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AN INTRAMOLECULAR ANIONIC FRIES REARRANGEMENT OF N-ACYLPHENOTHIAZINES

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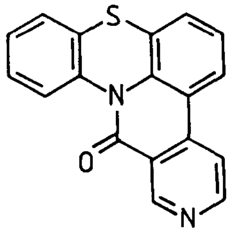
Abstract: *Certain 2-substituted N-acylphenothiazines undergo a rapid intramolecular N→C migration on reaction with lithium N,N-dialkylamides at -78°. Preliminary studies of the scope and mechanism of this anionic version of the Fries rearrangement are reported.*

Our interest in phenothiazine derivatives with conformationally restricted basic side chains led us to attempt the synthesis of the pentacyclic analogue **1** as a key intermediate. We hoped to prepare **1** by ring closure of 10-nicotinoyl-2-chlorophenothiazine (2_d) wherein intramolecular reaction between the 4-lithiated nicotinoyl[2] and 1,2-dehydrophenothiazine moieties of hypothetical intermediate **3**, generated in situ, was envisioned. Previous work in our laboratory had shown that 2-chlorophenothiazine readily forms 1,2-dehydrophenothiazine via a metalated intermediate on reaction with alkyl lithium reagents.[3] Unfortunately, when 2_d was subjected to conditions expected to bring about 1,2-dehydrophenothiazine formation (2 to 3 equivalents of either sec-butyl lithium or LDA in THF for 30 minutes at -78°), only cleavage of the nicotinoyl group occurred. A similar result was observed when 6 equivalents of sec-butyl lithium were employed. However, when 2_c was reacted with 6 equivalents of LDA at -78° for 30 minutes, the 1-nicotinoyl derivative 4_d was unexpectedly obtained. Since this transformation represents an example of an anionic N→C migration rarely observed heretofore,[4,5] we decided to further examine the scope and mechanism of the reaction. A summary of the results of our preliminary investigation are given in the table.



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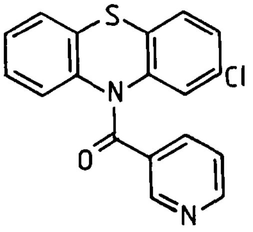
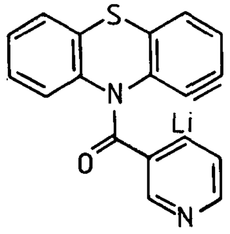


2_d



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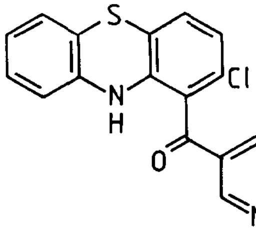
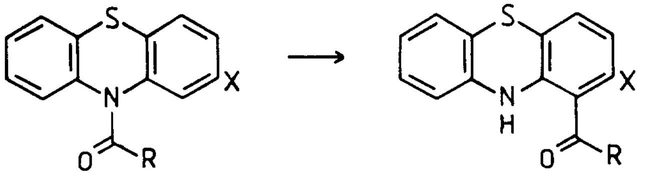


4_d

TABLE

Anionic Fries Migration of 10-Acylphenothiazines



2 4

Substrate	Product	Reagents[a,b]	Chromatogr[c,d] Solvents	Physical State	M. P. °C	$(M^+(m/e)^e$	IR(cm^{-1})	Yield %
2_a R=CF_3 X=H	4_a	LTPA	H/EA 1:1	red crystals	90-100	295	3300/ 1740	34^f
2_b R=3-Pyridyl X=H	None	LDA: LTPA	---	---	---	---	---	$0^{f,g}$
2_c R=CF_3 X=Cl	4_c	LDA	H/EA 19:1	red crystals	65-67	329	3400; 1740	30
2_d R=3-Pyridyl X=Cl	4_d	LDA	H/EA 1:1	orange crystals	163-165	338	3400; 1740	44
2_e R=CH_3 X=Cl	None	LDA	---	---	---	---	---	0^h
2_f R=CF_3 X=CF_3	4_f	LDA	H/EA 3:2	red oil	---	363	3350; 1740	44
2_g R=3-Pyridyl X=CF_3	None	LDA; LTPA	---	---	---	---	---	$0^{f,g}$

[a] LDA = Lithium diisopropylamide

[b] LTPA = Lithium 2,2,6,6-tetramethylpiperidylamide

[c] Carried out on silica

[d] H = Hexanes; EA = Ethyl acetate

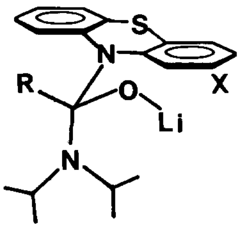
[e] Low resolution

[f] Only cleavage of the acyl group occurred with LDA.

[g] Starting material was quantitatively recovered with LTPA.

[h] Starting material was quantitatively recovered.

