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N-Alkylamidomethylation at Electron-rich Carbons in the 1,3,5-Trialkylhexahydro-1,3,5-triazine–Acetyl Chloride System

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A new *N*-alkylamidomethylation reaction at electron-rich carbons has been developed using 1,3,5-trialkylhexahydro-1,3,5-triazine in the presence of acetyl chloride. This reaction was carried out not only with aromatics such as phenols, alkoxybenzenes and aromatic amines, but also olefins such as styrene and vinyl ethers.

Keywords——*N*-alkylamidomethylation; electrophilic substitution; 1,3,5-trialkylhexahydro-1,3,5-triazines; acetyl chloride; aromatics; styrene; vinyl ethers

1,3,5-Trialkylhexahydro-1,3,5-trizaines (**1**) are potential synthetic tools which may react in the same way as *N*-alkylmethylenimines, which are too labile to handle.[2] In a previous patent[3] *N*-alkyl-*N*-chloromethylamides (**2**), which correspond to the adducts of acyl halides to *N*-alkylmethylenimines, were reported to be produced by the reaction of 1,3,5-trialkylhexahydro-1,3,5-triazines (**1**) with several acyl halides. Böhme *et al.*[4] have reported that *N*-alkyl-*N*-chloromethylamides (**2**), synthesized by an alternative route, act as *N*-alkylamidomethylation agents towards a number of aromatics in the presence of aluminum chloride.

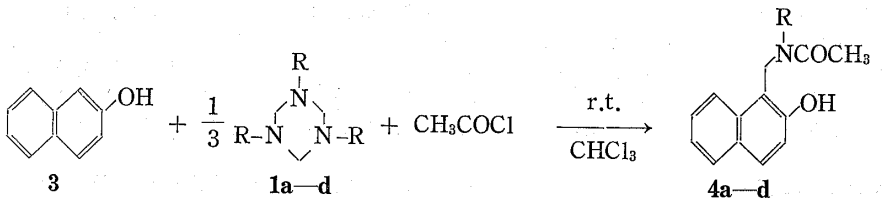


Table I. Yields and Analytical and Spectral Data for 1-(*N*-Alkylamidomethyl)-2-naphthols (**4a—d**)[a]

Compd.	R	Yield[b] (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	IR ν_{max}^{KBr} (cm^{-1}) C=O	Selected NMR[c] δ (ppm) (DMSO-d_6) CH_2 2H, s	CH_3CO 3H, s	OH 1H, br s
4a	CH_3	61	201—202	$C_{14}H_{15}NO_2$	73.34 (73.45	6.59 6.65	6.11 6.10)	1590	4.96	2.04	9.96
4b	C_2H_5	35	211—212	$C_{15}H_{17}NO_2$	74.05 (74.05	7.04 7.08	5.76 5.74)	1596	5.01	2.12	9.92
4c	i-C_3H_7	46	187—189	$C_{16}H_{19}NO_2$	74.68 (74.78	7.44 7.48	5.44 5.41)	1582	5.07	2.19	9.98
4d	C_4H_9	51	165—167	$C_{17}H_{21}NO_2$	75.24 (75.12	7.80 7.79	5.16 5.13)	1578	5.12	2.09	9.90

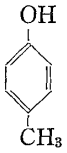
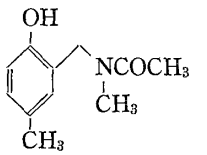
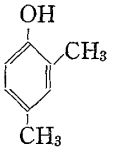
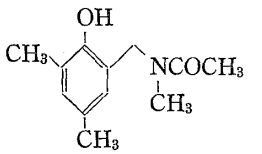
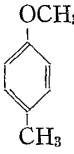
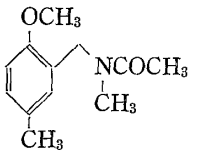
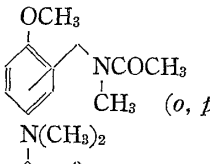
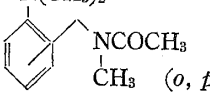
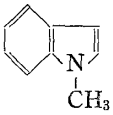
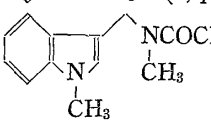
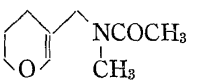
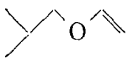
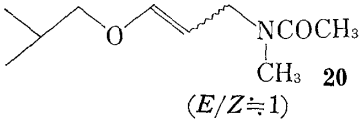
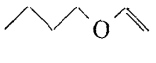
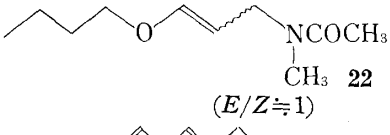
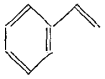
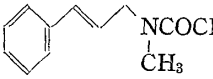
a) Reaction conditions—molar ratio of **3**: **1a—d**: CH_3COCl=1.0: 0.4: 1.2; solvent, $CHCl_3$; at room temperature.
b) Based on the product actually isolated.
c) Abbreviations: s=singlet, br s=broad singlet.

