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Preparation of a novel 16-DPA-P_2S_5 adduct and its application as a masked α,β-unsaturated ketone in [4+2]cycloaddition reactions

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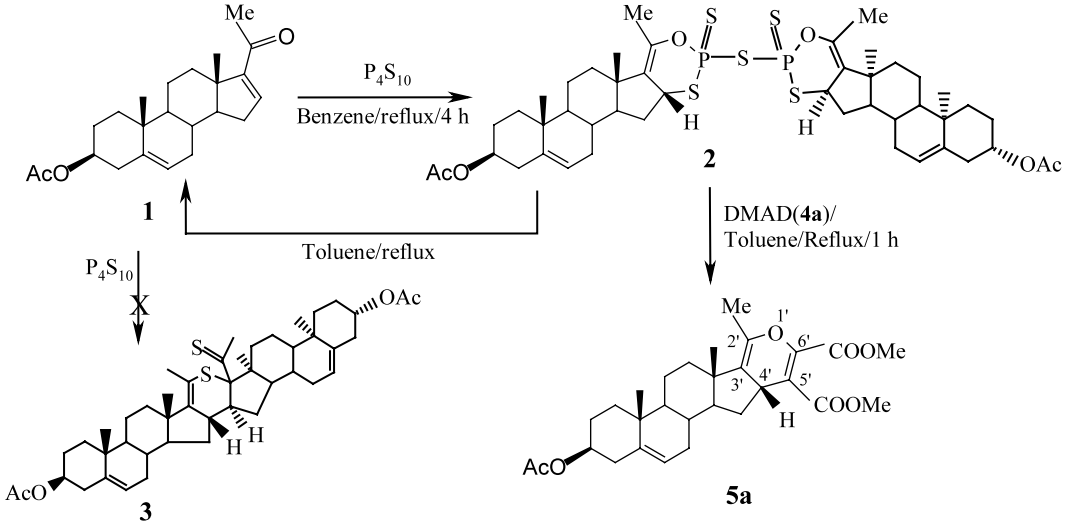
Abstract—The reaction of 16-DPA with P_4S_{10} in refluxing benzene afforded a novel adduct 16-DPA-P_2S_5 instead of the expected thione. The adduct undergoes [4+2]cycloaddition with alkyne dienophiles to afford steroidal (17,16-*c*)pyrans.

α,β-Unsaturated ketones attract attention because of their potential as key functions in organic synthesis.[1] However, α,β-unsaturated thiones are little known due to their instability in the monomeric form.[2] Although thionation of non-enolizable ketones by P_4S_{10} proceeds with ease in refluxing toluene or xylene, the attempted conversion of an α,β-unsaturated ketone to the corresponding thione was reported to be unsuccessful.[3] Instead, thionation of α,β-unsaturated ketones in CS_2/Et_3N led to thione dimers. Consequently, the conversion of α,β-unsaturated ketones into the corresponding thiones remains a challenging problem for organic chemists. The steroidal molecule 16-dehydropregnenolone acetate (16-DPA) **1** is a key intermediate for the synthesis of antitumor drugs[4] and bears a conjugated enone group in ring-D.

We have explored[5] the potential of conjugated steroidal enone moieties for the synthesis of azasteroids via ring-D manipulations. In continuation of this research,



Scheme 1.

Keywords: 16-Dehydropregnenolone acetate; tetraphosphorous decasulfide; [4+2]cycloaddition; steroidal (17,16-*c*)pyran.
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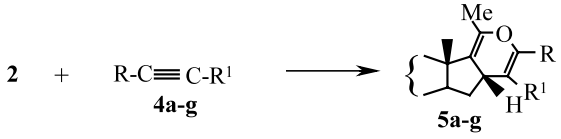
we focussed our attention on the synthesis of steroidal ring-D thiopyrans[6] via [4+2]cycloaddition reactions. However, our efforts in this direction did not afford the expected thione dimer **3**. Herein, we report our results on the reaction of 16-DPA with P_4S_{10} which gives a novel 16-DPA-P_2S_5 adduct and its subsequent application as a reactive masked enone for the preparation of pyrano(17,16-*c*)steroids under thermal conditions.

