Communications to the Editor

[Chem. Pharm. Bull. 32(3)1264—1267(1984)]

ACRIDONES FROM THE REACTION OF N-LITHIO ANTHRANILATES WITH BENZYNES. A SHORT SYNTHESIS OF ACRONYCINE

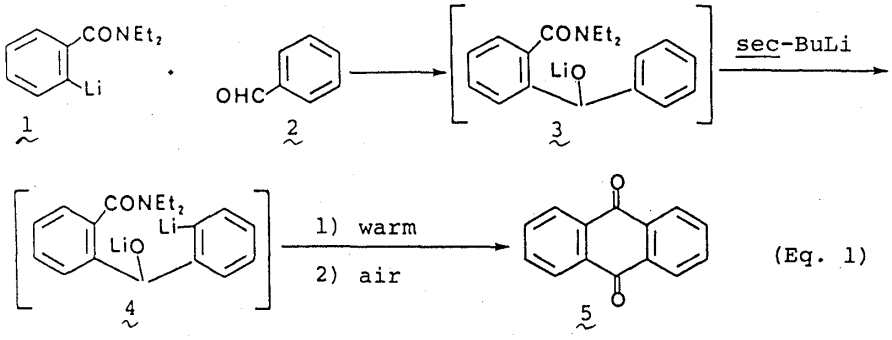
Mitsuaki Watanabe,* Akio Kurosaki, and Sunao Furukawa
Faculty of Pharmaceutical Sciences, Nagasaki University
Bunkyo-machi, Nagasaki 852, Japan

The lithium salt of methyl N-methylanthranilate reacted with the benzyne derived in situ from aryl halides to give a N-methylacridone derivatives in a one-pot process. Using this method, a short synthesis of acronycine has been achieved.

KEYWORDS ——— acridone; acronycine; benzyne; lithium N-isopropylcyclohexylamide; N-lithio anthranilate

Since Hughes[1] and coworkers in 1948 discovered acridones as alkaloidal constituents of certain Australia flora, the acridone skeleton has achieved a prominent position in alkaloid chemistry. Although there are many syntheses of acridones,[2] the most widely used preparation involves acid-catalyzed cyclization of diphenylamine-2-carboxylic acids, which are generally accesible by the Ullmann reaction.[3] It is known[4] that small amounts of acridones are formed during generation of benzynes by diazotization of anthranilic acids. The acridones in these cases result from the reaction of benzynes with undiazotized anthranilic acids. We report here a convenient, regiospecific, single-step synthesis of N-methylacridones by the coupling reaction of benzynes derived from corresponding halobenzenes with the lithium salt of methyl N-methylanthranilate.

In 1980, we reported on the tandem directed metalation synthesis[5] of anthraquinones as illustrated in Chart 1 (Eq. 1). Ortho-lithiated benzamide (1) was treated



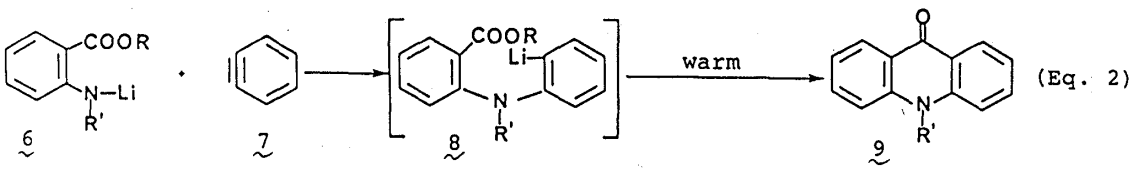


Chart 1

with benzaldehyde (2) to give intermediate 3. Product 3 was again lithiated with sec-butyllithium to form dilithio species 4 which subsequently underwent intramolecular cyclization to afford product 5. Using this analogy, we envisaged that intermediate 8, generated by the nucleophilic addition of the lithium salt of anthranilate (6) to benzyne (7), should undergo similar cyclization to form the acridone skeleton in a one-pot process (Chart 1, Eq. 2).

