

A NEW EFFICIENT COUPLING REAGENT FOR CYCLIC N-METHYLANILIDE FORMATION

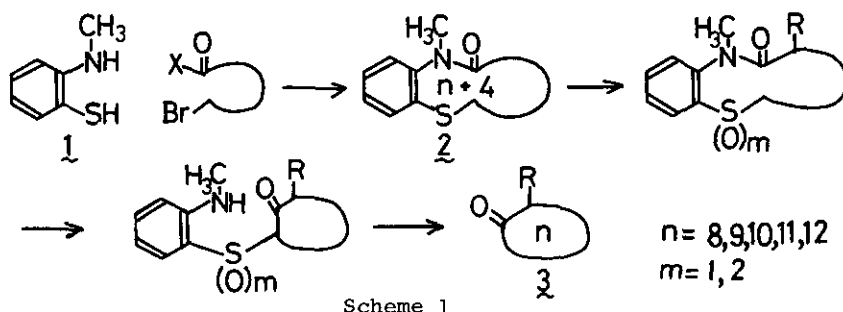
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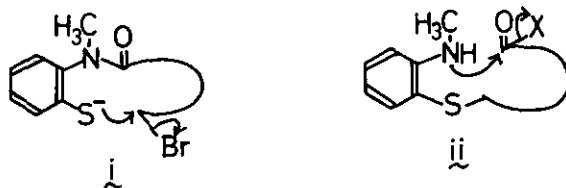
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Abstract—Treatment of the reagent (5) with the amino acid (11) in DMF afforded the active ester (12), which was added slowly to toluene at 95–100°C to produce the 15-membered cyclic N-methyl-anilide (13). The reaction proceeds under essentially neutral conditions.

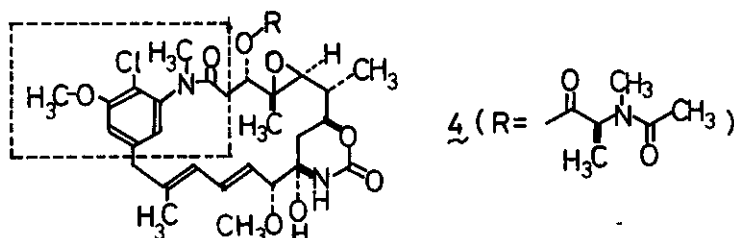
We have recently developed an efficient method for the construction of medium ring ketones (3) by cyclization.¹⁾ The principle of our method is to minimize an unfavourable entropy effect by forcing both reacting terminals to come closely. This was achieved by the formation of a link with o-methylaminothiophenol (1). The outline of the method was shown in scheme 1.



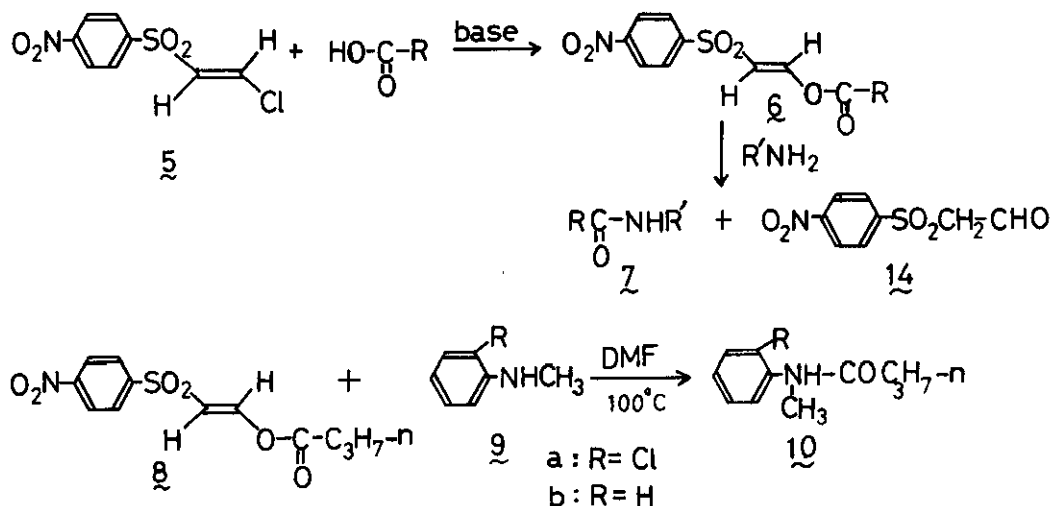
It is apparent that formation of the large membered lactam sulfides (2) is initially required. We previously prepared these key intermediates (2) by C-S bond formation as illustrated in i. All attempts to construct 2 by a lactam forming process (see ii) gave only unsatisfactory results, although a wide variety of



