(5): 1.65 g (75% yield); $[\alpha]^{25}_D$ +45° (c 1.2); IR (KBr, cm^{-1}) 2910, 1750, 1500, 1310, 1100, 1060, 1040, 820; ^1H NMR (100 MHz) δ 1.2–1.8 (4 H, m), 2.35 (6 H, s), 3.05–3.35 (2 H, m), 6.35–6.65 (2 H, m), 6.85–7.35 (8 H, m). This material was used directly in the modified Tschugaeff reaction that follows.

The (+)-bis(*O*-*p*-tolyl thionocarbonate) ester mixture (5) from above (1.65 g, 3.73 mmol) was pyrolyzed at 170 °C under vacuum (2 Torr).[12] The pyrolysate was collected at liquid nitrogen temperature and the barrelene product (1) was separated by preparative gas chromatography at 130 °C as a highly volatile oil (17 mg, 4%). It was >99.9% pure by analytical gas chromatography and had a retention time identical with that of an authentic sample of barrelene-d_0:[26] UV (*n*-heptane) ϵ^{238}_{max} 125, ϵ^{215} 185, ϵ^{190} 2850; CD (*n*-heptane) $\Delta\epsilon^{246}_{max}$ +0.0083, $\Delta\epsilon^{215}_{max}$ −0.071; UV (TFE) ϵ^{235}_{max} 132, ϵ^{225} 113, ϵ^{215} 260, ϵ^{190} 2650; CD (TFE) $\Delta\epsilon^{248}_{max}$ +0.0018, $\Delta\epsilon^{225}_{max}$ −0.036, $\Delta\epsilon^{215}_{max}$ −0.003 (CD data corrected to 100% ee); IR (CCl_4, cm^{-1}) 3060, 2980, 1550, 1300, 1190; ^1H NMR (100 MHZ) δ 4.83 (2 H, m), 6.76 (4 H, m); ^{13}C NMR (ppm) 48.07 (d, C_1, C_4), 140.36 (d, C_3, C_6, C_7, C_8), 141.29, 140.24, 139.19 (wt, C_2, C_5).

(1*R*)-2,5-Dideuteriobicyclo[2.2.2]octa-2,5,7-triene (*ent*-1). Reduction of **3b** (510 mg, 3.74 mmol) with $LiAlD_4$ (158 mg, 3.74 mmol) in dry tetrahydrofuran (40 mL) as described above gave 499 mg (94%) of *ent*-4. A cold (0 °C) solution of these diols in dry pyridine (10 mL) was treated dropwise under argon with *p*-tolyl chlorothioformate (1.73 mL, 11.2 mmol). This mixture was stirred in the dark for 7 days and processed in the predescribed manner. Flash column chromatography of the crude product on silica gel (elution with benzene–petroleum ether (1:3)) gave 1.37 g (88%) of a mixture of thionocarbonates.

Pyrolysis of the above solid at 180 °C and 20 Torr followed by preparative gas chromatographic purification of the condensate afforded 65 mg (20%) of *ent*-1. Hydrocarbon prepared in this manner exhibited ^1H and ^{13}C NMR spectra identical with those of 1, but with CD effects of opposite sign.

(−)-(1*S*,5*S*)-2-Oxobicyclo[2.2.2]oct-7-en-5-ol *p*-Toluenesulfonylhydrazone (7). A mixture of (−)-(1*S*,5*S*)-2-oxobicyclo[2.2.2]oct-7-en-5-ol (6) ($[\alpha]^{25}_D$ −328° (c 0.16)) (550 mg, 4 mmol), *p*-toluenesulfonylhydrazine (Aldrich) (745 mg, 4 mmol), and formic acid (3 drops) in dichloromethane (25 mL) was stirred at room temperature overnight. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel (elution with ethyl acetate–hexane (2:1)) to give a white solid (930 mg, 76%): mp 152–155 °C; $[\alpha]^{25}_{589}$ −141° (c 0.65); UV (CH_3CN) ϵ^{229}_{max} 1225, ϵ^{206}_{max} 1198; IR (KBr, cm^{-1}) 3400, 3180, 3040, 2920, 1710, 1640, 1590, 1320, 1150, 1020, 910; ^1H NMR (100 MHz) δ 1.25 (2 H, t, *J* = 7 Hz), 1.99 (3 H, m), 2.42 (3 H, s), 3.01 (1 H, m), 3.18 (1 H, m), 4.15 (2 H, m), 6.29 (2 H, m), 7.3 (2 H, d, *J* = 8 Hz), 7.81 (2 H, d, *J* = 9 Hz).

(−)-(1*R*,2*S*)-*endo*-Bicyclo[2.2.2]oct-5-en-2-ol (8). To a suspension of tosylhydrazone 6 (615 mg, 2 mmol) in dry dichloromethane (10 mL) at 0 °C was added Dibal (1 M in hexane; 6 mL, 6 mmol). The mixture was allowed to stir at room temperature for 15 min. The excess hydride was then decomposed by adding 3 M sodium hydroxide (2 mL), and the solution was diluted with dichloromethane. The organic solution was washed with brine and dried. The solvent was removed by distillation through a Vigreux column (bath temperature 60 °C). The residue was sublimed at 120 °C (5 mm) to give alcohol 8 as a white solid (125 mg, 50%): mp 163–165 °C; $[\alpha]^{25}_{589}$ −76.5° (c 1.0) (lit.[18] mp 166.2–166.8 °C, $[\alpha]^{23}_D$ +48.3° (c 1), 66 ± 2% ee); IR (KBr, cm^{-1}) 3440, 3030, 2920, 2850, 1440, 1370, 1320, 1270, 1220, 1080, 1050, 1020, 960, 920, 850; ^1H NMR (100 MHz) δ 0.95–1.35 (4 H, m), 1.7–2.05 (3 H, m), 2.4–2.75 (2 H, m), 3.86 (1 H, m), 6.05 (1 H, t, *J* = 7 Hz), 6.37 (1 H, t, *J* = 6.5 Hz); ^{13}C NMR (ppm) 21.77 (t, C_7), 23.88 (t, C_8), 29.96 (d, C_4), 37.57 (d, C_1), 38.97 (t, C_3), 70.27 (d, C_2), 129.65 (d, C_6), 136.44 (d, C_5). The present solid had the same GC retention time and same IR and NMR spectral properties as that of an authentic sample of *endo*-alcohol.[23]

