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OXIDATIVE REMOVAL OF N-(p-METHOXYBENZYL) GROUP ON DIKETOPIPERAZINE SKELETON WITH CERIC AMMONIUM NITRATE

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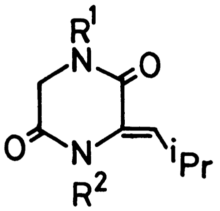
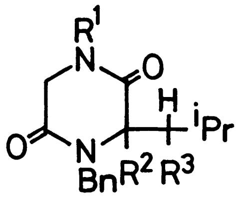
N-(p-Methoxybenzyl) groups in some diketopiperazine derivatives were proved to be readily and efficiently removed with ceric ammonium nitrate in acetonitrile-water under mild conditions, where N-benzyl, methoxyl in the aminal structure, and isolated vinyl groups remained unchanged.

Recently, many biologically active diketopiperazines such as bicyclomycin[1] and sirodesmin[2] have been discovered, and their synthetic studies have been carried out intensively. In order to protect the amido nitrogen of the diketopiperazine some alkyl groups such as methylthiomethyl[3] and methoxymethyl[4] and acyl groups[5] such as acetyl and benzoyl were reported. These protecting groups, however, have some difficulties in chemical stability and deprotection. Here we would like to report p-methoxybenzyl group as a new candidate of the protection which can be introduced easily and removed under mild oxidative conditions.

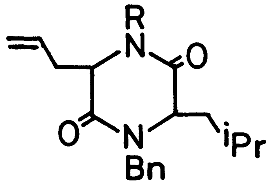
Four model diketopiperazine derivatives (4, 6, 8, and 11) were prepared from 1-acetyl-3-(2-methylpropylidene)-piperazine-2,5-dione (1).[6] Benzylation of 1 with sodium hydride and benzyl bromide in N,N-dimethylformamide (DMF) overnight at room temperature gave, in 73% yield, 4-benzyl derivative (2), which was converted into 1-benzyl-6-(2-methylpropylidene)-piperazine-2,5-dione (3, mp 124-126°C) quantitatively by deacetylation with hydrazine hydrate in DMF at 0°C for 2 h. p-Methoxybenzylation of 3 gave, in 80% yield, the first model compound (4, mp 98.5°C) having the exocyclic double bond, which was further converted into the third model compound (8) in 62% yield by treatment with N-bromosuccinimide in methanol and catalytic reduction in



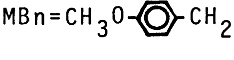
1 R^1=Ac, R^2=H
2 R^1=Ac, R^2=Bn
3 R^1=H, R^2=Bn
4 R^1=MBn, R^2=Bn



5 R^1=R^2=R^3=H
6 R^1=MBn, R^2=R^3=H
7 R^1=MBn, R^2=OMe, R^3=Br
8 R^1=MBn, R^2=OMe, R^3=H
9 R^1=H, R^2=ONO$_2$, R^3=OH
10 R^1=H, R^2=OMe, R^3=H



11 R=MBn
12 R=H



ethanol in the presence of 10% palladium-charcoal and ammonium acetate, where removal of neither p-methoxybenzyl nor benzyl group was observed. Catalytic reduction of 3 in ethanol in the presence of 10% palladium-charcoal followed by alkylation with sodium hydride and p-methoxybenzyl chloride in DMF overnight at room temperature gave the second model compound (6, mp 104-105°C) having both N-benzyl and N-(p-methoxybenzyl) groups. The fourth model compound (11, mp 123-124°C) having an isolated double bond was prepared by alkylation of 6 with lithium diisopropylamide and allyl bromide.

Various oxidative and selective removal of p-methoxybenzyl groups in the above model compounds was examined using some oxidants such as 2,3-dichloro-5,6-dicyanobenzoquinone7), chromium trioxide8) and ceric ammonium nitrate (CAN).9) The most practical results were obtained with CAN as shown in the Table. Thus the p-methoxybenzyl group could be removed quantitatively with CAN in acetonitrile containing water (2-50%), giving the corresponding amount of p-methoxybenzaldehyde. The concentration of this oxidant seems to be critical as shown in the unsuccessful run 4. Further, an interesting difference of double bonds against CAN was observed between 4 and 11. The former gave an oxidative addition compound (9, mp 137°C), while the latter not. These results indicate a promising aspect of p-methoxybenzyl group for protection of amido nitrogen on diketopiperazine skeleton, together with benzyl group, which was recently used for the total synthesis of bicyclomycin.10)

Table Oxidative Removal of Methoxybenzyl Group with CAN

Run	Substrate	CAN		H_2O/CH_3CN	Temperature	Time	Product and its yield (%)	
		Molar equivalent	Concentration mol/l		°C	h		
1	6	2.5	0.33	1:2	0	12	5	93.7
2	6	3.8	0.33	1:2	r.t.	2	5	98.6
3	6	5.0	1.32	1:100	r.t.	2	5	97.6
4	6	2.0	0.05	1:2	r.t.	3 d	no reaction	
5	4	7.6	0.50	1:1	r.t.	10	9	50.2
6	8	10.8	0.45	5:6	0	10	10	91.9
7	11	2.5	0.30	1:2	0	12	12	

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