Cleavage of the acyl group is observed in both successful and unsuccessful reactions, suggesting that a tetrahedral intermediate (5) is formed between the lithium amide reagent and the acyl group. The regioselectivity observed in the N→C migrations of substrates 2_c, 2_d and 2_f indicates that the rearrangement is preceded by metalation at the more acidic ortho position (by excess LDA or by intramolecular proton abstraction by the lithium alkoxide of 5) to give the dilithiated intermediate 6.[6,7] A rapid, irreversible 1,3-N→C shift to form the dilithiated intermediate 7 is then believed to occur.[8] Quenching of 7 in water gives the observed 1-acyl product. An intermolecular rearrangement was ruled out by a crossover experiment using equivalent amounts of 2_a and 2_d; thus, only the intramolecular rearrangement products 4_a and 4_d (plus phenothiazine and 2-chlorophenothiazine), but neither of the crossover products 4_b or 4_c, were obtained. The migration must be very fast since 2-chlorophenothiazines are known to readily form benzynes,[3,9] even at low temperature.[3] Failure to achieve a successful rearrangement, as in substrates 2_b and 2_g, is probably either due to steric hindrance to the formation of a tetrahedral intermediate or to the relatively weak acidity of the ortho hydrogen atom. It will be noted, for example, that the stronger base, lithium 2,2,6,6-tetramethylpiperidylamide (LTPA), was required to achieve a successful rearrangement of 2_a, a substrate lacking an electronegative meta substituent. Failure of 2_e to undergo either acyl migration or cleavage probably results from the formation of a stable enolate.



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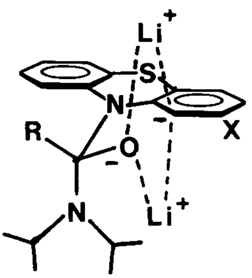

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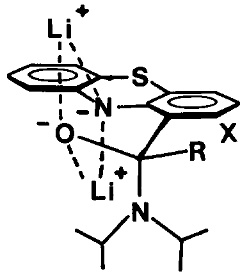

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Streitweiser[10] has suggested that dianions capable of forming clusters with monovalent cations (notably Li^+) are stabilized by electrostatic forces. Such stabilization could occur in the dianionic intermediates 6 and 7 which can form triplet clusters wherein the two anionic centers are coordinated to two lithium ions in each. The recently reported ortho directed lithiation of phenoxide ion[11] is apparently an example of such a triplet cluster involving lithium ion stabilization of carbanionic and oxygen anionic centers.

Although the scope is limited and the yields are modest, the title reaction provides a useful alternative to the acid catalyzed[12] and photochemically induced[13] versions of the Fries rearrangement. These reactions tend to give low yields and, depending on the substitution pattern of the anilide, mixtures of ortho and para substituted products. The anionic Fries rearrangement, on the other hand, is regiospecific providing the ortho product exclusively. Further studies exploring the scope and utility of the reactions are currently underway in our laboratories.

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3. A. Hallberg, P. Dunbar, N. M. Hintermeister, A. Svensson and A. R. Martin, J. Chem. Soc. Perkin I, 969 (1985).
4. An analogous anionic N C migration of arylsulfonamides has been reported [D. Hellwinkel and M. Supp, Angew. Chem. Int. Ed. Engl., **13**, 270 (1970); Tetrahedron Letters, 1499 (1975); Chem. Ber., **109**, 3749 (1976); S. J. Shafer and W. D. Closson, J. Org. Chem., **40**, 889 (1975)].
5. The anionic O→C 1,3-migration of O-aryl carbamates has also been described [M. P. Sibi and V. Snieckus, J. Org. Chem., **48**, 1937 (1983)]. This reaction differs from ours in two important respects: (1) only one equivalent of metalating reagent is required; and (2) the migration is sufficiently slow to permit trapping of the ortho metalated intermediate with electrophiles.
6. Although the metalation step 5→6 is somewhat analogous to the reported ortho metalation of aromatic aldehydes by n-butyl lithium in the presence of dialkyl lithium amides [D. L. Comins and J. D. Brown, J. Org. Chem., **49**, 1079 (1984)], we do not think that a directed metalation is occurring in our reaction since lithium amide reagents are known to be poor coordinating species that are considered unsuitable for heteroatom directed metalations [H. W. Gschwend and H. R. Rodriguez, Organic Reactions, **26**, 1 (1979)].
7. We have previously invoked such an intermediate to explain the selectivity of various electrophiles for the N versus C acylation of 1,10-dilithiophenothiazines [A. Hallberg and A. Martin, J. Heterocyclic Chem., **19**, 433 (1982)].
8. We propose that the rearrangement 6→7 proceeds via an internal nucleophilic substitution ($S_{N}i$) mechanism, involving an ion pair intermediate, wherein C-N bond breaking precedes C-C bond formation.
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