A NOVEL SYNTHETIC METHOD OF LACTAMS FROM 1,3-DIOXIN-4-ONES VIA INTRAMOLECULAR KETENE TRAPPING[1]

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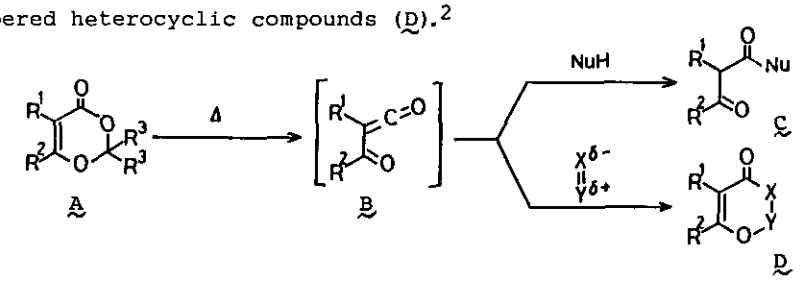
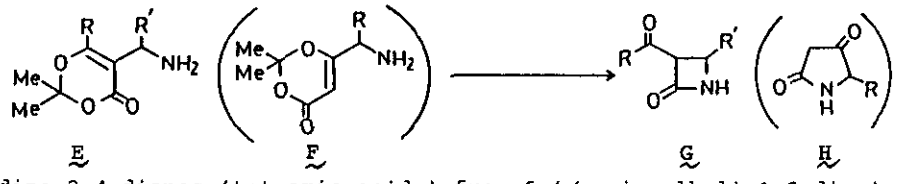
Abstract—— A novel route to four- and five-membered lactams from 1,3-dioxin-4-ones having an α-aminoalkyl side-chain at 5- or 6-position through cycloreversion to acylketenes followed by intramolecular ketene trapping by the amino function is described.

Previously, we have shown that 1,3-dioxin-4-ones (A), when heated in an aprotic solvent, undergo cycloreversion to acylketenes (B), which react either with nucleophiles to give β-ketoacid derivatives (C) or with dipolar dienophiles to give six-membered heterocyclic compounds (D).[2]

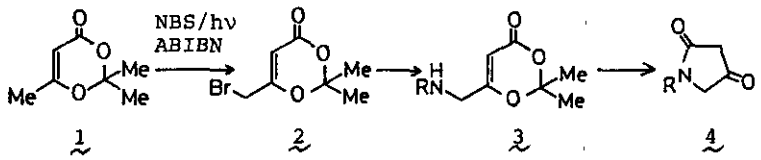


In this paper, we wish to report a new synthetic method of functionalized lactams (G or H) from 1,3-dioxin-4-ones having an α-aminoalkyl group at either 5- or 6-position (E or F) via the ring opening followed by intramolecular ketene trapping by the amino function in the side-chain. New photochemical ring-opening of the dioxinones, which is useful either for the cycloreversion at room temperature or for synthesis of heat-labile compounds, is also reported.



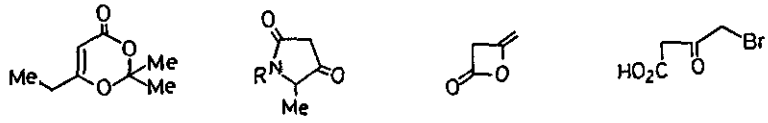
Pyrrolidine-2,4-diones (tetramic acids) from 6-(α-aminoalkyl)-1,3-dioxin-4-ones

6-Aminomethyl-1,3-dioxin-4-ones (3)[3] were prepared from 6-methyl-1,3-dioxinone (diketene-acetone adduct: 1)[4] via photo-assisted bromination with NBS,[5] followed by treatment of the 6-bromomethyl derivative (2) with a variety of amines. Each reaction proceeded in high overall yields. When these aminomethyl derivatives (3) were heated in toluene or xylene at reflux, the corresponding tetramic acids (4) were obtained as almost sole products, respectively.



	R
a	H
b	CH_2Ph
c	OCH_2Ph
d	C_6H_5
e	C_6H_4-OMe(p)
f	C_6H_4-Cl(p)

