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REACTIONS OF 1-AMINO-2,4,6-TRIPHENYLPYRIDINIUM CATIONS WITH α,β-UNSATURATED COMPOUNDS

SYNTHESIS OF HIGHLY SUBSTITUTED PYRAZOLO[1,5-a]PYRIDINE DERIVATIVES

Hector Beltrami * and Jesus Mallen

Universidad Simon Bolivar, Departamento de Quimica
Apdo. 80659, Sartenejas, Caracas, Venezuela

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Abstract: The cycloaddition reaction of 1-amino-2,4,6-triphenylpyridinium cations 2a-f with acrylonitrile, diethyl maleate, ethyl acrylate and methyl acrylate provides a convenient route for the synthesis of nitrogen-bridged heterocyclic pyrazolo[1,5-a]pyridines and their dihydro-derivatives.

Although intermolecular cycloaddition reactions of pyridinium ylides with various reagents have been extensively studied[1,2], intermolecular cyclizations of disubstituted or trisubstituted pyridine N-imines, in which the mesomerism of the imino group and the pyridine ring is hindered, have not been thoroughly investigated.

The cycloaddition reactions of unsubstituted pyridinium salts occur with spontaneous dehydrogenation or elimination of the dihydrointermediate to a completely aromatic product[3,4]. Whereas, N-substituted pyridinium compounds in which such rearomatization is impossible, seldom undergo 1,3-dipolar cycloaddition reactions, unless a considerable change of the molecular structure takes place[5].

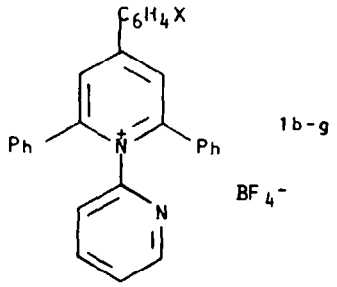
Recently, Katritzky and coworkers[6] reported the reactions of 1-amino-2,4,6-triphenylpyridinium tetrafluoroborate with alkyl halides and α,β-unsaturated compounds giving monoalkylation products, with the exception of one example in which a tetrahydrobicyclic-adduct was isolated. The formation of this cycloadduct was surprising in view of the presence of the bulky phenyl substituents on the N-aminopyridinium salt.

We wish to report here the synthesis and further intermolecular reactions of some 1-aminopyridinium cations with α,β-unsaturated compounds leading to the formation of trisubstituted tetrahydropyrazolo[1,5-a]pyridine derivatives.

Several ring substituted 1-aminopyridinium salts 2 were synthesized from 1-(2-pyridyl)pyridinium tetrafluoroborates 1, following the method described by Katritzky and coworkers[7]. The new salts 1b-g and 2b-g were characterized by their spectroscopic properties and elemental analyses (Tables I and II).

Treatment of pyridinium N-imine tetrafluoroborates 2b-g with acrylonitrile in the presence of potassium carbonate in acetonitrile/water mixtures at room temperature, gave the corresponding tetrahydropyrazolo[1,5-a]pyridines 4b-g in varying yields (30 to 92%). These products 4b-g are pale green or orange crystals, which are well characterized by their strong fluorescence, their low melting points and their low solubility in polar solvents. Each IR Spectrum showed a characteristic absorption band

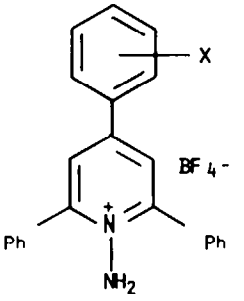
Table I. 1-(2-pyridyl)-2,4,6-triphenylpyridinium tetrafluoroborates