When a mixture of 16-DPA **1** (2.8 mmol) and P_4S_{10} (0.70 mmol) was refluxed in dry benzene (50 ml) for 4 h, the 16-DPA-P_2S_5 adduct **2** was isolated in 78% yield (Scheme 1). The adduct was purified by silica gel column chromatography and recrystallized from methanol, mp 94–95°C. It was characterized on the basis of its analytical and spectroscopic data.[7] The ^{1}H NMR of **2** indicated the absence of the characteristic C-16 olefinic proton at δ 6.26. The mass spectra (ESI) of **2** showed a molecular ion peak at 958 (M^++23) corresponding to the proposed structure. In order to investigate its thermal stability, the adduct 16-DPA-P_2S_5 **2** was heated in dry toluene at 110°C for 1 h, which resulted in regeneration of **1**. The thermal reaction was catalyzed by pyrrolidine. Our observation on the formation of **1** from adduct **2** supplements the literature report on the failure of the thionation reactions of α,β-unsaturated ketones in refluxing toluene or xylene,[8] as we found **2** to be unstable above 110°C.

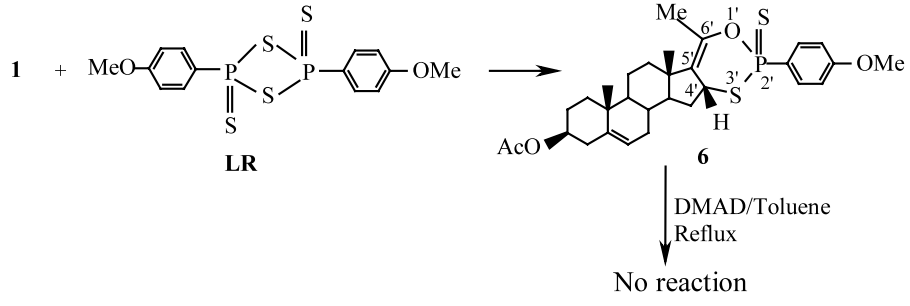
The [4+2]cycloaddition reaction of **2** (0.5 mmol) with DMAD **4a** (1 mmol) in refluxing dry toluene (50 ml) led to complete reaction within 1 h (TLC). The usual work-up and purification using silica gel preparative TLC with 20% ethyl acetate in hexane and recrystallization from methanol afforded 3β-acetoxy-5′,6′-dicarbomethoxy-2′-methyl-pyrano(17,16-*c*)-androst-5-ene **5a** in 81% yield. The product was characterized from its spectroscopic and analytical data.[9] The cycloaddition reaction of **2** with other alkynes **4b–g** afforded **5b–g** in 73–80% yields (Table 1). However, when the [4+2]cycloaddition reaction of **1** with DMAD in refluxing benzene was attempted for a prolonged period, it failed in our hands.

Encouraged by this unexpected result from the reaction of 16-DPA with P_4S_{10}, we attempted the thionation of **1** (2.8 mmol) with 2,4-bis-4-(methoxyphenyl)-1,3,2,4-dithiaphosphetane[10] (Lawesson's reagent **LR**, 2.8 mmol) in refluxing benzene (Scheme 2). The reaction was completed in 24 h and work-up of the reaction afforded 3β-acetoxy-2′-(*p*-anisyl)-2′-thio-6′-methyl-2′*H*,4′*H*-1′,3′,2′-oxathiaphosphinino(16,17-*d*′)androst-5-ene **6** in 82% yield.[9] However, this was found to be a thermally stable product, which did not participate in [4+2]cycloaddition reactions with DMAD or any other dienophile in refluxing toluene.

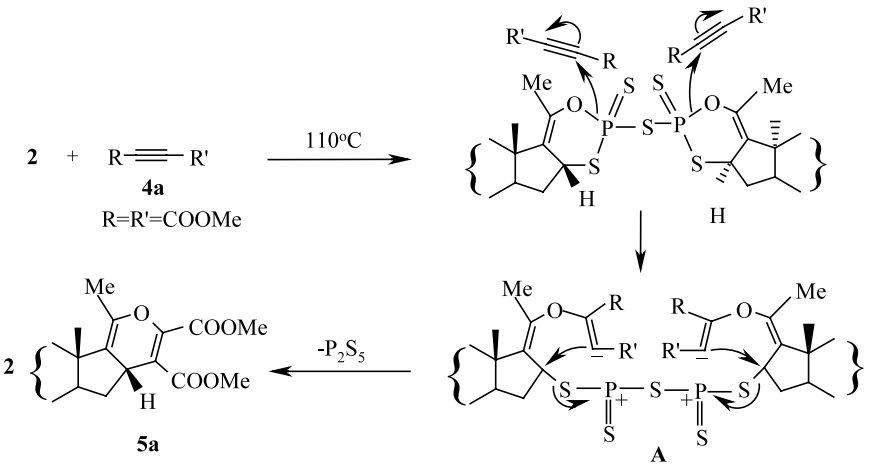
Table 1. [4+2]Cycloaddition reactions of 16-DPA-P_2S_5 adduct **2** with dienophiles **4a–g**



Entry	Dienophile	Product	R	R^1	Yield (%)
1	DMAD **4a**	**5a**	COOMe	COOMe	81
2	Ethyl propiolate **4b**	**5b**	H	COOEt	75
3	Methyl propiolate **4c**	**5c**	H	COOMe	74
4	Phenyl acetylene **4d**	**5d**	H	Ph	76
5	Ethyl phenylpropiolate **4e**	**5e**	Ph	COOEt	77
6	Methyl phenylpropiolate **4f**	**5f**	Ph	COOMe	80
7	1-Hexyne **4g**	**5g**	H	$CH_3(CH_2)_3$	73



Scheme 2.