(−)-(1*S*)-Bicyclo[2.2.2]oct-5-en-2-one (9). To a stirred solution of bicyclic *endo*-alcohol 8 ($[\alpha]^{25}_D$ −76.5° (c 1.0)) (100 mg, 0.8 mmol) in dry dichloromethane (10 mL) was added pyridinium chlorochromate (170 mg, 0.8 mmol). The mixture was allowed to stir at room temperature for 30 min and passed through a short column of silica gel. The silica gel was then washed with dichloromethane. The dichloromethane was removed by distillation through a Vigreux column (bath temperature ~60 °C). The residue was sublimed at 40 °C (2 mm) to give 8 as a white solid (4.6 mg, 47%): mp 75–78 °C; $[\alpha]^{25}_{589}$ −485° (c 0.153) [(lit.[18] mp 90.5–93 °C, $[\alpha]^{28}_D$ +267° (c 1.2) from *endo*-alcohol precursor having $[\alpha]^{26}_D$ +39.6° ($CHCl_3$)]; UV (*n*-heptane) ϵ^{317}_{max} 54, ϵ^{306}_{max} 103, ϵ^{296}_{max} 110, ϵ^{287}_{max} 90, ϵ^{217}_{max} 1069; IR (KBr, cm^{-1}) 3040, 2930, 2850, 1720, 1440, 1400, 1350, 1250, 1200, 1150, 1070, 850; GC retention time (analytical column) same as that of a sample of the authentic ketone.[23]

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(26) We are grateful to professor I. Erden (San Francisco State University) for a generous sample of authentic material.

Oxidative Cyclization of Arylhydrazones of Chalcones and Benzalacetones to Pyrazoles by Thianthrene Cation Radical

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Phenyl-, (*p*-nitrophenyl)-, and (2,4-dinitrophenyl)hydrazones of chalcone (benzalacetophenone), benzalacetone, and of some of their derivatives undergo oxidative cyclization in reactions with thianthrene cation radical perchlorate. The products are, respectively, 1,3,5-triaryl- (3) and 3-methyl-1,5-diarylpyrazoles (4) and are formed in excellent yields. Cyclization appears to occur by way of the arylhydrazone cation radical and not via the preliminary, acid-catalyzed formation of the corresponding pyrazoline.

Introduction

Recently, we have described the oxidative cycloaddition of arenealdehyde phenylhydrazones to nitriles, induced by the thianthrene cation radical ($Th^{\bullet+}$).[1,2] We have found now that reaction of $Th^{\bullet+}$ with arylhydrazones of chalcones (1) and benzalacetones (2) causes their oxidative, intramolecular cyclization into pyrazoles (3 and 4) in excellent yields.

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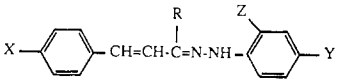
Table I. Arylhydrazones 1 and 2 and Some of Their Cyclic Derivatives[a]

no.	X	Y	Z	R	mp, °C	lit. mp, °C	ref
1a	H	H	H	C_6H_5	118–120	120	6
1b	H	NO_2	H	C_6H_5	172–174[b]	149–150	15
1c	H	NO_2	NO_2	C_6H_5	248–249	248–249	17, 18
1d	H	NO_2	NO_2	$pClC_6H_4$	180–181		*c*
1e	H	NO_2	NO_2	$pMeOC_6H_4$	143–145		*c*
1f	Cl	NO_2	NO_2	C_6H_5	242–243		*c*
2a	H	H	H	Me	155–156	156	19
2b	H	NO_2	H	Me	165–167	165–167	20
2c	H	NO_2	NO_2	Me	222–223	223	16
2f	Cl	NO_2	NO_2	Me	250–252		*c*
2g	Cl	H	H	Me	155–156	154–157	8
2h	NO_2	H	H	Me	194–196	194–196	22
3a	H	H	H	C_6H_5	135–137	139–140	4
3b	H	NO_2	H	C_6H_5	119–120	121–122	4
3c	H	NO_2	NO_2	C_6H_5	149–150	150–151	23
4a	H	H	H	Me	oil	63	24
4b	H	NO_2	H	Me	99–100	100	25
4c	H	NO_2	NO_2	Me	131–132	133–134	23
5a	H	H	H	C_6H_5	132–134	133–135	7
5b	H	NO_2	H	C_6H_5	175–176	178–179	4
5c	H	NO_2	NO_2	C_6H_5	158–159		*c*
6a	H	H	H	Me	111–112	112–113	22
6b	H	NO_2	H	Me	148–149	149	20

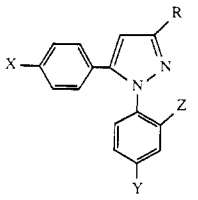
[a] Most of the compounds listed here were prepared by standard procedures and are to be found in the literature, as referenced. [b] See Experimental Section. [c] These compounds were not found in the literature. See Experimental Section.

Oxidative cyclization of chalcone phenylhydrazone (**1a**, see Table I) into the pyrazole (**3a**) has been reported by others. For example, anodic oxidation gave **3a** in 15–28% yield in the absence and 40% yield in the presence of pyridine.[3] Oxidation by lead tetraacetate gave **3a** in 74% yield[4] and by manganese dioxide in 73% yield.[5]

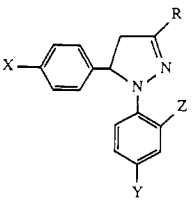
Arylhydrazones of the type **1** and **2** (Y = Z = H) readily undergo acid-catalyzed cyclization into the isomeric 2-pyrazolines (**5** and **6**). For example, **1a** (see Table I) is



1, R = aryl; **2**, R = methyl

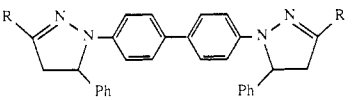


3, R = aryl
4, R = methyl

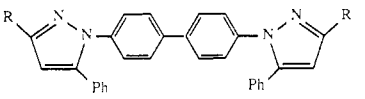


5, R = aryl
6, R = methyl

converted into **5a** by heating in acetic acid[6] or by treatment with methanolic hydrochloric acid.[7] The kinetics of acid-catalyzed cyclization of a number of arylhydrazones of benzalacetones (**2**, X = H only) have been reported by Jackson and co-workers.[8] On the other hand, (2,4-dinitrophenyl)hydrazones (2,4-DNPs) of unsaturated aryl ketones do not cyclize into 2-pyrazolines so easily, as is witnessed by the fact that these hydrazones are prepared in strongly acidic solutions. Cyclization of the 2,4-DNP of phenyl vinyl ketone by heating with hydrobromic acid in acetic acid has been described by Chambers and Willard.[9] Acid-catalyzed cyclization of arylhydrazones into 2-pyrazolines has a role in considerations of oxidative cyclizations into pyrazoles, because 2-pyrazolines can be oxidized, themselves, into pyrazoles by a variety of oxidizing agents. Thus, **5a** is oxidized into **3a** by manganese dioxide in 93% yield[5] and by lead tetraacetate in 89% yield.[4] Other chemical oxidants have been listed by Marchetti and co-workers.[10] Consequently, the question has been asked if, in the oxidative cyclization of arylhydrazones (**1** and **2**), the pyrazoles (**3** and **4**) are obtained, in fact, from the 2-pyrazolines (**5** and **6**) formed first, adventitiously. The answer, that oxidative cyclization does not occur through the adventitious, prior formation of a 2-pyrazoline, has been provided insofar as anodic oxidation is concerned, from the work of Pragst[11] and of Tabakovic[3] with **1a**, **3a**, and **5a**. Thus, these workers showed that **5a** underwent anodic oxidation successively to the pyrazoline dimer (**7**), the dication (7^{2+}), and the pyrazole dimer (**9**).



