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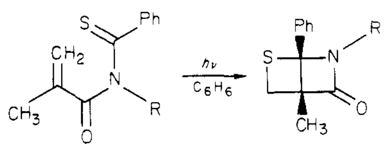
A New Synthesis of β-Lactams: 3-Oxo-6-thia-2-azabicyclo[2.2.0]hexanes via Photochemical Reactions of *N*-(Thiobenzoyl)methacrylamides

Summary: Irradiation of *N*-(thiobenzoyl)methacrylamides in benzene gave thietan-fused β-lactams in good yields, and these were converted to other β-lactams by reduction or oxidation.

Sir: The synthesis of β-lactam compounds has been of continuing interest for many years because of the medical importance of penicillin and cephalosporin antibiotics. Much effort has been put into the preparation of simple β-lactams for testing as antibiotics, antidepresents, and sedatives.[1] Syntheses involving photochemical reactions have been reported, most of them involving hydrogen abstraction,[2] ring contraction,[3] electrocyclization,[4] or the rearrangement of diazo compounds.[5] Other photochemical reactions[6] have also been used to synthesize a variety of β-lactam structures. In this paper, we report a new photochemical synthesis of β-lactams via intramolecular [2 + 2] reaction of *N*-(thiobenzoyl)methacrylamides (**1**). This reaction provides structurally interesting 3-oxo-6-thia-2-azabicyclo[2.2.0]hexanes (thietan-fused β-lactam) (**2**).

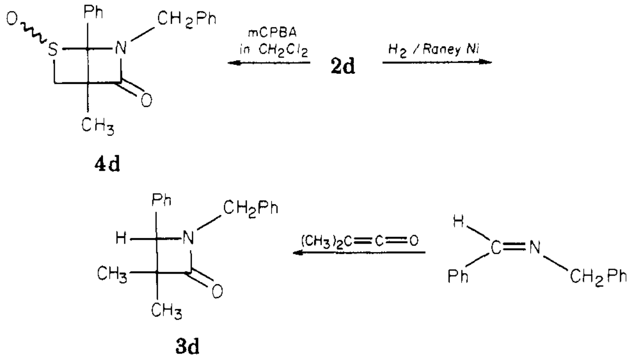
N-(Thiobenzoyl)methacrylamides (**1**) were easily obtained by the reaction of the corresponding thiobenzamides with methacrylyl chloride in the presence of triethylamine at room temperature. The UV spectrum of *N*-benzyl-*N*-(thiobenzoyl)methacrylamide (**1d**) exhibited maxima at 298 nm (ϵ = 9100), 322 nm (ϵ = 9900), and 462 nm (ϵ = 190). When **1d** in benzene was irradiated with a high-pressure mercury lamp under argon at room temperature and the crude product was chromatographed on silica gel (C_6H_6:AcOEt = 20:1), 2-benzyl-4-methyl-1-phenyl-3-oxo-6-thia-2-azabicyclo[2.2.0]hexane (**2d**) was obtained in 95% yield as a crystalline compound. Photolysis of other *N*-(thiobenzoyl)methacrylamides under the same conditions gave the corresponding β-lactams in high yields (Table I).

Table I. Photolysis of 1



compd	R	yield, %	mp, °C
a	CH_3	55	103-104.5
b	CH_2CH_3	96	oil
c	$CH(CH_3)_2$	73	82-83
d	CH_2Ph	95	81-82
e	Ph	77	103-104

Scheme I



The structure of **2d** was deduced from spectra. The IR spectrum ($CHCl_3$) exhibited a carbonyl frequency at 1750 cm^{-1} characteristic of β-lactams. The ^{1}H NMR spectrum ($CDCl_3$) showed signals at δ 1.07 (s, 3 H, CH_3), 3.10 and 3.41 (AB q, 2 H, J = 10.0 Hz, 5-CH_2), 4.46 and 4.51 (AB q, 2 H, J = 15.0 Hz, N-CH_2), and 7.1-7.4 (m, 10 H, Ph), and ^{13}C NMR exhibited resonances at δ 14.8 (q), 29.1 (t), 45.5 (t), 68.3 (s), 76.5 (s), 127.6 (d), 128.4 (d), 128.6 (d), 128.7 (d), 129.3 (d), 134.1 (s), 134.9 (s), and 171.4 (s). The mass spectrum (MS) showed peaks at m/e 295 ($M^{+\cdot}$), 262 (M − S), and 176, (M − $PhCH_2NCO$). In confirmation of the structure, **2d** was desulfurized with Raney nickel to give **3d** (82%), which was identified by direct comparison with an authentic sample (Scheme I).[7] The lactam **2d** was oxidized by mCPBA to produce the corresponding sulfoxide **4d** (56%) as a mixture of two stereoisomers (scheme I). The structures of other photoproducts were assigned on the basis of elemental analysis and spectral data.