Scheme 3.

The formation of adduct **2** may be accounted[10] by the [4+2]cycloaddition reaction of two molecules of **1** with two –P=S bonds of one molecule of P_2S_5 derived from P_4S_{10}.[11] Under thermal conditions, possibly 1 mol of **2** reacts with two moles of DMAD **4a** and undergoes a [4+2]cycloaddition reaction to afford the cycloadducts **5a** via a diion intermediate **A**[12] as depicted in Scheme 3. The isolation of the pyrano (17,16-*c*)steroids instead of the corresponding thio pyrano derivatives excluded the possibility of the formation of a thione dimer **3**.[3]

In conclusion, we have reported a facile preparation of steroidal D-ring annelated pyrans in high yield using an adduct of 16-DPA-P_2S_5 as a masked conjugated enone. The reaction provides a novel strategy for the activation of conjugated enones towards unreactive dienophiles. Further work to generalize the scope of this reaction in other related systems, is in progress.

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7. Spectral and analytical data of **2**, $R_f=0.5$ (toluene/ethyl acetate=95/5); yield 78%; mp 94–95°C; IR (KBr) ν_{max} 3439, 2941, 1726, 1622, 1595, 1376 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.38 (bs, 2H), 4.60 (bs, 2H), 4.28 (bs, 2H), 2.08 (s, 6H), 2.03 (s, 6H), 1.09 (s, 6H), 1.06 (s, 6H), 2.34–0.86 (m, 34H); ^{13}C NMR ($CDCl_3$) δ 169.64, 138.97, 128.15, 127.34, 120.92, 72.80, 53.84, 52.59, 48.88, 48.54, 37.11, 35.63, 35.52, 30.64, 30.00, 29.80, 26.76, 20.55, 19.99, 18.37, 17.38, 17.29, 16.86; MS ESI *m/z* 958 (M^++23). Anal. calcd for $C_{46}H_{64}O_6P_2S_5$: C, 59.07; H, 6.89; S, 17.14. Found: C, 59.31; H, 6.25; S, 16.26.
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9. Spectral and analytical data of **5a**, $R_f=0.5$ (hexane/ethyl acetate=80/20); yield 81%; mp 54–55°C (methanol); IR (KBr) ν_{max} 2950, 1728, 1588, 1435, 1364, 1251 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.39 (bs, 1H), 4.50 (bs, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H), 1.03 (s, 3H), 1.06 (s, 3H), 2.80–1.03 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 169.40, 164.30, 163.86, 138.23, 127.54, 120.62, 119.55, 116.76, 114.82, 72.36, 54.11, 52.62, 49.02, 48.61, 36.53, 36.21, 34.86, 31.22, 30.96, 30.33, 26.19, 20.87, 20.10, 18.96, 17.82, 16.95, 16.20, 15.86, 15.32; MS EI *m/z* 498 (M^+). Anal. calcd for $C_{29}H_{38}O_7$: C, 69.86; H, 7.68. Found: C, 69.51; H, 7.25. Compound **6**, $R_f=0.5$ (toluene/ethyl acetate=95/5); yield 82%; mp 158–59°C (methanol); IR (KBr) ν_{max} 2926, 1716, 1610, 1504, 1243, 930 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.80–6.65 (m, 4H), 5.15 (bs, 1H), 4.42 (bs,

1H), 4.18 (bs, 1H), 3.65 (s, 3H), 2.05 (s, 3H), 1.90 (s, 3H), 1.10 (s, 3H), 0.98 (s, 3H), 2.20–1.05 (m, 17H); ^{13}C NMR ($CDCl_3$) δ 169.52, 137.85, 127.66, 121.50, 118.76, 116.34, 114.82, 113.60, 112.92, 110.86, 109.52, 72.92, 53.26, 52.10, 48.54, 48.10, 37.03, 35.98, 35.10, 30.10, 30.44, 29.88, 29.62, 26.40, 21.08, 19.10, 17.87, 17.20, 16.33, 15.44. Anal. calcd for $C_{30}H_{39}O_4S_2P$: C, 64.50; H, 7.04; S, 11.47. Found: C, 64.20; H, 7.28; S, 10.98.

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