1b-g

Compound N°	M.p. °C	Crystal Form	Solvent for recryst.	Yield %	Found % C	H	N	Formula	Calc. % C	H	N
1b X = p-(CH_3)	255-257	needles	CH_2Cl_2/Et_2O	71	71.90	4.78	5.53	$C_{29}H_{23}BF_4N_2$	71.62	4.77	5.76
1c X = p-(OCH_3)	232-234	needles	CH_2Cl_2/Et_2O	74	68.96	4.59	5.29	$C_{29}H_{23}BF_4N_2O$	69.34	4.62	5.58
1d X = p-(Cl)	236	needles	CH_2Cl_2/Et_2O	90	66.24	3.97	5.24	$C_{28}H_{20}ClBF_4N_2$	66.37	3.98	5.53
1e X = p-(Br)	231-233	needles	CH_2Cl_2/Et_2O	92	60.99	3.74	4.82	$C_{28}H_{20}BrBF_4N_2$	61.01	3.66	5.08
1f X = p-(NO_2)	258-260	orange needles	CH_2Cl_2/Et_2O	75	64.79	3.93	7.86	$C_{28}H_{20}BF_4N_3O_2$	65.01	3.90	8.12
1g X = m-(NO_2)	233-234	pink plates	CH_2Cl_2/Et_2O	94	64.60	3.76	7.96	$C_{28}H_{20}BF_4N_3O_2$	65.01	3.90	8.13

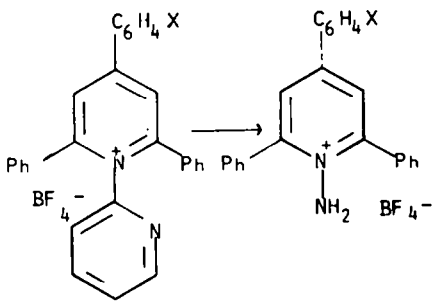
Table II. 1-Amino-2,4,6-triphenylpyridinium tetrafluoroborates.



2b-g

Compound N°	M.p. °C	Crystal Form	Solvent for recryst.	Yield %	Found % C	H	N	Formula	Calc. % C	H	N
2b X = p-(CH_3)	188-190	needles	CH_2Cl_2/Et_2O	86	67.70	4.82	6.72	$C_{24}H_{21}BF_4N_2$	67.93	4.99	6.63
2c X = p-(OCH_3)	170-172	prisms	CH_2Cl_2/Et_2O	64	65.39	4.81	6.11	$C_{24}H_{21}BF_4N_2O$	65.48	4.81	6.36
2d X = p-(Cl)	182-184	needles	CH_2Cl_2/Et_2O	75	62.14	4.09	5.95	$C_{23}H_{18}ClBF_4N_2$	62.13	4.08	6.30
2e X = p-(Br)	186-188	prisms	CH_2Cl_2/Et_2O	75	56.51	3.78	5.36	$C_{23}H_{18}BrBF_4N_2$	56.48	3.71	5.73
2f X = p-(NO_2)	230-232	orange plates	CH_2Cl_2/Et_2O	42	60.45	3.84	9.15	$C_{23}H_{18}BF_4N_3O_2$	60.68	3.99	9.23
2g X = m-(NO_2)	161-163	yellow plates	CH_2Cl_2/Et_2O	76	60.43	3.98	9.29	$C_{23}H_{18}BF_4N_3O_2$	60.68	3.99	9.23

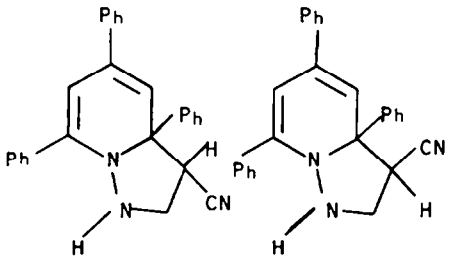
at 3200 - 3250 cm^{-1} due to a secondary amine group and at 2240 - 2290 cm^{-1} due to a cyano group. The NMR spectra of these derivatives showed a typical pattern of signals which were assigned as follows: the complex multiplet at δ 7-8.4 was attributed to the aromatic protons of the phenyl substituents, among which could be distinguished for compound 4f a doublet of doublets at δ 8.20 for the protons of the nitrophenyl ring. The C_4 and C_6 protons appeared as two sharp doublets centered at δ 6. The NH proton coupled with the two non-equivalent protons at C_2 gave a doublet of doublets at δ 4.23 - 4.31, which for the chloro and nitro derivatives 4d, 4f and 4g were shifted downfield to δ 4.99 - 5.43. The two protons at C_2 and that at C_3 gave a very complex pattern which under D_2O exchange produced a simpler ABC pattern.