The quantum yield of the photoreaction of **1d** was 0.18 (for the formation of **2d**).[8] The photoreaction also proceeded when **1d** was irradiated in the $n\pi^*$ region of the thiocarbonyl group (>400 nm) selectively. The photocyclizations were sensitized by Michler's ketone (E_T = 62 kcal mol^{-1}).[8b] Quenching of the reaction by 1,3-pentadiene or stilbene was quite inefficient. These results suggest that the cyclization proceeds from the $n\pi^*$ triplet state of the thiocarbonyl group, although a singlet-state reaction cannot be excluded from the available data.

Although transformation of a penicillin derivative to a 3-oxo-6-thia-2-azabicyclo[2.2.0]hexane was recently reported,[9] there have been no general synthetic methods of

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thietan-fused β-lactams. Since the starting materials **1** are easily obtained by acylation of thiobenzamides and the yields of these photoreactions are high, these reaction provides a useful synthetic method of some thietan-fused β-lactams.

Registry No. **1a**, 88295-93-6; **1b**, 88295-94-7; **1c**, 88295-95-8; **1d**, 88295-96-9; **1e**, 88295-97-0; **2a**, 88295-98-1; **2b**, 88295-99-2; **2c**, 88296-00-8; **2d**, 88296-01-9; **2e**, 88296-02-0; **3d**, 7468-30-6; **4d** (isomer 1), 88296-03-1; **4d** (isomer 2), 88315-26-8; $CH_2{=}C(CH_3)COCl$, 920-46-7; $PhCSNHCH_3$, 5310-14-5; $PhCSNHCH_2CH_3$, 39203-76-4; $PhCSNHCH(CH_3)_2$, 5310-15-6; $PhCSNHCH_2Ph$, 14309-89-8; PhCSNHPh, 636-04-4.

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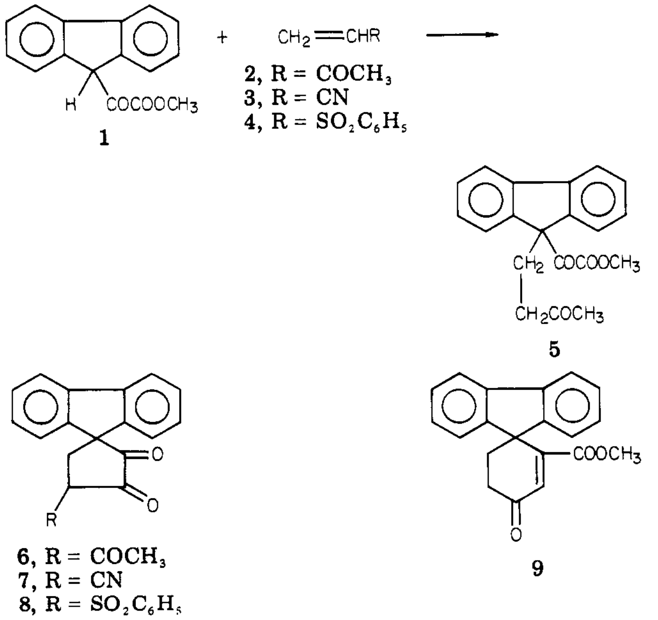
A New Cyclization Leading to Vicinal Cyclopentanediones

Summary: Reaction of methyl 9-fluoreneglyoxylate with methyl vinyl ketone, acrylonitrile, and phenyl vinyl sulfone in the presence of 1 equiv of potassium *tert*-butoxide produced 4-acetylspiro[cyclopentane-1,9′-[9*H*]fluorene]-2,3-dione, 4-cyanospiro[cyclopentane-1,9′-[9*H*]fluorene]-2,3-dione, and 4-[(phenylsulfonyl)oxy]spiro[cyclopentane-1,9′-[9*H*]fluorene]-2,3-dione, respectively.