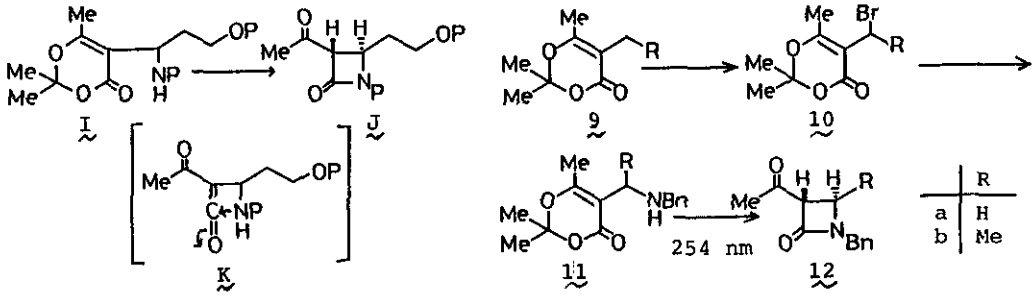
5-Methyltetramic acids (6) can also be synthesized in the same manner using 6-ethyl-1,3-dixinone (5)[6] as the starting material. Satisfactory yields (65-90%) of 4 and 6 indicate that such intramolecular ketene trapping (5-exo-trig cyclization in Baldwin's terminology[7]) is an efficient process. It should be noted that the bromide (2) can also be synthesized from diketene (7) via 4-bromoacetoacetic acid using an acid-catalyzed condensation of β-ketoacid with acetone. The method was found in our laboratory and can be applicable to large scale preparation of the 2,2-dimethyl dioxinone derivatives.[6] Thus, treatment of 7 with bromine in CCl_4 followed by mild hydrolysis gave the bromoacid (8), which cyclized to 2 by the above procedure.



Though tetramic acid (4a) and its derivatives are important building blocks for some antibiotics (such as streptolydigin and tirandamycin having tetramic acid system[8] or even for cepharosporin-type β-lactams[9]), only practical synthesis of 4a so far reported is the cyclization of the condensation product of alkyl glycinate and alkyl hydrogen malonate, followed by dealkoxycarbonylation.[9] Thus, the present method has provided an another useful preparative route to tetramic acid and its 1- and/or 5-substituted derivatives.

β-Lactams from 5-(α-aminoalkyl)-1,3-dioxin-4-ones

Importance of 4-(2-hydroxyalkyl)azetidin-2-ones having the oxygenated ethyl group at 3-position (e.g. J) in the synthesis of thienamycin[10,11] suggests that if one can synthesize 6-methyl-5-(1-amino-3-hydroxypropyl)-1,3-dioxinone (I: P=an appropriate protecting group), it may afford the former compound (J) via ketene (K), through the corresponding 4-exo-trig cyclization (indicated by arrow symbols in formula K). Regioselective introduction of benzylamino group into 5-



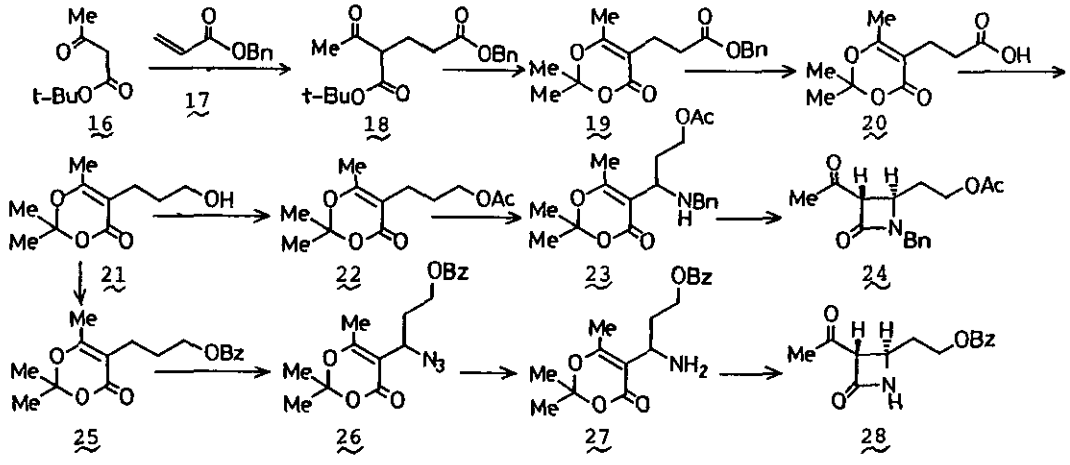
	R
a	H
b	Me

methyl group of 5,6-dimethyl derivative (9a)[6] can be accomplished readily. Thus, bromination of 9a afforded the mono-bromide (10a), which without further purification, was treated by benzylamine to afford the desired compound (11a) in 48% overall yield. It should be noted that the thermal cycloreversion of these dioxinones to acylketenes is affected seriously either by the kind of substitueut or by the pattern of the substitution. As for 2,2-dimethyl derivatives, the required temperature for the cycloreversion increases in the order of 5,6-unsubstituted (ca. 80 °C)< 5- or 6-alkylated (ca. 110-130 °C)< 5,6-dialkylated ones (160-170 °C). Even for 5,6-unsubstituted derivatives, spiro compound (13)[12] cycloreverts only at around 170 °C.[13]

Actually, when 11a was refluxed in xylene, the starting material was recovered unchanged. If the same reaction was carried out at 170 °C in o-dichlorobenzene, 11a was consumed rapidly but none of the desired β-lactam was obtained. In order to attain desired cycloreversion under more mild conditions, two dioxinones (9a and 13) which resist the thermal ring-opening below 160 °C were irradiated at 254 nm in ethanol. As a result, the corresponding ethyl acetates (14 and 15[14]) were obtained in ca. 40% yields, respectively. This fact shows that the cycloreversion of these dioxinones can proceed even at room temperature via their singlet excited states (S_1).[15,16] As expected, 12a was obtained in ca. 40% yield, when 11a was irradiated at 254 nm in acetonitrile.