1 2

a) X = H
b) X = p-(CH_3)
c) X = p-(OCH_3)
d) X = p-(Cl)
e) X = p-(Br)
f) X = p-(NO_2)
g) X = m-(NO_2)

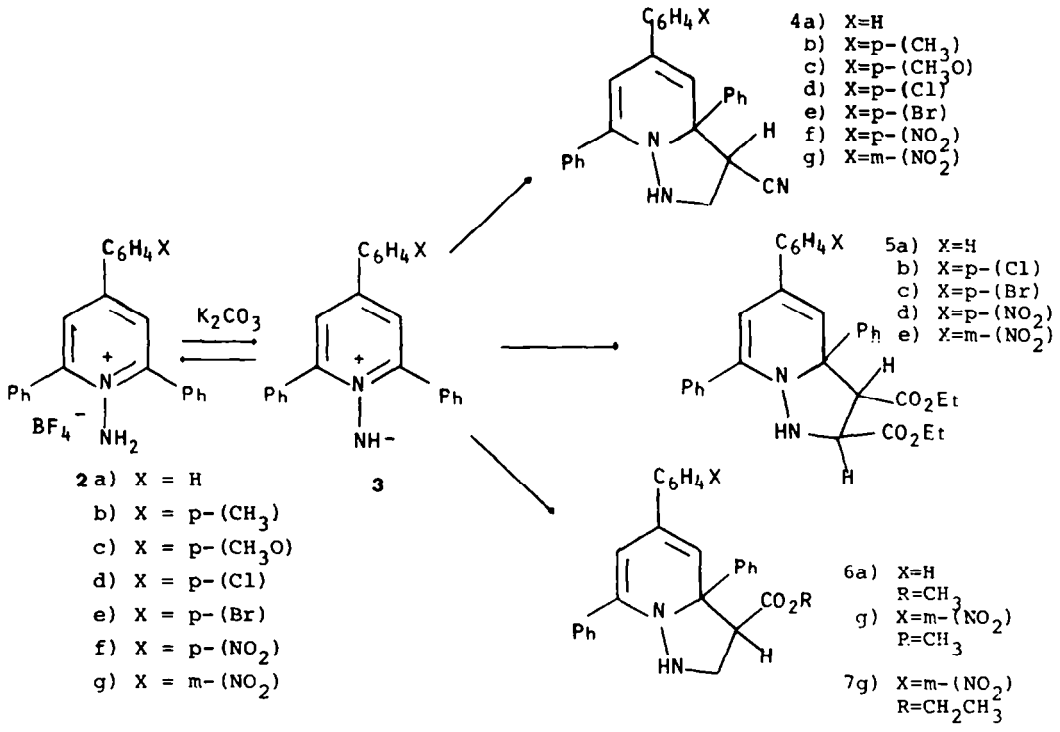
Based mainly on the NMR analysis, the cycloadduct 4a was found to be a mixture of two isomeric compounds in a 1/10 ratio. The NMR spectrum of 4a showed, in addition to the pattern already described for the adducts 4b-g, a doublet of doublets at δ 4.70 and two doublets at δ 5.72 and 5.93, which were assigned to the NH proton and to the C_4 and C_6 protons of the isomeric cycloadduct. The physical data of the tetrahydro-derivatives 4b-g are listed in table III.



4a

Similar conversion of the ylides 3a, 3f and 3g (prepared in situ from the reaction of the N-amino salts with potassium carbonate) to the corresponding pyrazolo[1,5-a]pyridine derivatives 5a, 5f, 5g, 6a, 6g and 7g was accomplished in moderate yields, by reaction with diethyl maleate and methyl and ethyl acrylates, respectively. The N-amino pyridinium salts 2b and 2c failed to undergo cyclization with diethyl maleate under the experimental conditions used. The failure may be explained in terms of a greater stability of the switterionic species 3b and 3c and subsequent lack of reactivity to cyclize in the presence of the dipolarophile. The salts 2d and 2e, on reaction with diethyl maleate afforded the corresponding bicyclic derivatives 5d and 5e and although, they could not be isolated from the reaction mixture, their structures were indicated by IR and NMR spectroscopy.