1) Location: *2-2-1, Oshika, Shizuoka, 422, Japan.*
2) D.D. Reynolds and B.C. Cossar, *J. Heterocycl. Chem.*, **8**, 597 (1971); *idem, ibid.*, **8**, 605 (1971); *idem, ibid.*, **8**, 611 (1971).
3) Farbenfabriken Bayer A.-G., Belg. 621378 (1962) [*C.A.*, **59**, 9816*f* (1963)].
4) H. Böhme, A. Dick, and G. Driesen, *Chem. Ber.*, **94**, 1879 (1961).

We have found that several compounds possessing electron-rich carbon react with 1,3,5-trialkylhexahydro-1,3,5-triazines (**1**) in the presence of acetyl chloride in chloroform, undergoing *N*-alkylamidomethylation. This reaction may involve electrophilic attack of *N*-alkyl-*N*-chloromethylamides (**2**) formed *in situ*.

The initial experiments using 2-naphthol (**3**) were conducted by allowing this compound to react with 1,3,5-trialkylhexahydro-1,3,5-triazines (**1a**—**d**) possessing various alkyl moieties in the presence of acetyl chloride in chloroform at room temperature to give the corresponding

Table II. *N*-Methylamidomethylation[a] at Electron-rich Carbons

Starting material	No.	Reaction time (hr)	Product	No.	Yield (%)[b]
	**5**	3		**6**	41
	**7**	3[c]		**8**	58
	**9**	25		**10**	23
	**11**	20		**12**	16
	**13**	7[d]		**14**	41
	**15**	3[d]		**16**	52
	**17**	8[d]		**18**	27
	**19**	12[d]		**20** ($E/Z \fallingdotseq 1$)	41
	**21**	13[d]		**22** ($E/Z \fallingdotseq 1$)	35
	**23**	25		**24**	20

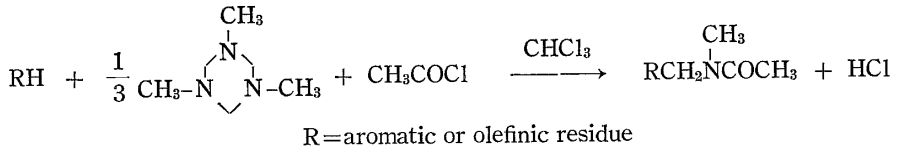
a) Reaction conditions—molar ratio of starting material: $(CH_3NCH_2)_3$: CH_3COCl=1.0: 0.4: 1.2; solvent, $CHCl_3$; heated under reflux.
b) Based on the product actually isolated.
c) At room temperature.
d) Triethylamine equivalent to acetyl chloride was added to the reaction mixture.