Sir: The reaction of methyl vinyl ketone, **2**, with ketones under Michael reaction conditions followed by cyclization represents a standard route to cyclohexenones. In the review article on the Michael reaction[1] only one reference was made of the reaction of **2** with a polyfunctional α-keto ester. The only example of a reaction of **2** with a simple α-keto ester is that describing the condensation[2] of methyl 9-fluoreneglyoxylate, **1**. In repeating this reaction, using catalytic amounts of potassium *tert*-butoxide, an 82% yield of the known[2] Michael addition product, **5**, was obtained. From the mother liquor a small amount of 4-acetylspiro[cyclopentane-1,9′-[9*H*]fluorene]-2,3-dione, **6**, was obtained. The structure was established by IR, NMR, MS, and elemental analysis.



1

2, R = $COCH_3$
3, R = CN
4, R = $SO_2C_6H_5$

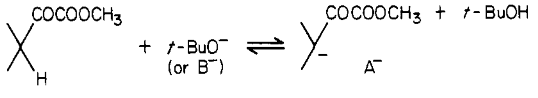
5

6, R = $COCH_3$
7, R = CN
8, R = $SO_2C_6H_5$

9

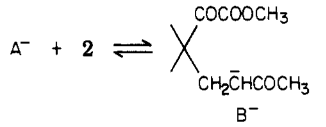
This finding seemed important for two reasons: (1) a cyclization different from that which yields the known methyl 4-oxospiro[cyclohex-2-ene-1,9′-fluorene]-2-carboxylate, **9**[2] was at hand and (2) a new route to vicinal cyclopentanediones was discovered.[3]

When the reaction of **1** with **2** was carried out with 1 equiv of t-BuOK, a 57% yield of **6** and a very small amount of **5** was obtained. Furthermore, when **5** was treated with 1 equiv of t-BuOK, a complicated mixture of products was obtained which is under study. These results can be explained by the consideration of the reactions pictured in eq 1–5.

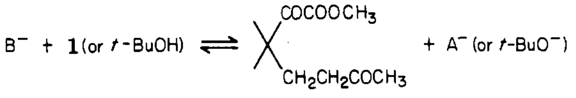


(1)

1

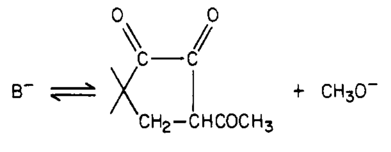


(2)



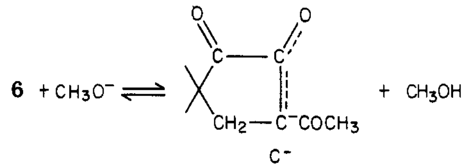
(3)

5



(4)

6



(5)

The keto ester **1** is a mixture of keto and enol forms (NMR shows two CH_3 groups at δ 4.05 and 3.75, corresponding to keto and enol forms). The amount of each varies with the time of contact with the $CDCl_3$ solvent before measurement and with the solvent used for recrystallization. In the condensation of **1** with **2** when a catalytic amount of t-BuOK is used the anion B^- rapidly reacts with the acidic keto ester **1** to form **5**, as shown in eq 3.[4] However, when an equivalent of t-BuOK is used there is no **1** to react with B^- and the latter cyclizes by displacing methoxide ion, as shown in eq 4. Then **6** is converted to anion C^- as shown in eq 5. Interestingly, when **5** is treated with 1 equiv of t-BuOK under conditions similar to those used in the reaction of **1** with **2** and 1 equiv of t-BuOK, no more than a trace of **5** and **9** are produced.[5] The latter reaction is under study.

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[1] The Michael Reaction: Bergmann, E. D.; Ginsburg, D.; Pappo, R. "Organic Reactions", R. E. Krieger: Huntington, NY, 1959; Vol. 10; pp 179–555.

[2] Plieninger, H.; Ege, G.; Ullah, M. I. *Ber.* **1963**, *96*, 1610.

[3] For references concerning synthesis of adjacent cyclopentanediones, see: Ho, T-L.; Liu, S-H. *Synth. Commun.* **1983**, *13*, 685.

[4] A referee suggested that B^- reacts with t-BuOH rather than **1**. If this were the case, one would expect a good yield of **5** when 1 equiv of t-buOK is used, but this is not the case.

[5] In the Plieninger reference[2] cyclization of **5** to **9** occurs in high yield when catalyzed by piperidine and acetic acid.