We have found that the lithium salt of methyl N-methylanthranilate easily reacts with benzynes to give various N-methylacridones in good yield. The results are summarized in the Table. Chloro, bromo, and fluoro benzene derivatives may be used as benzyne sources for this reaction. In the methoxy substituted halobenzenes, the regioisomer with stabilization of the intermediate lithiated species with inductive and chelating effects of the methoxy group[6] was isolated as a major product.[7] For the generation of benzynes from halobenzenes, lithium N-isopropylcyclohexylamide (LiICA)[8] was found to be much more effective[9] than lithium diisopropylamide (LDA) and lithium 2,2,6,6-tetramethylcyclohexylamide (LiTMP).

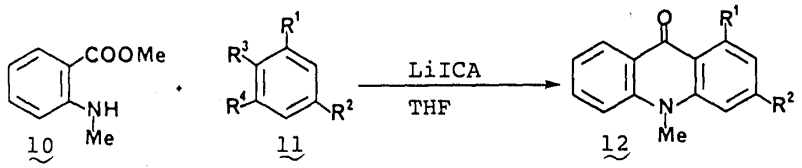


Table. Synthesis of Acridones

Entry	10 (mmol)	11 R1	11 R2	11 R3	11 R4	11 (mmol)	LiICA (mmol)	12	12 R1	12 R2	Yield (%)
1	2.5	11a H	H	Cl	H	2.5	6	12a	H	H	67
2	2.5	11b H	H	Br	H	2.5	6	12a	H	H	57
3	2.5	11c H	H	F	H	2.5	6	12a	H	H	40
4	2.5	11d OMe	H	H	Cl	2.5	6	12b	OMe	H	30
5	2.5	11e OMe	H	H	Br	2.5	6	12b	OMe	H	32
6	2.5	11f OMe	H	Br	H	5	8.25	12b	OMe	H	50
7	2.5	11g OCH_2OMe	H	H	Cl	5	8.25	12c	OCH_2OMe	H	37
8	2.5	11h OMe	OMe	H	Cl	2.5	6	12d	OMe	OMe	36
9	2.5	11h OMe	OMe	H	Cl	5	8.25	12d	OMe	OMe	68

A typical experimental procedure is as follows: Methyl N-methylanthranilate (10, 412 mg, 2.5 mmol) in tetrahydrofuran (THF)(5 ml) was added to the THF solution (50 ml) of LiICA (6 mmol), prepared from n-butyllithium (6 ml, 6 mmol) and N-isopropylcyclohexylamine (1 ml, 6 mmol), at -78°C under nitrogen. The mixture was stirred at -78°C for 1 h, warmed to -10°C during 10 min, and then chlorobenzene (11a, 281 mg, 2.5 mmol) in THF (5 ml) was added to the mixture. This mixture was stirred at room temperature for 12 h to yield 350 mg (67%) of N-methylacridone (12a) after flash chromatography. This procedure was also used to synthesize of other acridones. 1-Methoxy-N-methylacridone (12b)[2f, 10] was obtained using m-haloanisole (Entry 4 and 5) or o-haloanisole (Entry 6) as benzyne precursors. 1,3-Dimethoxy-N-methylacridone (12d)[2f, 11] was obtained as a single isomer by the coupling reaction of methyl N-methylanthranilate (10) with 3,5-dimethoxychlorobenzene (11h)(Entry 8 and 9). Maximized yields are obtained when two eq of benzyne precursors are employed (Entry 6 and 9). Compared with previous procedures for N-methylacridone synthesis,[2, 3] our benzyne coupling reaction has the advantages of greater generality, convenience,

and yield.