TABLE III. Analytical and Spectral Data for *N*-Methylacetamidomethylation Products

Compd.	Component	bp (°C) (mm Hg) mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	IR $\nu_{max}^{liq.}$ (cm^{-1}) C=O	NMR[a] δ ppm ($CDCl_3$) J=Hz CH_3CO 3H s	CH_3N 3H s	CH_2N 2H s	Others
6		130—135 (0.25) 108—109	$C_{11}H_{15}NO_2$	68.37 (68.30	7.82 7.73	7.25 7.27)	1600[b]	2.10	3.08	4.38	2.28 (3H, s, CH_3), 6.78 (1H, d, J=8, $H_{(6)}$), 6.9 (1H, $H_{(3)}$), 6.98 (1H, dd, J=2, 8, $H_{(5)}$), 9.32 (1H, br s OH)
8		135—137 (0.08)	$C_{12}H_{17}NO_2$	69.54 (69.62	8.27 8.58	6.76 6.79)	1613	2.08	3.07	4.36	2.21 (6H, s, 2×CH_3), 6.74 (1H, d, J=2) and 6.89 (1H, d, J=2, $H_{(3)}$ and $H_{(5)}$), 9.36 (1H, br s, OH)
10		128—130 (0.3)	$C_{12}H_{17}NO$	69.54 (69.54	8.27 8.32	6.76 6.76)	1638	2.13	2.94	4.46	2.27 (3H, s, CH_3), 3.80 (3H, s, OCH_3), 6.76 (1H, d, J=8, $H_{(6)}$), 6.81 (1H, d, J=2, $H_{(3)}$), 7.00 (1H, dd, J=2, 8, $H_{(5)}$)
12	*o*,*p*-mixt.	149—153 (2.0)	$C_{11}H_{15}NO_2$	68.37 (67.61	7.82 7.80	7.25 7.52)	1638	2.11	2.90 2.92	4.47 4.60	3.80, 3.76 (3H, s and s, OCH_3)[e] 6.70—7.30 (4H, m, C_6H_4)
14	*o*,*p*-mixt.	118—126 (0.01)	$C_{12}H_{18}N_2O$	69.87 (69.80	8.80 8.85	13.58 13.51)	1639	2.10 2.18	2.91 2.84	(4.57) (4.72) (4.44) (4.37)[d]	2.67 (6H, s, $N(CH_3)_2$), 6.55—7.25 (4H, m, C_6H_4)
16		59— 60	$C_{13}H_{16}N_2O$	72.19 (72.70	7.46 7.47	12.95 12.98)	1630[b]	2.07 2.24	2.88 2.96	4.70 4.63	3.72 (3H, s, NCH_3), 6.97 (1H, s, =CH–), 7.1—7.7 (4H, m, C_6H_4)
18		94— 98 (2.0)	$C_9H_{15}NO_2$	63.88 (63.55	8.94 8.99	8.28 8.16)	1632	2.10	2.88 2.81	3.75 3.85	1.75—2.00 (4H, m, $(CH_2)_2$), 2.9 (2H, d, J=5, CH_2O), 6.34 (1H, s, =CH–)
20	*E*,*Z*-mixt.	109—110 (2.5)	$C_{10}H_{19}NO_2$	64.83 (64.85	10.34 10.33	7.56 7.96)	1632	2.11 2.08	2.89 2.92 2.94	3.70 ⟨ m 4.10	0.95 (6H, d, J=7, 2×CH_3), 1.96 (1H, hept, J=7, >CH–), 3.40—3.60 (2H, CH_2O), 4.23—5.02 (1H, =CH–) 6.13 and 6.43 (1H, d, J=6 and d, J=12, –OCH=)[e]
22	*E*,*Z*-mixt.	115—118 (2.5)	$C_{10}H_{19}NO_2$	64.83 (64.97	10.34 10.38	7.56 7.57)	1632	2.08 2.04	2.89 2.93 2.95	3.80 ⟨ m 4.10	0.95 (3H, t, J=6, CH_3), 1.10—1.95 (4H, m, $(CH_2)_2$), 3.40—3.75 (2H, CH_2O), 4.1—5.0 (1H, m, =CH–), 6.12 and 6.39 (1H, d, J=6 and d, J=12, –OCH=)[e]
24		127—129 (0.01)	$C_{12}H_{15}NO$	76.15 (76.69	7.99 8.16	7.40 7.48)	1641	2.10	2.96	4.02 d, J=5 4.11 d, J=5	6.40 (1H, d, J=16, –CH=), 6.11 (1H, dt, J=16, 5, =CH–CH_2) 7.28 (5H, s, C_6H_5)

a) Abbreviations: s=singlet, d=doublet, dd=doublet of doublets, dt=doublet of triplets, br=broad, m=multiplet, hept=heptet.
b) KBr disk.
c) Relative intensity of the two singlets is *ca.* 2: 1.
d) Relative intensity of the two sets of two singlets is *ca.* 4: 1.
e) Relative intensity of the two doublets is *ca.* 1: 1.