7, R = phenyl
8, R = methyl



9, R = phenyl

Only traces of **3a** were formed,[3] whereas a significant amount of **3a** was obtained only when a base (pyridine) was added to the anolyte, the relative amount of **3a** increasing with increasing amount of pyridine.[11] It was further shown that **5a** was not part of the anodic pathway from **1a** to **3a** with the use of diagnostic electrochemical criteria.[3] That is, anodic oxidation of **1a** took it directly via its cation radical on the path to **3a**. During the anodic

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Table II. Oxidative Cyclization of Arylhydrazones of Chalcones 1 into Pyrazoles 3 by $TH^{\bullet+}ClO_4^-$

arylhydrazone	solvent[a]	reactant ratio[b]	products (%)[c] Th	ThO	pyrazole	remarks
1a	AN	2.0	93.4	4.3	3a 98.7	
1a	AN	2.14	85.5	15.0	3a 97.1	
			85.4	16.1	93.7	d
1a	MC	2.9	89.0	10.5	3a 74.5	e
1a	MC	3.0	92.7	5.3	3a 66.4	e
1a	MC	3.0	97.5	1.3	3a 79.8	e
1a	MC	2.0	87.3		3a 87.3	g
1b	AN	2.2	94.7	5.8	3b 98.7	
			94.4	6.0	3b 100	d
1b	MC	2.9	84.4	16.4	3b 99.2	
1c	AN	2.1	93.0	7.4	3c 99.0	
1c	AN	2.25	91.0	9.7	3c 98.4	
1c	AN	2.0	92.8	7.6	3c 94.0	f
1c	MC	3.0	83.8	16.5	3c 98.2	
1c	MC	2.75	84.8	14.8	3c 95.0	f
1d	AN	2.2	95.0	5.0	3d 100	d
1e	AN	2.2	94.9	4.8	3e 100	d
1f	AN	2.25	93.1		3f 99.5	d

[a] AN, acetonitrile; MC, methylene chloride. [b] mmol of $Th^{\bullet+}ClO_4^-$ per mmol of arylhydrazone. [c] Analysis of products by GLC, except where noted. [d] All products were isolated by preparative-scale TLC. [e] Presence of dimer 7 cation radical was indicated. [f] About 4–5% of unreacted arylhydrazone was obtained. [g] Two equiv of 2,6-di-*tert*-butylpyridine were added.

oxidation of **1a**, the 2-pyrazoline (**5a**) was indeed formed, by adventitious acid-catalyzed cyclization, but instead of being oxidized to **3a**, the **5a** went on to its dimeric forms **7** and **9**.[3]

In these ways it was shown that $\mathbf{1a}^{\bullet+}$ cyclized, whereas $\mathbf{5a}^{\bullet+}$ dimerized, unless pyridine were present, in which case $\mathbf{5a}^{\bullet+}$ was converted into **3a**. The rationale for these reactions lies in the structures of $\mathbf{5a}^{\bullet+}$ and of cyclized $\mathbf{1a}^{\bullet+}$, that is, **11**, as has been set out by Tabakovic and coworkers.[3] The cyclized cation radical (**11**) is eminently suitable to further deprotonation and oxidation, ending in **3a**. In contrast, spin density in $\mathbf{5a}^{\bullet+}$ appears to be concentrated in the *N*-phenyl ring, leading on, in the absence of base, to dimerization at the para position of that ring (Scheme I).

Analogous findings have been reported from the oxidation of **5a** with pyridinium hexachloroantimonate in chloroform solution. That is, **7** was formed in the absence and **3a** (67%) in the presence of pyridine.[12] Blocking the para position of an *N*-aryl-2-pyrazoline, for example, with the NO_2 group (**5b**, see Table I), prevents oxidative dimerization at the *N*-aryl ring,[3,12,13] and allows for oxidation to the pyrazole.[12] Here, also, dimerization may take another route, through the 4-position of the pyrazoline ring. Thus, Barbey and Caullet obtained 40% of **3b** and 30% of **10** by anodic oxidation of **5b** in acetonitrile.[14]

Following our discovery of the oxidative cycloaddition of the phenyl- and benzylhydrazones of benzaldehyde to solvent nitriles, with the formation of 1,2,4-triazoles,[1,2] we carried out the reactions of the phenylhydrazones of cinnamaldehyde and chalcone (**1a**) with $Th^{\bullet+}ClO_4^-$ in acetonitrile. Instead of cycloaddition with solvent, clean oxidative, intramolecular cyclizations to 1,5-diphenyl- and 1,3,5-triphenylpyrazole (**3a**), respectively, occurred. We have now found that this is a common reaction for the arylhydrazones of chalcones and benzalacetones.

Results and Discussion

Oxidations of arylhydrazones of chalcones (**1a–f**) and benzalacetones (**2a–c,f–h**) were carried out in both acetonitrile and methylene chloride solution. The corresponding pyrazoles (**3** or **4**) were formed in excellent yield in each case. Pyrazoles were identified by isolation, followed by GC/MS and/or ^1H and ^{13}C NMR, and by comparison with the literature where possible. The yields of products thianthrene (Th), thianthrene 5-oxide (ThO), and pyrazole were assayed by gas–liquid chromatography (GLC) and/or preparative-scale thin layer chromatography (TLC). Results are given in Tables II and III.