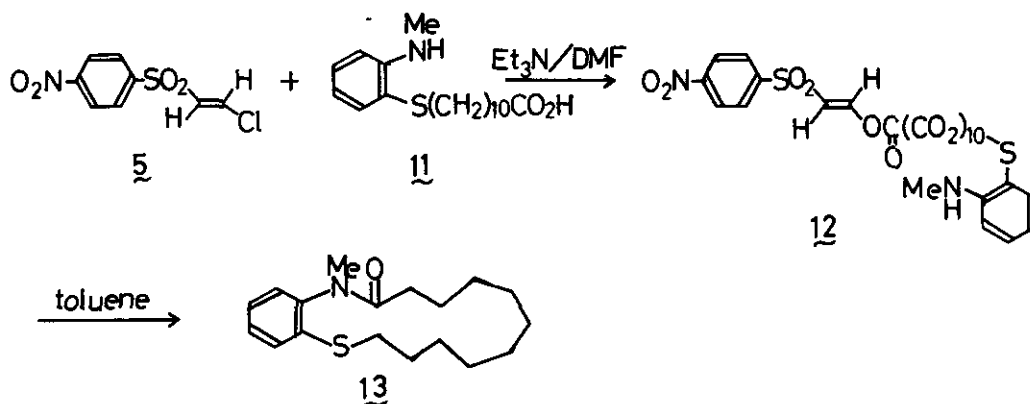
the known methods were employed.²⁾ Nevertheless, we continued an effort to develop a new method for cyclic N-methylanilide formation in general, because such particular lactam is involved in the framework of maytansine (4),³⁾ a typical ansamitosis antibiotics having remarkable bioactivity, as well as in the present compounds (2), and found that the two-carbon Michael acceptor 5 newly developed in this laboratory⁴⁾ was a reagent of choice for this purpose.



The reagent (5) having a β -chlorovinyl sulfone structure can be considered as a vinylogous sulfonyl chloride and so, is expected to react with various nucleophiles.⁵⁾ In fact, treatment of 5 with carboxylic acids at room temperature afforded the active esters (6), which underwent the condensation with aliphatic amines including Z- or Boc-amino acids under ice cooling⁴⁾ to give the amides (7). Encouraged with the high reactivity of 6, we carried out the reaction of 8 (6, R = n-C₃H₇) with o-chloro-N-methylaniline (9a), a weak nucleophile, and found that the reaction proceeded in DMF at 100° to afford the anilide (10a) in 68.5 % yield after eight hours. N-Methylaniline (9b) gives the corresponding amide (10b) in 72.2% yield.



Then, the present method was applied to the synthesis of the cyclic N-methyl-anilides (2). As a model case, the amino acid (11) was chosen and was subjected to the intramolecular amidation. Treatment of the reagent (5) (1.2 equiv) with 11 (1.0 equiv) in DMF at room temperature for 30 min in the presence of triethylamine (1.0 equiv) in a syringe afforded the active ester (12). The syringe was then directly attached to the reaction vessel and 12 in DMF thus prepared was slowly added (12 h) to a well stirred toluene at 95-100° using a microfeeder under nitrogen. During the addition, the syringe was cooled with running water to prevent polymerization of 12. After the work up, the desired 15-membered lactam sulfide (13) was obtained in 66.2 % yield.⁶⁾

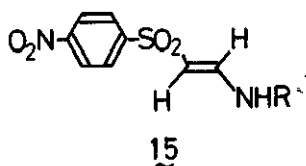


The compound produced from the active ester (12) must be the neutral aldehyde (14), although it was not actually isolated. The aldehyde (14) is expected to be very unstable because it involves the sulfonyl group at the β -position and should be polymerized during the reaction in this case⁷⁾. Therefore, the amidation can be carried out with this reagent under essentially neutral conditions. This particular feature of the present method would be quite helpful in the amidation of the acids involving base-sensitive functional group in the same molecule.

ACKNOWLEDGMENT: Thanks are due to Dr. Yasuo Ohtsuka of this laboratory for his helpful discussions and technical assistances.

REFERENCES AND NOTES

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2. The following methods were examined: a) J. F. Normant and H. Deshayes, Bull. Soc. Chim. France, 1972, 2854; b) J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, and M. Yamaguchi, Bull. Chem. Soc. Jpn., 1979, 52, 1989; c) E. J. Corey, L. D. Weigel, D. Floyd, and M. G. Bock, J. Am. Chem. Soc., 1978, 100, 2916; d) M. Bodanszky and V. du Vigneaud, ibid., 1959, 81, 5688; e) F. H. C. Stewart, Chem. and Ind., 1967, 1960; f) T. Mukaiyama, R. Matsda, and M. Suzuki, Tetrahedron Lett., 1970, 1901; g) L. E. Barstow and V. J. Hruby, J. Org. Chem., 1971, 36, 1305. Among them, the methods a), b), and c) gave the lactam (2) (n=11) in ca 20% yields.
3. Total synthesis of maytansine has recently been achieved by two groups: a) E. J. Corey, L. O. Weigel, A. R. Chamberlin, H. Cho, and D. H. Hua, J. Am. Chem. Soc., 1980, 102, 6615; b) A. I. Meyers, P. J. Reider, A. L. Campbell, ibid., 1980, 102, 6597. Corey and co-workers have accomplished the cyclic amidation by treating the tetra-n-butylammonium salt of the amino acid derivatives with mesitylenesulfonyl chloride-diisopropylethylamine in benzene. See ref. 2c).
4. M. Shimagaki and T. Oishi, The 98th Annual Meeting of Pharmaceutical Society of Japan, Okayama, 1978. Abstracts of Papers, p. 211; M. Shimagaki, H. Koshiji, T. Oishi, The 99th Annual Meeting of Pharmaceutical Society of Japan, Sapporo, 1979. Abstracts of Papers, P. 312.
5. cf. I. Hori and T. Oishi, Tetrahedron Lett., 1979, 4087.
6. The lactam (13) thus prepared was identical in every respect with the authentic sample prepared by the C-S bond formation. See ref. 1.
7. In the cases of amidation with aliphatic amines, condensation proceeds even at -10~-20°C. In these conditions, however, the aldehyde (14) retains unpolymerized and reacts with the remaining amines to give undesirable amino-vinyl sulfone (15).



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