1-(*N*-alkylacetamidomethyl)-2-naphthols (**4a—d**). The results are summarized in Table I. All the *N*-alkylacetamidomethylation products (**4a—d**) gave consistent nuclear magnetic resonance (NMR) and infrared (IR) spectra (see Table I), indicating hydrogen bonding of the amide carbonyl oxygen with the phenolic proton, and satisfactory elemental analyses.



R=aromatic or olefinic residue

The *N*-methylamidomethylation was tested with compounds possessing electron-rich carbon; not onyl aromatics but also some olefins. The results are summarized in Table II. Among aromatics, phenols (**5, 7**), alkoxybenzenes (**9, 11**) and amines (**13, 15**), and among olefins, styrene (**23**) and vinyl ethers (**17, 19, 21**) underwent *N*-methylacetamidomethylation. In the runs with aromatic amines (**13, 15**) and vinyl ethers (**17, 19, 21**) addition of triethylamine to the reaction mixtures was necessary or at least favorable for completion of the reactions.

Spectral and analytical data for the N-methylacetamidomethylation products are shown in Table III. Due to the partial double bond character of the nitrogen-carbonyl bond of the *N*-methylacetamidomethyl groupings of the products, their NMR spectra exhibit splitting of each of the singlets of *N*-methyl and *N*-methylene protons into two singlets, and in the cases of **14, 16, 20** and **22**, there were two additional singlets due to the acetyl protons, except in *ortho*-substituted phenols (**6, 8**), for which the IR and NMR spectra indicate hydrogen bonding between the phenolic proton and amide carbonyl oxygen, as in the cases of the *N*-alkylacetamidomethylated naphthols (**4a—d**). The NMR spectra of the products, **12** and **14**, exhibited splitting of the methoxy protons into two singlets in the former and splitting of the two singlets of methylene protons into four singlets. The IR spectra of the two products exhibit out-of-plane CH deformation vibration bands of four adjacent ring hydrogens (757 cm^{-1} for **12** and **14**), characteristic of 1,2-substitution, and also of two adjacent ring hydrogens (817 cm^{-1} for **12**, 816 cm^{-1} for **14**) characteristic of 1,4-substitution. From these spectral data and the results of gas–liquid chromatographic (GLC) analysis, the products, **12** and **14**, appear to be *ortho* and *para* mixtures in molar rations of about 2: 1 and 4: 1, respectively. Böhme *et al.*[4] have reported the formation of *N*-methyl-*N*-(4-methoxybenzyl)acetamide by reaction in the *N*-methyl-*N*-chloromethylacetamide–aluminum chloride system, but did not give its spectral data. The NMR spectrum and GLC behavior of **24** are suggestive of the *E* isomer for the most part, while **20** and **22** appear to be mixtures of *E* and *Z* isomers in a 1: 1 ratio, as shown in Table III.

Experimental

All boiling and melting points are uncorrected. IR spectra were taken on a Hitachi EPI-G2 spectrophotometer. NMR spectra were recorded on a Hitachi R-24 spectrometer and all chemical shifts are given in ppm downfield from TMS. GLC analyses were carried out with a Hitachi 163 gas chromatograph using a column (3 mm × 1 m) packed with 10% SE-30 on Chromoscrb W 80–100 mesh at a column temperature of 200° and a flow rate of carrier gas (N_2) of 60 ml/min.