The structural elucidation of the tetrahydropyrazolo[1,5-a]pyridines 5, 6, 7 was accomplished on the basis of physical and spectral analyses. The IR spectra of 5a, d, e, f and g showed a secondary amine absorption at 3200 - 3250 cm^{-1} and a carbonyl absorption at 1740 cm^{-1}. The NMR spectral patterns of the pyrazolopyridine derivatives are similar to each other, as shown in table IV. The NMR spectrum of 5a in $CDCl_3$, for example, showed a multiplet at δ 7.16 - 7.90 for the phenyl protons, two doublets at δ 6.02 (1H, J=2Hz) and



2a) X = H
b) X = p-(CH_3)
c) X = p-(CH_3O)
d) X = p-(Cl)
e) X = p-(Br)
f) X = p-(NO_2)
g) X = m-(NO_2)

3

at δ 5.86(1H, J=2Hz) attributed to the C_4 and C_6 protons of the pyridine ring and a doublet centered at δ 5.80(1H, J=14Hz) for the NH proton, which undergoes deuterium exchange with D_2O, with simplification of the spectrum. The C_2 protons, coupled with C_3 and NH protons, appeared as a complex multiplet, overlapped by the signal corresponding to the methylene group of the ester moiety. The C_3 proton was shown as a doublet (J=6Hz) at δ 3.62 and, the multiplet and the two triplets at δ 3.45, 1.16 and 0.84 were assigned to the methylene and methyl protons of the esters respectively. D_2O exchange of the NH proton resulted in a simple AB pattern for the C_2 and C_3 protons at δ 4.06 and δ 3.62. Based on the NMR evidence, these cycloadducts 5a, 5f and 5g, were assigned as the trans rather than the cis configuration at the C_2 and C_3 positions. In particular, signals at δ 4.06 and 3.62 coupling each other with the coupling constant of 6Hz attributable to the protons attached at C_2 and C_3 positions indicate its trans configuration and coupling constants of 13-14Hz have been reported[8,9] and assigned to the cis configuration.

Compounds 6a, 6g and 7g showed similar NMR spectra to those of the bicyclic derivatives 4b-g, except that the complex ABC pattern was overlapped by the methyl and methylene signals of the ester groups. It should be noted that the NMR spectrum of 6g, after D_2O addition for NH proton exchange, showed two additional doublets at δ 5.90 and 6.04 which can be attributed to the presence of the other isomer as in 4a. This result is in agreement with those obtained by Tamura and coworkers[10] in the reaction of phenanthridine N-benzoilimine with acrylates, in which the reaction is nonstereospecific.

The cycloaddition of N-aminopyridinium salt 2f with methyl acrylate did not produce the expected tetrahydropyrazolo-[1,5-a]pyridine derivative and further studies are in progress.

EXPERIMENTAL

All m.ps. are uncorrected. IR spectra were obtained using a Perkin Elmer 735-B spectrometer. ^1H NMR spectra were recorded at 60MHz and at 100MHz using a Varian T-60 and XL-100

Table III. Bicyclicadducts obtained from the reactions of 1-aminopyridinium salts and α,β-unsaturated compounds.

Compound N°		Method	M.p. °C	Crystal Form	Solvent for recryst.	Yield %	Found % C	H	N	Formula	Calc. % C	H	N
4b	X = p-(CH_3)	A	143-145	Green needles	$CHCl_3$/PE	30	82.87	5.73	10.85	$C_{27}H_{23}N_3$	83.26	5.95	10.79
4c	X = p-(OCH_3)	B	146-148	Green prisms	$CHCl_3$/PE	63	79.70	5.45	10.24	$C_{27}H_{23}N_3O$	79.97	5.72	10.36
4d	X = p-(Cl)	B	139-142	Yellow prisms	CH_3CN	85	75.85	4.72	9.86	$C_{26}H_{20}ClN_3$	76.18	4.92	10.20
4e	X = p-(Br)	C	138-141	Green prisms	CH_3CN	62	68.45	4.46	9.09	$C_{26}H_{20}BrN_3$	68.73	4.44	9.25
4f	X = p-(NO_2)	C	170-173	Orange needles	CH_3CN	91	74.10	4.79	13.17	$C_{26}H_{20}N_4O_2$	74.27	4.79	13.32
4g	X = m-(NO_2)	C	130-132	Yellow prisms	CH_3CN	92	74.23	4.75	13.34	$C_{26}H_{20}N_4O_2$	74.27	4.79	13.32
5a	X = (H)	A	129-132	Green prisms	CH_3CN	39	75.65	6.14	5.70	$C_{31}H_{30}N_2O_4$	75.28	6.11	5.66
5f	X = p-(NO_2)	A	137-140	Orange needles	$CHCl_3$/PE	71	69.10	5.37	7.73	$C_{31}H_{29}N_3O_6$	69.00	5.42	7.79
5g	X = m-(NO_2)	A	122-124	Yellow needles	$CHCl_3$/PE	85	68.83	5.35	7.78	$C_{31}H_{29}N_3O_6$	69.00	5.42	7.79
6a	X = H	A	94-97	micro	Ether/PE	33	-	-	-	-	-	-	-
6g	X = m-(NO_2)	C	119-122	micro	CH_3CN/H_2O	87	71.43	5.20	9.13	$C_{27}H_{23}N_3O_4$	71.51	5.11	9.27
7g	X = m-(NO_2)	C	96-99	micro	$CHCl_3$/PE	72	71.80	5.24	8.70	$C_{28}H_{25}N_3O_4$	71.93	5.39	8.99