The stoichiometry of these oxidative cyclizations is given in Scheme I (oxidant, $Th^{\bullet+}$), although we do not have appropriate mechanistic detail for establishing the sequence of steps shown with $Th^{\bullet+}$ as oxidant. The stoichiometric ratio (2:1) of $Th^{\bullet+}$ to arylhydrazone is reflected reasonably well in the material balance given by the yields of products (Tables II, III). The formation of ThO is not related to the cyclization reaction but stems from the reaction of $Th^{\bullet+}$ with water which was present in the solvent or was added in workup. This is evident, particularly, where a large excess of $Th^{\bullet+}$ was used. In most of the reactions in methylene chloride, more $Th^{\bullet+}ClO_4^-$ was used than is required by the 2:1 stoichiometry. The need to use more $Th^{\bullet+}ClO_4^-$ was noticed first in reactions with **1a**, in which not all of the **1a** was consumed with the use of the 2:1 ratio of reactants. The reason for this is that **1a** was more prone to acid-catalyzed cyclization to the pyrazoline (**5a**) in methylene chloride than in the more basic acetonitrile. Consequently, $Th^{\bullet+}ClO_4^-$ was also consumed in oxidizing **5a**, resulting in the formation of the dimer (**7**) cations. In some cases, as reported, for example, with the oxidation of **2a,h** (Table III), the pyrazole itself consumed some of the $Th^{\bullet+}$, forming a 5-thianthrenium perchlorate. As a matter of practice, therefore, a 3:1 ratio of $Th^{\bullet+}ClO_4^-$ to arylhydrazone was used for reactions in methylene chloride. This resulted, in some cases, in much unused $Th^{\bullet+}ClO_4^-$, which was hydrolyzed during workup into Th and ThO. It was not possible to follow the cyclization reaction by monitoring the disappearance of the purple color of $Th^{\bullet+}$, because oxidized byproducts and, no doubt, intermediate cation radicals, were themselves highly colored. Reactions were continued, therefore, for 24 h or longer, probably much longer than was necessary.

In some cases (e.g., with **1a**) the changes of color which occurred suggested that small amounts of the corresponding pyrazoline dimer cation radical had been formed (see Table II). The possibility that a pyrazole could be

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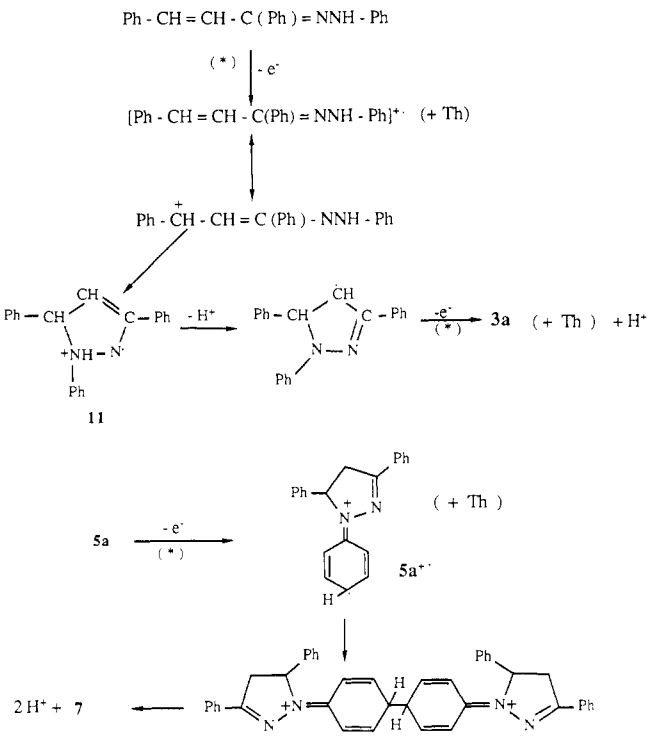
Table III. Oxidative Cyclization of Arylhydrazones of Benzalacetones 2 into Pyrazoles 4 by $TH^{\bullet+}ClO_4^-$

arylhydrazone	solvent[a]	reactant ratio[b]	products (%)[c] Th	ThO	pyrazole	remarks
2a	AN	2.25	90.2	7.7	**4a** 99.4	*d*
2a	MC	3.0	85.6	7.5	**4a** 91.7	*d*, *e*
2a	MC	3.0	84.9	10.5	**4a** 94.8	*d*, *e*
2b	AN	2.25	90.6	9.6	**4b** 97.5	
			91.2	9.6	96.7	*d*
2b	MC	3.0	92.4	7.0	**4b** 96.7	
2c	AN	2.25	90.3	8.6	**4c** 99.9	
			91.2	8.7	99.1	*d*
2f	AN	2.2	96.5	3.3	**4f** 99.1	
			96.2	3.5	100	*d*
2f	AN	2.2	96.2	2.8	**4f** 99.6	*d*
2f	MC	2.95	85.7	15.0	**4f** 99.2	
2g	AN	2.25	92.8	4.2	**4g** 98.7	*d*
2h	AN	2.25	92.4	6.7	**4h** 99.7	*d*
2h	AN	2.25	94.8	5.9	**4h** 99.0	
			92.1	5.9	99.0	*d*
2h	MC	2.95	87.6	6.0	**4h** 92.1	*e*

[a-d] See Table II. [e] Another product, believed to be a sulfonium perchlorate was also isolated. See Experimental Section.

Scheme I[a]



[a] * = Anodic or $Th^{\bullet+}$ oxidation.

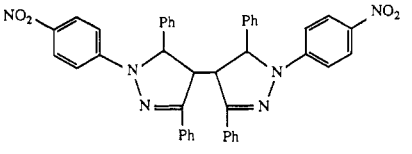
arising, in fact, from the oxidation of first-formed pyrazoline was a concern to us. Hydrolysis of $Th^{\bullet+}ClO_4^-$ by water, which is present adventitiously in a solvent, cannot be avoided and produces $HClO_4$ along with ThO. We were concerned, therefore, that adventitiously formed acid may have caused the cyclization of the hydrazones (**1** and **2**) into the pyrazolines (**5** and **6**) and that the pyrazolines were the precursors of the pyrazoles (**3** and **4**). This possibility was tested insofar as **1a** and **2a** are concerned, by carrying out the oxidations of pyrazolines **5a** and **6a** with $Th^{\bullet+}$. Oxidation led not to the pyrazoles (**3a** and **4a**) but (after reduction with zinc) to the dimeric biphenyls **7** and **8**, respectively, in excellent yield (Table IV). These observations parallel those of earlier workers[3,11] in the anodic oxidations of **1a** and **5a**, to which we referred earlier. The two sets of results suggest that a pyrazoline is not an intermediate in the pathway to a pyrazole in these cases. However, we cannot be sure of this diagnosis until more definitive tests are carried out.

Table IV. Oxidation of Pyrazolines 5 and 6 by $Th^{\bullet+}ClO_4^-$

pyrazoline	solvent[a]	reactant[b] ratio	products (%)[c] Th	ThO	other
5a	AN	2.0	87.7	11.1	**7** 98.8[d]
5a	AN	2.1	96.1	3.7	**7** 98.8[d]
5a	MC	2.1	98.5	0	**7** 93.3[e]
5b	AN	2.0	95.6	7.6	**3b** 85.4
5b	AN	2.0	87.2	9.6	**3b** 63.7
5b	MC	2.0	99.7	1.8	**3b** 94.4
5b	MC	2.0	95.9	3.9	**3b** 98.7[f]
6a	AN	2.0	95.4	2.9	**8** 92.4[d]
6a	MC	2.0	99.3	0	**8** 93.9[e]
6b	MC	2.1	92.3	7.0	**4b** 64.7[g]

[a-c] See Table II. [d] For product isolation, see Experimental Section. [e] For isolation of this dimer, the solvent (MC) was evaporated on a rotary evaporator and replaced with 20 mL of AN. Treatment with zinc dust, and isolation as described in footnote *d*, followed. [f] Two equiv of 2,6-di-*tert*-butylpyridine were added. [g] 15.3% of **6b** was recovered.

