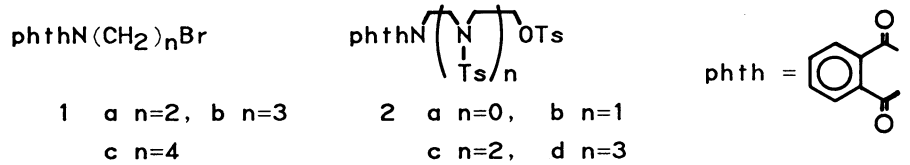
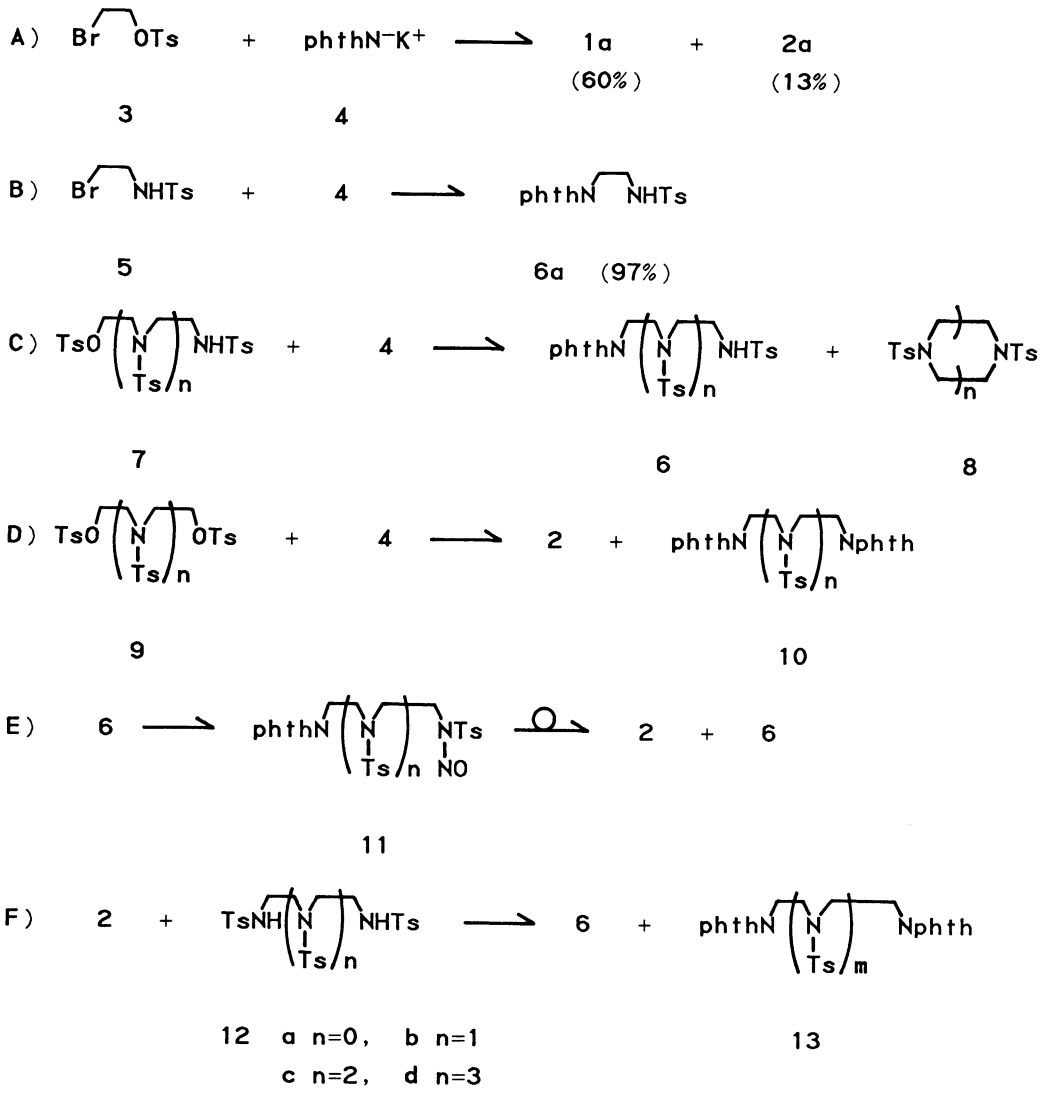
New synthetic routes to *N*-(ω-tosyloxyalkyl)phthalimides (2) were developed and the synthetic utility of 2 as alkylating reagents was exemplified in the open-chain polyamine synthesis involving the "self-proliferative" process.

Reactive alkylating reagents including the properly protected amino group at another terminal for the consecutive elongation of the polyamine chain have long been sought in the field of the synthetic polyamine chemistry. Although *N*-(ω-bromoalkyl)phthalimides (1)[1] have been supposed to be the best candidates for the purpose, the reactivity of the bromo group, the limited preparative method for the general use, and the lability of the phthaloyl group exposed to prolonged basic conditions, required usually for the alkylation reaction, prevent from the versatile utility of the alkylating reagents. In consideration of the difference in electrophilic reactivity between halogenated and sulfonated alkyl groups,[2] we were intrigued to synthesize *N*-(ω-tosyloxyalkyl)phthalimides (2) as new alternatives by use of the recently refined *N*-nitrososulfonamide-sulfonate rearrangement reaction[3] and to appraise their quality in the synthetic polyamine chemistry.