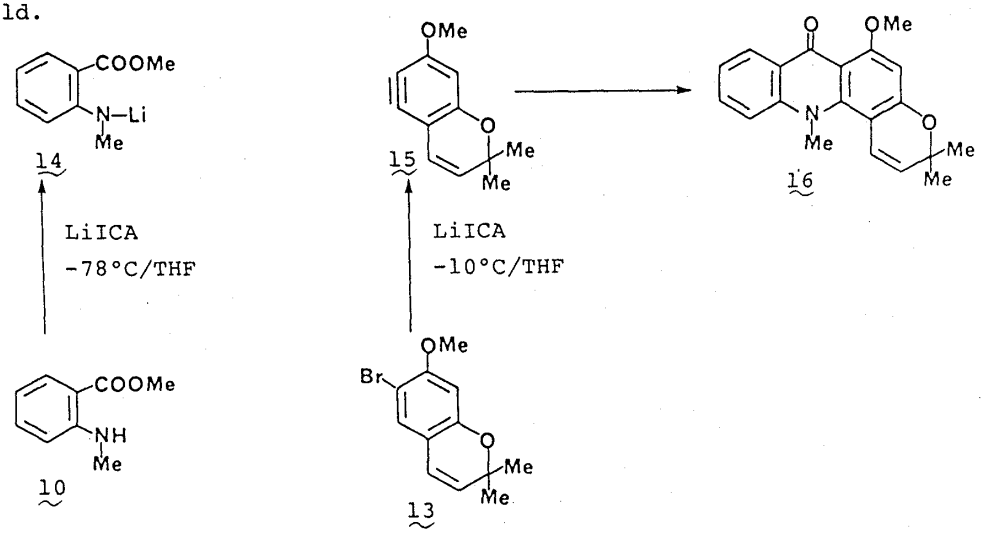


Chart 2

We also demonstrate the utility of this method for the short synthesis of the naturally occurring alkaloid, acronycine. Acronycine[12)] is an acridone alkaloid isolated from the bark of Acronychia bauri Schott, a scrub ash indigenous to Australia, and it possesses a broad spectrum of antitumor activity against experimental neoplasmas in laboratory animals. The key bromide (13) was easily synthesized from 7-hydroxy-2,2-dimethyl-4-chromanone[13)] by three steps in 80% overall yield according to the procedure of Blechert.[12m)] Reaction of methyl N-methylanthranilate (10) with 6-bromo-7-methoxy-2,2-dimethylchromene (13) gave acronycine (16) directly in 41% yield, which was identical with authentic material[11, 12g)] in melting point, and spectroscopic and thin-layer chromatographic comparisons.

The results reported herein may have extensions for construction of other hetero-atom ring systems.[14)]

ACKNOWLEDGEMENT We are indebted for provision of samples and spectral data to Dr. W. R. Fields, Lilly Research Laboratories, U. S. A. (acronycine); Professor W. C. Taylor, University of Sydney, Australia (acronycine); and Professor V. Snieckus, University of Waterloo, Canada (1-methoxy-N-methylacridone, 4-methoxy-N-methylacridone, and 1,3-dimethoxy-N-methylacridone).

REFERENCES AND NOTES

1) G. K. Hughes, F. N. Lahey, J. R. Price, and L. J. Webb, Nature, 162, 223 (1948).
2) Recent work: a) J. H. Adams, P. Gupta, M. S. Khan, and J. R. Lewis, J. Chem. Soc. Perkin Trans. I, 1977, 2173; b) A. I. Meyers and R. Gable, J. Org. Chem., 42, 2654 (1977); c) M. G. Clancy, M. M. Hesabi, and O. Meth-Chohn, J. Chem. Soc., Chem. Commun., 1980, 1112; d) R. A. Scherrer and H. R. Beatty, J. Org. Chem., 45, 2127 (1980); e) Y-I. Mao and V. Boekelheide, ibid., 45, 1547 (1980); f) M. Iwao, J. N. Reed, and V. Snieckus, J. Am. Chem. Soc., 104, 5531 (1982).
3) R. M. Acheson Ed. "Acridones," Interscience Publishers, Inc., New York, 1956.
4) a) S. K. Dyke, A. R. Marshall, and J. P. Watson, Tetrahedron, 22, 2515 (1966); b) R. Howe, J. Chem. Soc. (C), 1966, 478; c) H. Heaney and J. M. Jablonski, ibid., 1968, 1895; d) H. Heaney, K. G. Mason, and J. M. Sketchley, ibid., 1971, 567; e)