The same diagnostic test of the pathway in oxidative cyclizations of most of the other hydrazones (e.g. **1b–f**, **2b,c,f**) could not be performed, because the corresponding pyrazolines, possessing blocked *N*-aryl para positions, do not readily undergo oxidative dimerization. Pyrazoline **5b** has been reported to undergo some oxidative dimerization at its C-4 position, giving **10**,[14] but we did not find this type



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of dimerization in the oxidation of **5b** with $Th^{\bullet+}$ (Table IV). Circumstantial evidence which, in all likelihood, rules out the formation of pyrazoles from first-formed pyrazolines in our oxidations of 2,4-DNPs (**1c–f**, **2c,f**) is seen in that 2,4-DNPs are formed in strongly acidic solution and, in fact, cannot be easily cyclized by acid catalysis.

It is noteworthy that **5a** is oxidized cleanly into **3a** by manganese dioxide[5] and lead tetraacetate,[4] whereas anodic oxidation and oxidation by $Th^{\bullet+}ClO_4^-$ and by ferric chloride (see Experimental Section) leads to cations of the dimer (**7**).

As noted earlier, above, in some of our oxidations of arylhydrazones, small amounts of a 5-thianthrenium

(sulfonium) perchlorate were obtained, e.g., with **2a** and **2h** (Table III). The sulfonium salts were identified by ^1H NMR as products of reaction of $Th^{\bullet+}$ with the corresponding pyrazole and will be described more fully in a later communication.

Experimental Section

Acetonitrile (Kodak, No. 106 3072) and methylene chloride (EM Science, No. DX0831-1), used as solvents for reactions of thianthrene cation radical perchlorate ($Th^{\bullet+}ClO_4^-$), were distilled over P_2O_5 under an argon atmosphere prior to use. GLC was performed on a Varian FID gas chromatograph, Model 3700, with an 18-in. stainless steel column, $^1/_8$ in. diameter, packed with 5% OV-101 on GHP 100/120-mesh support. Preparative TLC was carried out on 20 × 20 cm plates of silica gel (Brinkmann, P/UV 254, No. 81638) with methylene chloride development. Thianthrene (Fluka) was purified by chromatography on a column of silica gel and crystallized from acetone, mp 152–154 °C. $Th^{\bullet+}ClO_4^-$ was prepared as described earlier.[27] Melting points were determined with a Mel-Temp apparatus and are uncorrected.

Arylhydrazones were prepared in standard ways and are listed in Table I. Most of the arylhydrazones that were used are to be found also in the literature, and references to them are also given in Table I. Solvents used to recrystallize the arylhydrazones were methanol, ethanol, ethyl acetate, or mixtures of these solvents. Chalcone (*p*-nitrophenyl)hydrazone (**1b**) was prepared in two ways, since its melting point (172–174 °C) differed from that (149–150 °C) reported.[15] In the first method, a solution of 2.0 g (9.6 mmol) of chalcone, 1.5 g (9.6 mmol) of *p*-nitrophenylhydrazine, and 1 mL of acetic acid in 30 mL of 95% ethanol was heated to boiling on a hot plate, allowed to cool, and placed in the refrigerator overnight. The solid thus obtained was crystallized three times from 95% ethanol, giving 350 mg (11%) of **1b**, mp 172–174 °C. In the second method, a solution of 2.0 g of chalcone and 1.5 g of *p*-nitrophenylhydrazine in 20 mL of methanol was acidified with five drops of concentrated hydrochloric acid. The solution was kept in the refrigerator for 3 h and the solid product was treated as describe above. From three such preparations, 140 mg (4.3%) of **1b** was obtained, mp 172–174 °C. When an attempt to prepare **1b** using a standard method[28] was made, the product had mp 149–150 °C but was found by GC/MS to be a mixture of **1b** and *p*-nitrophenylhydrazine. The (2,4-dinitrophenyl)-hydrazones **1c–f** and **2c,f** were prepared by Allen's method;[16] **1c** (43%) was crystallized from ethyl acetate; **1d** (88%) was crystallized from methanol–ethyl acetate; **1e** (87%) and **1f** (95%) were crystallized from 95% ethanol–ethyl acetate; **2c** (59%) and **2f** (95%) were crystallized from ethyl acetate.

Pyrazoles (**3** and **4**) and pyrazolines (**5** and **6**) were prepared in general from the arylhydrazones, also by methods given in the literature and are listed in Table I. **3c** was prepared by reaction of 1,3-diphenyl-1,3-propanedione with 2,4-dinitrophenylhydrazine, according to the procedure of Jones et al.[23] The same procedure was used in preparing **4b** and **4c** from 1-phenyl-3,4-butanedione and the corresponding arylhydrazine. The products were crystallized either from methanol or 95% ethanol. **5c** was prepared by the reaction of **1c** with hydrobromic acid in acetic acid, according to the procedure of Chambers and Willard,[9] and was crystallized from 95% ethanol (73% yield).

The pyrazoline dimers **7** and **8** were prepared by Pragst's method.[26] **7** (52%, crystallized from *N,N*-dimethylformamide) had mp 235–237 °C; lit. mp 234–235 °C.[26] **8** (40%, from benzene–methanol) had mp 233–235 °C.

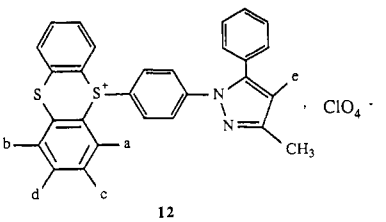
Oxidative Cyclizations. Representative examples are given. (A) With **1a** in Acetonitrile. **1a** (100 mg, 0.336 mmol) and 228 mg (0.721 mmol) of $Th^{\bullet+}ClO_4^-$ were placed in a 100-mL, round-bottomed flask. The flask was capped with a septum, evacuated, and filled with argon. Acetonitrile (20 mL) was added, and the mixture was stirred for 24 h. During this time the color of the solution changed from purple ($Th^{\bullet+}$) through brown to bluish purple. The solution was then poured into 75 mL of water, made basic with sodium carbonate, and extracted with 4 × 30 mL of methylene chloride. The methylene chloride solution was dried over magnesium sulfate and worked up to give 273 mg of pale yellow solid. This was dissolved in 10 mL of methylene chloride for GLC analysis and for separation by TLC. The results are given in Table II.