For the synthesis of 2, several possible routes could be designed by use of accessible synthetic intermediates prepared effectively *via* the rearrangement





Scheme 1. Designed Routes to *N*-(ω-Tosyloxyalkyl)phthalimides (Route A-E) and "Self-Proliferative" Elongation of the Open-Chain (Route F).

Table 1. Isolated Product Yields (%) in the Reactions C-F). (Conversion yield is shown in the parentheses.)

Route C			Route D			Route E			Route F			
7 → 6 + 8			9 → 2 + 10			6 → 2 + 6			2 + 12 → 6 + 13			
a n=0	q.y.	0	a	77	tr	a	86(100)	14	a	a	32(70)	tr
b n=1	5	77	b	52	43	b	44(94)	53	a	b	49(68)	2.6
c n=2	25	71	c	34	35	c	47(77)	40	a	c	1.7	tr
d n=3	32	42	d	37	18	d	34(85)	60	a	d	4 >	tr
									d	b	23(39)	16(27)

reaction (Scheme 1); *i.e.*, through the reaction of potassium phthalimide (4)[1] with compounds (3 or 9[3c]) possessing different or the same two electronegative groups at both terminals (route A, D) or with bifunctional intermediates (5, 7[3c]) (route B, C) followed by the application of the rearrangement reaction[3] (route E). All the reactions in routes A-D were performed in *N,N*-dimethylformamide (DMF) at less than 50 °C in the presence of 1.1-1.2 mol equiv. of 4 until the starting materials disappeared. The results are summarized in Scheme 1 and Table 1.[4]

The result of the route A) demonstrates that the tosylate group reacts almost five fold faster than the bromo group in coincidence with the trend seen in the previous report[2] and that this route is inadequate to synthesize 2a. Synthesis of 6 (route B, C) from the bifunctional bromo- and tosyloxy-amides, 5 and 7, proceeded quantitatively for the shorter congeners (n=0). However, 7 possessing the longer chain (n>0) gave mainly the corresponding cyclized polyamines (8) in yields depending on the chain length. The formation of 8 is interpreted in such a way that the exchange of tosylamide proton of 7 with potassium ion of 4 occurs considerably fast in the equilibrium, and, then, the conformational relationship and the group reactivity between both terminals govern the overall processes, either *N*-alkylation to give 6 or cyclization to 8. The reactions with α,ω-ditosylates (9) (route D) afforded 2, accompanied by undesirable diphthalimides (10) in considerable yields depending on the chain length, even if 1.2 mol equiv. of 4 was employed. The alternative designed route to 2 is the direct application of the *N*-nitrososulfonamide-sulfonate rearrangement[3a] to 11 prepared quantitatively[5] from 6 (route E). The results (in Table 1) demonstrate that the rearrangement reaction merits the preparation of 2 over the other routes (A,D). Although the apparent product yields of 2 decrease with the elongation of the chain, the conversion yields (shown in parentheses) remain very high since the by-product of the reaction is anything but recyclizable 6.

Through unsatisfactory attempts of alkylation by use of 2a and 12 (n=1) in the presence of excess amount of K_2CO_3 or 9 and sodium salt of 6a in DMF, critical *N*-monoalkylation conditions were eventually found; *i.e.*, the best yield for the monoalkylation was achieved when 1 mol equiv. of 2a, in a typical case, reacted with sodium salt of 12b prepared by 2 mol equiv. of 12b and 1.5 mol equiv. of sodium metal (route F). These conditions reasonably avoid the destruction of the base-sensitive phthalimide group to great extent, resulting in the achievement

of high conversion yields of the *N*-monoalkylated products (6) and the depression of the yield of the dialkylated by-product (13). In the cases of 12c and 12d, however, the poor solubility of these sodium salts in ethanol and DMF seems to be a crucial factor for the low *N*-alkylation. Indeed, under the similar conditions, soluble 12b was alkylated by 2d in unexpected reasonable yield for such a large molecule. The factors governing the formation of 13 in high ratio are not clear at the present stage.

These results demonstrate, as a consequence, that 2 are reactive synthons upon the *N*-alkylation of α,ω-disulfonamides and could be employed tactically in various fields of organic synthesis. Furthermore, since the phthalimide group is easily removed by the conventional method[6] and tosylation of the resulting amine proceeds without difficulty, the attainment of *N*-alkylation with 2 assures the defined synthesis of open-chain polyamines with arbitrary chain length. The consequence of the present synthetic elaboration combined with the preceding works[3a,c] is conceptually related to "self-proliferative" process as a whole because congeners of 12 with one unit longer chain, *e.g.*, could be prepared from the same 12 by the sequence of reactions exemplified. As an extension of the "self-proliferative" approach, the synthesis of naturally occurring open-chain polyamines is undertaken and will be reported in due course.

References

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4) All the product structures shown were confirmed by ^{1}H-NMR and IR spectra, and by elemental analyses (C, H, N, S).

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