Table IV. IR and NMR Spectra of Tetrahydropyrazolo[1,5-a]pyridines 4,5,6,7.

Compound N°	Pyridine [a] 4H	6H	Aromatic Multiplets	NH [b,c] proton	C_2H protons	C_3H proton	Others	ν max (KBr) cm^{-1} ν(NH)	νCN	νCO
4b	5.78[d]	5.96	7.00-7.76(14H)	4.23(dd)	2.74-3.08(m)	3.71(dd,J=7,9Hz)	2.34(s,3H)	3200	3250	-
4b	5.82[e]	6.02	7.08-7.90(14H)	-	3.38(dd,J=8,12Hz) 2.94(dd,J=10,12Hz)	3.72(dd,J=8,10Hz)	2.34(s,3H)			
4c	5.76[d]	6.03	7.23-7.83(12H) 6.92(dd,2H)	4.31(dd)	3.60-3.83(m) 2.76-3.16(m)	f	3.86(s,3H)	3200	2270	-
4c	5.83[e]	6.00	7.24-7.83(12H) 6.92(dd,12H)	-	2.84-3.62(m)	f	3.83(s,3H)			
4d	5.80[g]	6.09	7.14-7.84(14H)	5.35(dd)	3.42-3.66(m) 2.69-2.85(m)	3.92(dd,J=7,9Hz)	-	3220	2280	-
4d	5.82[h]	6.10	7.30-7.86(14H)	-	3.57(dd,J=9,12Hz) 2.76(br.t)	3.97(dd,J=6,9Hz)	-			
4e	5.81[h]	6.12	7.24-7.88(14H)	-	3.53(dd,J=10,12Hz) 2.76(dd,J=7,12Hz)	3.93(dd,J=7,10Hz)	-	3220	2290	-
4f	5.76[g]	6.16	8.20(dd,2H) 7.26-7.84(12H)	4.99(dd)	3.38-3.70(m) 2.74-2.95(m)	3.90(dd,J=6,8Hz)	-	3250	2250	-
4f	5.70[h]	6.12	8.15(dd,2H) 7.32-7.72(12H)	-	3.47(dd,J=7,12Hz) 2.83(dd,J=10,12Hz)	3.90(dd,J=7,10Hz)	-			
4g	5.90[g]	6.24	7.20-7.86(14H)	5.43(dd)	3.48-3.78(m) 2.74-2.96(m)	4.06(dd,J=6,9Hz)	-	3200	2240	-
4g	5.92[h]	6.28	7.36-8.60(14H)	-	3.65(dd,J=6,12Hz) 2.80(dd,J=10,12Hz)	4.07(dd,J=6,10Hz)	-			
5a	5.86[d]	6.02	7.16-7.90(15H)	5.80(d)	i	3.62(d,J=6Hz)	4.16(m,3H),3.45(m,2H) 1.16(t,3H),0.84(t,3H)	3220	-	1750
5a	5.70[e]	5.82	6.96-7.80(15H)	-	4.06(d,J=6Hz)	3.62(d,J=6Hz)	3.96(q,2H),3.45(q,2H) 1.12(t,3H),0.84(t,3H)			
5f	5.92[g]	5.96	8.18(dd,2H) 7.16-7.88(m,12H)	5.82(d)	i	3.84(d,J=6Hz)	4.11(m,3H),3.63(m,2H) 1.14(t,3H),0.86(t,3H)	3220	-	1750
5f	5.90[h]	5.94	8.16(dd,2H) 7.16-7.86(m,12H)	-	4.15(d,J=6Hz)	3.84(d,J=6Hz)	4.08(q,2H),3.63(m.2H) 1.14(t,3H),0.86(t,3H)			
5g	6.14[g]	6.54	7.18-8.48(m,14H)	5.78(br.d)	i	i	4.11(m,3H),3.67(m,3H) 1.14(t,3H),0.86(t,3H)	3300	-	1740
6a	5.65[e]	5.90	7.22-7.84(m,14H)	4.32(dd)	3.00-3.72(m,3H)	j	3.75(s,3H)	3220	-	1750
6g	5.50[g]	5.68	7.18-8.26(m,14H)	4.28(br.t)	3.06-3.32(m,2H)	3.62-4.06(m,2H)	3.84(s,3H)	3240	-	1720
6g	5.60[h]	5.80	7.20-8.30(m,14H)	-	3.05-3.40(m,2H)	3.55-4.00(m,1H)	3.65(s,3H)			
7g	5.80[h]	5.96	7.06-8.34(m,14H)	-	3.30-3.48(m) 2.90-3.25(m)	i	3.70(q,2H) 0.98(t,3H)	3220	-	1730