(B) With **1a** in Methylene Chloride. The same procedure was adopted with 100 mg (0.336 mmol) of **1a** and 307 mg (0.973 mmol) of $Th^{\bullet+}ClO_4^-$ in 20 mL of methylene chloride. The color of the reaction solution changed from purple ($Th^{\bullet+}$) to the bluish violet characteristic of 7^{2+}. Workup of the methylene chloride solution gave 322 mg of a bluish solid, which was dissolved in 10 mL of tetrahydrofuran (THF) for GLC analysis. The result is given in Table II. Quantitative separation by TLC was not successful because of the presence of dimer forms. Attempts to reduce the contaminating dimer cation to isolable **7** with zinc dust were not successful.

(C) With **1c** in Methylene Chloride. $Th^{\bullet+}ClO_4^-$ (225 mg, 0.713 mmol) and 10 mL of methylene chloride were placed in a 100-mL, round-bottomed flask flushed with argon. A solution of 115 mg (0.25 mmol) of **1c** in 20 mL of methylene chloride was added during 15 min. After being stirred for 3 h, the solution was poured into 75 mL of water and workup was continued as described earlier. Results are given in Table II.

When solubility became a problem, a 2,4-DNP was weighed out for direct insertion into the 100-mL flask.

(D) With **2a** in Methylene Chloride. $Th^{\bullet+}ClO_4^-$ (401 mg, 1.27 mmol) and **2a** (100 mg, 0.424 mmol) were weighed into a 100-mL, round-bottomed flask, into which was added 20 mL of methylene chloride under argon. After 24 h of being stirred the solution was poured into 75 mL of water. The mixture was made basic with solution carbonate and was extracted with 4 × 30 mL of methylene chloride. Workup of the methylene chloride solution gave 379 mg of pale yellow solid. This was taken up in 5 mL of methylene chloride and to the solution was added 80 mL of dry ether. Overnight refrigeration caused the precipitation of 12 mg (5.1%) of solid, having a broad IR band (KBr pellet) at 1093 cm^{-1}. ^1H NMR (DMSO-d_6) δ (ppm) and J (Hz): 8.58 (d, 2 H, J_{ac} = 7.8, J_{ad} 1.1, H_a), 8.08 (d, 2 H, J_{bd} = 7.8, J_{bc} = 1.1, H_b), 7.92 (t, 2 H, J_{cd} = 7.5, $H_{c(d)}$), 7.85 (t, 2 H, J_{dc} = 7.5, $H_{d(c)}$), 7.36 (m, 5 H, phenyl), 7.17 (m, 4 H, phenyl), 6.49 (s, 1 H, H_e), 2.25 (s, 3 H, CH_3). ^{13}C NMR (DMSO-d_6) showed the pyrazole C-4 at 109.13 ppm. These data are consistent with the structure **12**.



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Evaporation of the methylene chloride–ether filtrate gave 362 mg of solid. This was dissolved in 10 mL of methylene chloride for GLC analysis; results are given in Table III, entry 3.

Reactions of Pyrazolines. (A) A solution of 125 mg (0.336 mmol) in **5a** in 20 mL of acetonitrile was added under argon to a flask containing 222 mg (0.705 mmol) of $Th^{\bullet+}ClO_4^-$. The solution, which became deep blue in color, was next stirred for 3

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h. Thereafter, 110 mg of zinc dust was added, and the color of the stirred solution changed to yellow. The mixture was stirred for 4 h and filtered to remove zinc dust and the dimer (**7**) which had precipitated. The filtered solid was stirred with 50 mL of 10% potassium hydroxide solution to dissolve the zinc. The alkaline mixture was extracted with benzene, and the dried benzene solution was evaporated to give 98.5 mg (0.165 mmol, 99%) of 4,4′-bis(3,5-diphenyl-2-pyrazolin-1-yl)biphenyl (**7**). Crystallization from DMF gave 62 mg (62%), mp 234–236 °C; lit. mp 234–235 °C.[26]

The original acetonitrile filtrate was poured into 75 mL of water, which was then made basic with sodium carbonate and extracted with 4 × 30 mL of benzene for GLC analysis. Results for Th and ThO are given in Table IV.

(B) Reaction was carried out, as described in A, between 398 mg (1.26 mmol) of $Th^{4+}ClO_4^-$ and 270 mg (0.631 mmol) of **5b**. The color of the solution after addition was brown. The solution was stirred for 2.5 h and was poured into 100 mL of water. Workup as described earlier for arylhydrazones gave 508 mg of solid. This was dissolved in 10 mL of methylene chloride for GLC analysis. The result is given in Table IV (entry 5).

(C) With **5b** in the presence of 2,6-di-*tert*-butylpyridine. A solution of 102 mg (0.238 mmol) of **5b** in 20 mL of methylene chloride was added to a flask containing 150 mg (0.475 mmol) of $Th^{4+}ClO_4^-$. The mixture became dark green in color. A solution of 91 mg (0.475 mmol) of 2,6-di-*tert*-butylpyridine in 2 mL of methylene chloride was added immediately. The color of the mixture became yellow, and after being stirred for 1 h the mixture was worked up in the usual way. GLC analysis gave the results listed in Table IV (entry 7).

Oxidative Cyclization of Cinnamaldehyde Phenylhydrazone. Reaction between 483 mg (1.53 mmol) of $Th^{4+}ClO_4^-$ and 425 mg (0.767 mmol) of the phenylhydrazone was carried out in acetonitrile essentially as described earlier. GLC analysis of the methylene chloride extract gave 97.1% of Th and 2.7% of ThO. Analysis for pyrazole content could not be made by GLC since we could not prepare a sample of pure 1,5-diphenylpyrazole for use as a control. Instead, the reaction mixture was separated on a column of alumina, giving 313 mg of Th (94.6% recovery) and 187 mg (93%) of 1,5-diphenylpyrazole as an oil. ^1H NMR (60 MHz) ($CDCl_3$) δ (ppm) and J (Hz): 7.8 (d, 1 H, $J \simeq 2$), 7.48 (m, 10 H), and 6.57 (d, 1 H, $J \simeq 2$).

Characterization of New Compounds and of Some Products. Some of the reactants which are listed in Table I were not found in the literature; also, the melting point of (*p*-nitrophenyl)hydrazone **1b** differed from that in the literature. Therefore, these compounds were characterized with elemental analysis and mass spectrometry.

1b. Anal. Calcd for $C_{21}H_{17}N_3O_2$: C, 73.5; H, 4.99; N, 12.2. Found: C, 73.2; H, 4.88; N, 12.3. MS, m/e (rel intensity): M^+ 343 (100).

1d. Anal. Calcd for $C_{21}H_{15}N_4O_4Cl$: C, 59.7; H, 3.58; N, 13.3; Cl, 8.38. Found: C, 59.4; H, 3.40; N, 13.2; Cl, 7.91, 8.00. MS, m/e (rel intensity): M^+ 424 (19.2), 422 (59.7).