S. Hayashi and N. Ishikawa, Chem. Lett., 1972, 99.
5) M. Watanabe and V. Snieckus, J. Am. Chem. Soc., 102, 1457 (1980).
6) It is well known that m-aminobenzene derivatives were usually prepared by the reaction of benzynes generated from o-halobenzene derivatives with alkali amides. Similar regiospecific additions were reported by P. G. Sammes and D. J. Dodworth, J. Chem. Soc., Chem. Commun., 1979, 33; C. A. Townsend, S. G. Davis, S. B. Christensen, J. C. Link, and C. P. Lewis, J. Am. Chem. Soc., 103, 6885 (1981); R. V. Stevens and G. S. Bisacchi, J. Org. Chem., 47, 2393 (1982); A. I. Meyers and W. Rieker, Tetrahedron Lett., 1982, 2091; A. I. Meyers and P. D. Pansegrau, ibid., 1983, 4935.
7) In entries 5 and 6, a small amount of an unidentified fluorescent substance was observed on TLC.
8) a) M. M. Rathke and A. Lindert, J. Am. Chem. Soc., 93, 2318 (1971); b) R. A. Olofson and C. M. Dougherty, ibid., 95, 582 (1973).
9) When LDA or LiTMP were used in the reaction of entry 6, 1-methoxy-N-methylacridone (12b) was obtained in 35% and 17% yield, respectively.
10) G. K. Hughes, N. K. Matheson, A. T. Norman, and E. Richie, Aust. J. Sci. Res., A5, 206 (1952).
11) J. Hlubucek, E. Rithie, and W. C. Taylor, Aust. J. Chem., 23, 1881 (1970).
12) Isolation and structure: a) R. D. Brown, L. J. Drummond, F. N. Lahey, and W. C. Thomas, Aust. J. Sci. Res., A2, 622 (1949); b) T. R. Govindachari, B. P. Pai, and P. S. Subraniam, Tetrahedron, 22, 3245 (1966); c) P. L. Macdonald and A. V. Robertson, Aust. J. Chem., 19, 275 (1966); Antitumor activity: d) G. H. Svoboda, G. A. Poore, P. J. Simpson, and G. B. Border, J. Pharm. Sci., 55, 758 (1966); e) H. R. Sullivan, R. E. Billings, J. L. Occolowitz, H. E. Boaz, F. J. Marshall, and R. E. McMahon, J. Med. Chem., 13, 904 (1970); Synthesis: f) J. R. Beck, R. N. Booher, A. C. Brown, R. Kwok, and A. Pohland, J. Am. Chem. Soc., 89, 3934 (1967); g) J. R. Beck, P. Kwok, R. N. Booher, A. C. Brown, L. E. Patterson, P. Pranc, B. Bockey, and A. Pohland, ibid., 90, 4706 (1968); h) W. M. Bandaranayake, L. Crombie, and D. A. Whiting, J. Chem. Soc., Chem. Commun., 1969, 970; i) J. Schneider, E. L. Evans, E. Grunberg, and R. I. Fryer, J. Med. Chem., 15, 266 (1972); j) F. N. Lahey and R. V. Stick, Aust. J. Chem., 26, 2311 (1973); k) W. Bandaranayake, M. J. Begley, B. O. Brown, D. G. Clarke, L. Crombie, and D. A. Whiting, J. Chem. Soc. Perkin Trans. I, 1974, 998; l) J. Adams, P. Gupta, and J. R. Lewis, Chem. and Ind., 1976, 109: m) S. Blechert, K-E. Fichter, and E. Winterfeldt, Chem. Ber., 111, 439 (1978); and also 11).
13) M. Miyano and M. Matsui, Bull. Chem. Soc. Jpn., 31, 397 (1958).
14) N-Unsubstituted acridone was obtained by the reaction of lithium salt of methyl anthranilate with benzyne derived from chlorobenzene in about 35% yield. Thioxanthone was also obtained by the reaction of lithium salt of methyl thiosalicylate with benzyne in about 72% yield. (M. Watanabe and A. Kurosaki, unpublished results).

(Received January 30, 1984)