[a] doublet $J_{4H,6H=2Hz}$. [b] $J_{NH,C_2H=6}$ and 12Hz for series 4, 6 and 7. [c] $J_{NH,C_2H=14Hz}$ for serie 5. [d] In $CDCl_3$. [e] In $CDCl_3/D_2O$ [f] signal overlapped by CH_3O protons. [g] In $(CD_3)_2CO$. [h] In $(CD_3)_2CO/D_2O$. [i] signal overlapped by CH_2 group. [j] signal overlapped by C_2H protons.

spectrometers respectively, with TMS as internal standard. The elemental analyses were carried out at the U.S.B Analytical Laboratory.

Physical and microanalytical data for the new compounds are presented in Tables I, II and III and spectroscopic data for the tetrahydropyrazolo[1,5-a] pyridine derivatives in Table IV.

The pyrilium tetrafluoroborates were prepared by known methods[11].

General procedure for the preparation of 1-(2-pyridyl)-2,4,6-triphenylpyridinium tetrafluoroborates 1a-g.

The pyrilium tetrafluoroborate (0.005 mole), 2-aminopyridine (0.0075 mole) in CH_2Cl_2 (50ml) were stirred at room temperature for 12h. The solvent was then evaporated under reduced pressure to give a residue, which was treated with ether. The resulting solid was filtered and recrystallized from mixtures of CH_2Cl_2/Et_2O (Table I).

General procedure for the preparation of 1-amino-2,4,6-triphenylpyridinium tetrafluoroborates 2a-g.

A mixture of the pyridinium salt (0.01 mole), hydrazine hydrate (0.06 mole) and CH_2Cl_2 (80ml) were heated under reflux with mechanical stirring for 6h. The solution was washed with water, (2x15ml) and the organic layer separated, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Ether was added to induce precipitation of the 1-amino salts 2, which were recrystallized from CH_2Cl_2/Et_2O mixtures (Table II).

General procedure for the reaction of 1-aminoheteroaryls with α, β-unsaturated compounds 4a-g.

Method A: To a stirred solution of the N-aminoheteroaryl (1.25mmole) in a mixture of acetonitrile/water (2/1), potassium carbonate (1.25mmole) was added. After 30 min., at room temperature, the dipolarophile (1.25mmole) was added and stirring continued for 1h. After addition or water (10ml), the mixture was extracted with CH_2Cl_2 (2x15 ml), dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure. The resultant oil was treated with ether or a mixture of chloroform/petroleum ether and cooled to 0°C to give the pyrazolo[1,5-a] pyridine derivative (Table III).

Method B: As for method A, except that after addition of water, the pyrazolo[1,5-a]pyridine derivative which separated out, was filtered, washed with water and crystallized (Table III).

Method C: As for method A, except that after addition of the dipolarophile, the bicyclicadduct which precipitated out, was filtered, washed with water and crystallized (Table III).

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