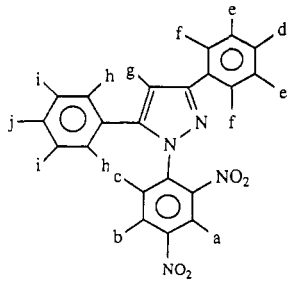
1e. Anal. Calcd for $C_{22}H_{18}N_4O_5$: C, 63.2; H, 4.34; N, 13.4. Found: C, 63.2; H, 4.21; N, 13.4. MS, m/e (rel intensity): M^+ 418 (65.7).

1f. Anal. Calcd for $C_{21}H_{15}N_4O_4Cl$: C, 59.7; H, 3.58; N, 13.3; Cl, 8.38. Found: C, 59.2; H, 3.46; N, 13.3; Cl, 7.72, 7.85. MS, m/e (rel intensity): M^+ 424 (26.0), 422 (87.1).

2f. Anal. Calcd for $C_{16}H_{13}N_4O_4Cl$: C, 53.3; H, 3.63; N, 15.5; Cl, 9.83. Found: C, 53.3; H, 3.53; N, 15.4; Cl, 9.63. MS, m/e (rel intensity): M^+ 362 (17.0), 360 (50.0).

5c. Anal. Calcd for $C_{21}H_{16}N_4O_4$: C, 64.9; H, 4.15; N, 14.4. Found: C, 65.0; H, 4.11; N, 14.4. MS, m/e (rel intensity): M^+ 388 (42.2).

Most of the pyrazole products of reaction were also not found in the literature and were characterized after isolation by 300-MHz ^1H and (in part) ^{13}C NMR and by mass spectrometry. For ^1H NMR purposes the pyrazoles are illustrated with structures **13** and **14**, in which the letters a–i signify H atoms except where noted. **4a** was also characterized because our authentic compounds was an oil.



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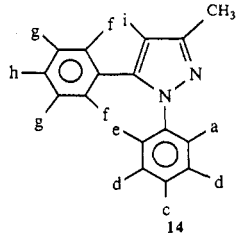
3d, d = Cl **3e**, d = OMe; **3f**, j = Cl

3d (mp 196–197 °C, ethanol). ^1H NMR ($CDCl_3$) δ (ppm) and J (Hz): 8.74 (d, H_a, J = 2.5), 8.37 (2 d, H_b, J = 8.8, 2.5), 7.78 (d, 2 H_e, J = 8.6), 7.48 (d, H_c, J = 8.8), 7.41 (d, 2 H_f, J = 8.6), 7.37 (m, 3 $H_{i-j(?)}$), 7.28 (m, 2 $H_{h(?)}$), 6.88 (s, H_g). MS, m/e (rel intensity): M^+ 422 (35.4), 420 (100), 330 (3.3), 328 (11.0), 105 (16.9).

3e (mp 190–191 °C, ethanol). ^1H NMR ($CDCl_3$) δ (ppm) and J = (Hz): 8.71 (d, H_a, J = 2.5), 8.33 (2 d, H_b, J = 8.8, 2.5), 7.77 (d, 2 H_e, J = 8.8), 7.46 (d, H_c, J = 8.8), 7.39 (m, 3 $H_{i-j(?)}$), 7.30 (m, 2 $H_{h(?)}$), 6.96 (d, 2 H_f, J = 8.8), 6.83 (s, H_g). MS, m/e (rel intensity): 417 (25.1), M^+ 416 (100), 401 (4.7), 369 (8.1), 280 (4.4).

3f (mp 153–155 °C, aqueous methanol). ^1H NMR (acetone-d_6) δ (ppm) and J (Hz): 8.88 (d, H_a, J = 2.6), 8.60 (2 d, J = 8.8, 2.6), 7.93 (d, 2 H_i, J = 6.8), 7.77 (d, H_c, J = 8.8), 7.49 (d, 2 H_h, J = 6.8), 7.44 (m, 5 H_{d-f}), 7.26 (s, H_g). MS, m/e (rel intensity): M^+ 422 (35.5), 420 (100), 339 (6.5), 139 (19.4), 77 (8.4).



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4a, a–h = H; **4f**, a = c = NO_2, h = Cl; **4g**, h = Cl; **4h**, h = NO_2

4a (oil). ^1H NMR (Me_2SO-d_6) δ (ppm): 7.30 (m, 6 H), 7.19 (m, 4 H), 6.41 (s, H_f), 2.26 (s, 3 H_j). ^{13}C NMR: 12.98 (CH_3, 107.52, pyrazole C-4). MS, m/e (rel intensity): 235 (31.2), M^+ 234 (99.5), 233 (100), 218 (23.6), 206 (10.3), 192 (21.1), 165 (23.1), 130 (18.6), 128 (11.8), 117 (11.5), 116 (21.6), 103 (10.8), 102 (20.0), 91 (18.6), 90 (12.3), 89 (30.2), 77 (99.5), 51 (99.5).

4f (mp 63–64 °C, sublimation). ^1H NMR ($CDCl_3$) δ (ppm) and J (Hz): 8.71 (d, H_b, J = 2.5), 8.36 (2 d, H_d, J = 8.7, 2.5), 7.41 (d, H_e, J = 8.7), 7.32 (d, 2 H_g, J = 8.3), 7.14 (d, 2 H_f, J = 8.3), 6.39 (s, H_i), 2.35 (s, 3 H_j). MS, m/e (rel intensity): M^+ 360 (37.7), 358 (100), 282 (11.5), 277 (10.4), 266 (13.3), 141 (11.0), 139 (31.7).

4g (mp 70–71 °C, sublimation). ^1H NMR ($CDCl_3$) δ (ppm) and J = (Hz): 7.29 (m, 5 H_{a-e}), 7.26 (d, 2 H_g, J = 8.3), 7.14 (d, 2 H_f, J = 8.3), 6.30 (s, H_i), 2.39 (s, 3 H_j). MS, m/e (rel intensity): M^+ 270 (35.7), 268 (100), 267 (71.1), 191 (12.2), 190 (12.4), 130 (12.2), 116 (18.7), 101 (10.1), 91 (13.3), 89 (12.6), 77 (77.1), 51 (75.5).

4h (mp 105–106 °C, aqueous ethanol). ^1H NMR (Me_2SO-d_6) δ (ppm) and J (Hz): 8.16 (d, 2 H_g, J = 8.8), 7.44 (d, 2 H_f, J = 8.8), 7.38 (m, 3 H), 7.23 (m, 2 H), 6.64 (s, H_i), 2.27 (s, 3 H_j). ^{13}C NMR: 13.22 (CH_3), 109.18 (pyrazole, C-4). MS, m/e (rel intensity): M^+ 279 (100), 278 (53.4), 249 (11.8), 232 (40.3), 191 (13.4), 190 (11.2), 91 (11.3), 77 (45.8), 51 (41.4).