Reaction of 2-Naphthol (3) with 1,3,5-Trialkylhexahydro-1,3,5-triazines (1a—d) in the Presence of Acetyl Chloride——A solution of 4.7 g (0.06 mol) of acetyl chloride in 10 ml of chloroform was added dropwise to a stirred solution of 0.02 mol of a 1,3,5-trialkylhexahydro-1,3,5-triazine (**1a—d**) in 40 ml of chloroform with cooling in an ice bath. After stirring for an additional 1 hr at room temperature, a solution of 7.2 g (0.05 mol) of 2-naphthol (**3**) in 10 ml of chloroform was added dropwise to the stirred reaction solution with cooling in a water bath. After additional stirring for several hours at room temperature, the reaction mixture was washed with aq. $KHCO_3$ and dried over anhyd. $MgSO_4$. Removal of the solvent left a crystalline residue, which was triturated with ether and filtered. Recrystallization from ethanol gave pure 1-(*N*-alkylacetamido-

methyl)-2-naphthol (**4a—d**) as prisms. Yields, mps and analytical and spectral data of **4a—d** are listed in Table I.

Reaction of Aromatics (5, 7, 9, 11, 13, 15) or Olefins (17, 19, 21, 23) with 1,3,5-Trimethylhexahydro-1,3,5-triazine (1a) in the Presence of Acetyl Chloride——General Procedure (A) (Addition of Triethylamine): *N*-Methylacetamidomethylation reactions of *N*,*N*-dimethylaniline (**13**), *N*-methylindole (**15**), 3,4-dihydro-α-pyran (**17**), isobutyl vinyl ether (**19**) and butyl vinyl ether (**21**) were carried out by the following procedure. A solution of 4.7 g (0.06 mol) of acetyl chloride in 10 ml of chloroform was added dropwise to a stirred solution of 2.6 g (0.02 mol) of **1a** in 30 ml of chloroform with cooling in an ice bath. After stirring for an additional 1 hr at room temperature, a mixture of 0.05 mol of **13**, **15**, **17**, **19** or **21** and 6.1 g (0.06 mol) of triethylamine in 10 ml of chloroform was added dropwise to the stirred reaction solution with cooling in a water bath. After refluxing for several hours, the reaction mixture was washed with water and dried over anhyd. $MgSO_4$. Removal of the solvent left an oily residue, which was fractionally distilled under reduced pressure to give the product (**14**, **16**, **18**, **20** or **22**). In the case of **16**, the solid distillate [bp 130—150° (0.04 mmHg)] was further purified by recrystallization from ether to give prisms.

General Procedure (B): *N*-Methylacetamidomethylation reactions of *p*-cresol (**5**), 2,4-xylenol (**7**), *p*-cresyl methyl ether (**9**), anisole (**11**) and styrene (**23**) were carried out by the following procedure. A solution of 4.7 g (0.06 mol) of acetyl chloride in 10 ml of chloroform was added dropwise to a stirred solution of 2.6 g (0.02 mol) of **1a** in 20 ml of chloroform with cooling in an ice bath. After stirring for an additional 1 hr at room temperature, a solution of 0.05 mol of **5**, **7**, **9**, **11** or **23** in 10 ml of chloroform was added dropwise to the stirred reaction solution with cooling in a water bath. After refluxing for several hours, the reaction mixture was washed with aq. $KHCO_3$ and dried over anhyd. $MgSO_4$. Removal of the solvent left an oily residue, which was fractionally distilled under reduced pressure to give the product (**6**, **8**, **10**, **12** or **24**). In the case of **6**, the solid distillate was further purified by recrystallization from AcOEt to give prisms.

The reaction times and yields of **6**, **8**, **10**, **12**, **14**, **16**, **18**, **20**, **22** and **24** are listed in Table II, and the analytical and spectral data in Table III. NMR data for the products **12** and **14** are suggestive of *ortho* and *para* mixtures, while those for the products **20** and **22** suggest *E* and *Z* mixtures. The presence of theses mixtures was supported by the results of GLC analyses. The *o*-, *p*-mixture of **12** exhibited two peaks at retention times of 87 sec and 99 sec in a ratio of *ca.* 2: 1 and that of **14** gave two peaks at 108 sec and 194 sec in a ratio of *ca.* 4: 1. The *Z*-, *E*-mixture of **20** exhibited two peaks at 171 sec and 185 sec (a column temp.: 150°) in a ratio of *ca.* 1: 1 and that of **22** gave two peaks at 103 sec and 113 sec (a column temp.: 170°) in a ratio of *ca.* 1: 1.

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