9a 14 13 15

The same reaction sequences afforded 12b from 9b. A small coupling constant (J=2.5 Hz) between protons at 3- and 4-positions of 12b clearly demonstrates their trans-relationship. This fact tells not only that the final protonation step (K→J) occurs under thermodynamic control, but also that this strategy fits well to the stereospecific synthesis of desired β-lactam (J). In order to synthesize J, 5-(3-hydroxypropyl)-2,2,6-trimethyl derivative (21) was synthesized from t-butyl acetoacetate (16) and benzyl acrylate (17) by i) addition to 18,



16 17 18 19 20 21 22 23 24 25 26 27 28

ii) cyclization with acetone to 19, catalytic reduction to 20, and iii) reduction by diborane. The acetate (22) was converted to 23, by the bromination followed by treatment with benzylamine. Unprotected amino derivative (27) can also be synthesized from the same intermediate (21) by i) benzoylation to 25, ii) bromination followed by treatment with sodium azide to 26, and iii) catalytic reduction over Pd/C. Both of these dioxinones (23 and 27) upon irradiation at 254 nm in acetonitrile gave the desired β-lactams (24 and 28) in ca. 40% yields. Stereochemistry of 24 and 28 is again verified as trans from nmr spectroscopy. The fact that only trace of 28 was detected, when 27 was heated at 170 °C in o-dichlorobenzene, indicates that photochemical cycloreversion has wider applicability than the corresponding thermal cycloreversion.

ACKNOWLEDGEMENT

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REFERENCES AND NOTES

1. Part XIV of "Synthesis of 1,3-dioxin-4-ones and their use in synthesis." Part XIII: M. Sato, N. Yoneda, and C. Kaneko, Chem. Pharm. Bull., 34, 4577 (1986).
2. M. Sato, N. Yoneda, and C. Kaneko, Chem. Pharm. Bull., 34, 621 (1986) and references cited therein.
3. All reactions described in this paper are not optimized. New compounds were identified by either elemental analysis or by high-resolution mass spectra, and the structures were supported by acceptable spectral data.
4. M. F. Carroll and A. R. Bader, J. Am. Chem. Soc., 74, 6305 (1952).
5. R. K. Boeckman, Jr. and A. J. Thomas, J. Org. Chem., 47, 2823 (1982).
6. M. Sato, H. Ogasawara, K. Oi, and T. Kato, Chem. Pharm. Bull., 31, 1896 (1983).
7. J. E. Baldwin, J. Chem. Soc., Chem. Commun., 1976, 734.
8. V. J. Lee, A. R. Branfman, T. R. Herrin, and K. L. Rinehart, Jr., J. Am. Chem. Soc., 100, 4225 (1978).
9. G. Lowe and H. Wing Yeung, J. Chem. Soc. Perkin I, 1973, 2907.
10. F. A. Bouffard, D. B. R. Johnston, and B. G. Christensen, J. Org. Chem., 45, 1130 (1980).
11. N. Katagiri, M. Sato, N. Yoneda, S. Saikawa, T. Sakamoto, M. Muto, and C. Kaneko, J. Chem. Soc. Perkin I, 1986, 1289 and references cited therein.
12. M. Sato, K. Sekiguchi, H. Ogasawara, and C. Kaneko, Synthesis, 1985, 225.
13. M. Sato, K. Takayama, N. Yoneda, H. Ogasawara, and C. Kaneko, unpublished results.
14. M. Sato, N. Yoneda, N. Katagiri, H. Watanabe, and C. Kaneko, Synthesis, 1986, 672.
15. Participation of 5,6-unsubstituted dioxinone and its 6-methyl derivative (e.g. 1) as equivalents of formyl-[a] and acetoacetic ester[b] in de Mayo reaction is well documented. Though the addition reactions proceed smoothly by direct irradiation at 300 nm, the reactions occur via T_1, as evidenced by acceleration of the reactions by the use of an appropriate sensitizer (e.g. acetone). UV spectra (MeOH) of 9a and 13: λ_{max} nm (ε) of 9a; 253 (8345) and that of 13; 244 (6078). a: M. Sato, H. Ogasawara, K. Sekiguchi, and C. Kaneko, Heterocycles, 22, 2563 (1984); b: S. W. Baldwin and J. M. Wilkinson, J. Am. Chem. Soc., 102, 3634 (1980).
16. Since the photo-cycloreversion only occurs efficiently by irradiation at 254 nm, it is evident that the reaction occurs via π-π^* excited state, while the addition reaction occurs through T_1 formed by intersystem crossing from S_1 (n-π^*).

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