8 (mp 220–222 °C), isolated from oxidation of **6a** with $Th^{4+}ClO_4^-$ in acetonitrile, was characterized by 300-MHz ^1H NMR. Solubility problems and overlap of solvent peaks with some of those of **8** caused us to use two separate solvents for complete recording of an ABX pattern. **8** was unstable (to oxidation apparently) in $CDCl_3$.

^1H NMR (Me_2SO-d_6) δ (ppm) and J (Hz): 7.79 (m, 14 H, aromatic), 7.29 (d, 4 H, J = 8.5, aromatic); (C_6D_6): 4.66 (2 d, 2 H_X, J_{AX} = 12.0, J_{BX} = 7.9), 2.63 (2 d, 2 H_A, J_{AX} = 12.0, J_{AB} = 17.4), 2.15 (2 d, 2 H_B, J_{BX} = 7.9, J_{BA} = 17.4), 1.66 (s, 6 H, methyl).

The ABX pattern was confirmed with the ^1H NMR spectrum of **6a** ($CDCl_3$), δ (ppm) and J (Hz): 4.98 (2 d, H_X, J_{AX} = 11.9, J_{BX} = 8.1), 3.37 (2 d, H_A, J_{AX} = 11.9, J_{AB} = 17.5), 2.68 (2 d, H_B,

J_{BX} = 8.1, J_{BA} = 17.5), 2.04 (s, 3 H, methyl). Second-order small splittings of about 1 Hz were seen also in the AB and methyl signals. The ABX pattern of pyrazoline **5a** has been reported.[4]

Anal. Calcd for $C_{32}H_{30}N_4$: C, 81.7; H, 6.42; N, 11.9. Found: C, 81.1; H, 6.38; N, 11.5.

Acknowledgment. Support of this research by the National Science Foundation (Grant No. CHE 8612031) and the Robert A. Welch Foundation (Grant No. D-028) is gratefully acknowledged. The NMR spectrometers used in this research were purchased in part with an instrument grant (No. CHE-8414104) from the National Science Foundation. This paper was written during the tenure of a Humboldt Foundation Senior U.S. Scientist Award. H.J.S. thanks the Foundation and the Institut für Organische Chemie, Universität Hamburg, for gracious hospitality.

Convenient Synthesis of C-Terminal Peptide Analogues by Aminolysis of Oxime Resin-Linked Protected Peptides

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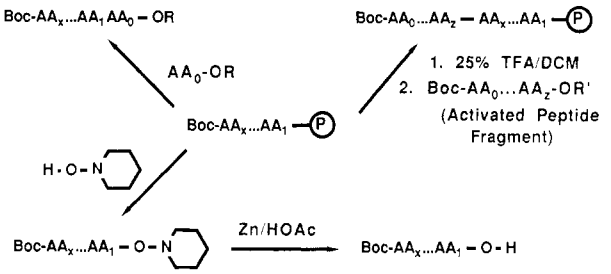
Methods for introducing C-terminal alkylamides into synthetic peptides have been either limited to special cases or restricted to peptides without ester side chain protecting groups. A structure activity research program required the preparation of a series of human epidermal growth factor (h-EGF) and renin inhibitor analogues with variable C-terminal functionalities. Peptides linked to *p*-nitrobenzophenone oxime resins are known to be displaced by amino acid esters or partially protected peptide fragments without disturbing side chain ester functionalities. We report now that the utility of oxime resins has been extended to the preparation of C-terminal alkylamides. Fully protected h-EGF (34–43)–*p*-nitrobenzophenone oxime resin was treated with ethylamine or cyclohexylamine in dichloromethane (DCM) for 1–5.5 h. The respective C-terminal amide products were produced in high purity. In addition, Boc-statine-Ile-oxime resin has been treated with 2-(aminomethyl)pyridine (AMP) in DCM for 2 h to give the respective Boc-statine-Ile-AMP in high purity. We conclude that the oxime resin offers a convenient and versatile method for the preparation of C-terminal peptide alkylamides. It also offers a convenient route for preparation of a wide variety of C-terminal analogues from a single synthesis.

Peptides systematically modified at the C-terminus with various alkylamide functionalities can be a useful addition to the biological evaluation of a peptide structural series. However, the methods for preparing such compounds are either severely limited or cumbersome. The (chloromethyl)polystyrene and [4-(methyloxy)phenyl](acetamidomethyl)polystyrene (1% divinylbenzene) (PAM) resins that are most commonly used for solid-phase peptide synthesis (SPPS) are not generally used for synthesis of peptides that contain C-terminal substituted amides.[1a,2] Benzhydrylamine and *p*-methylbenzhydrylamine resins have been developed primarily for the synthesis of unsubstituted C-terminal amides.[3] Recently a method for synthesizing *N*-methyl and *N*-ethyl carboxamide derivatives on polystyrene resins[4,5] has been reported, but its general utility, especially for hindered amines, is still unknown. Unfortunately this later approach suffers from the requirement that each desired carboxamide must be a separate synthesis on a separate resin. To date no general method has been recognized that will allow a wide variety of amines to displace on-resin peptides with ester side chain protecting groups or depsi backbone linkages.

One exception to the above generality might be met by polystyrene resins functionalized with an oxime group. Kaiser and co-workers[6,7] have explored the use of the *p*-nitrobenzophenone oxime resin in peptide synthesis and found that peptides attached to oxime resins could be displaced by nucleophilic agents (Scheme I). They found displacement could be effected by the C-α amines of amino acid esters under conditions mild enough to leave ester side chains unchanged and to allow the synthesis of depsi-

Scheme I. Displacement and Segment Condensation Options for Peptides on Oxime Resins



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(1) (a) Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149. (b) Abbreviations: HOBt, 1-hydroxybenzotriazole; DCC, dicyclohexylcarbodiimide; AMP, 2-(aminomethyl)pyridine; DMF, dimethylformamide; DCM, dichloromethane; TFA, trifluoroacetic acid; DIEA, diisopropylethylamine; DTT, dithiothreitol; Et, ethyl; Chx, cyclohexyl; Boc, *tert*-butyloxycarbonyl; h-EGF, human epidermal growth factor; HPLC, high pressure liquid chromatography; Sta, statine, 4(*S*)-amino-3(*S*)-hydroxy-6-methyl-L-heptanoic acid.[14] Single letter amino acid codes: C, Cys, cysteine; E, Glu, glutamic acid; G, Gly, glycine; I, Ile, isoleucine; R, Arg, arginine; V, Val, valine; Y, Tyr, tyrosine.

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