2-Acyloxy-4,6-dimethoxy-1,3,5-triazine – A New Reagent for Ester Synthesis

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Abstract: 2-Acyloxy-4,6-dimethoxy-1,3,5-triazines obtained in reaction between carboxylic acid and 2-chloro-4,6-dimethoxy-1,3,5-triazine were used as acylating agents for the synthesis of esters from primary, secondary, and tertiary alcohols. Because of mild acylation conditions the method could be applied to esterification of labile alcohols with aromatic and aliphatic (also α-branched) acids in good yields.

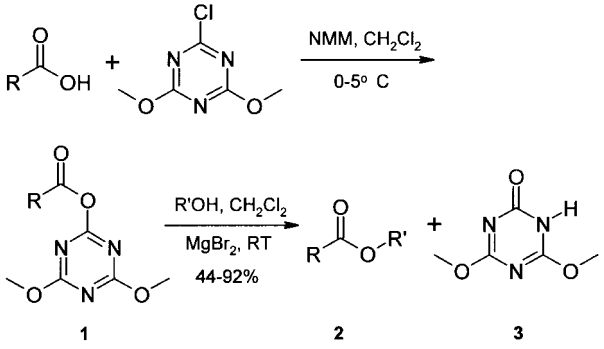
Key words: transesterification, alcoholysis, catalyst, magnesium bromide

Although numerous general methods of ester formation are well known, there are still cases when results achieved in these ways are not satisfactory. In recent years much attention has been paid to syntheses based on transesterifications,[1] and the best results are usually obtained when the reaction is irreversible. This is the case when vinyl esters act as acylating agents, because the vinyl alcohol formed is rapidly converted into the more stable keto tautomer, shifting the transesterification equilibrium in the desired direction. Especially difficult is the esterification of alcohols and/or acids, which are labile in acidic or basic medium (allyl or tertiary alcohols, sterically hindered α-substituted acids, and substrates containing other functional groups too sensitive to stand conditions employed in typical esterification procedures). Therefore we decided to check the possibility of application of 2-acyloxy-4,6-dimethoxy-1,3,5-triazines as acyl donors in ester bond formation as an alternative to classic esterification methods.

2-Chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) reacts under mild conditions with carboxylic acids yielding so called "superactive esters".[2] Aminolysis of these esters is a very efficient method for amide bond formation.[3,4] Presumably, during aminolysis of 2-acyloxy-4,6-dimethoxy-1,3,5-triazine, the driving force of the reaction is the tautomerization of 2-hydroxy-4,6-dimethoxy-1,3,5-triazine formed as a temporary intermediate, into more stable keto form.[5] Although acylating ability of acyloxytriazines in amide bond formation is already recognized, their potential in the esterification reaction remains unexplored.

Herein we report results of our study on alcoholysis of 2-benzoyloxy-, 2-(2-ethylhexanoyloxy)- and 2-trimethylacetoxy-4,6-dimethoxy-1,3,5-triazine with variety of alcohols.

All triazinyl esters were obtained from the corresponding acids (benzoic, 2-ethylhexanoic, and trimethylacetic) according to Kamiński's procedure.[6] Preliminary alcoholyses were performed on 2-benzoyloxy-4,6-dimethoxy-1,3,5-triazine in solution of the appropriate alcohol (propanol, isopropanol, *tert*-butanol) at room temperature (Method A). We have found that even without transesterification catalysts, primary and secondary alcohols were acylated at acceptable rates (2–4 days), while tertiary alcohols require longer reaction time or higher temperature. Searching for catalysts able to increase the rate of alcoholysis of 2-acyloxy-4,6-dimethoxy-1,3,5-triazines we have tested acids, bases, amines, metal alkoxides, transition metal salts, organotin compounds and others.[7] All compounds tested were added at a quantity of 5 mol% of acyloxytriazine. Progress of alcoholysis of 2-benzoyloxy-4,6-dimethoxy-1,3,5-triazine with cyclohexanol was monitored by GC and compared to esterification without catalyst. As the most efficient catalyst we found magnesium bromide and 4-(*N*,*N*-dimethylamino)pyridine, frequently used as the esterification catalyst. The increase in the rate of acylation in the presence of magnesium bromide (5 mol%) was sufficient to substantially reduce the excess of alcohol used (important when alcohol is not easily available). Following the general procedure (Method A or C) we have obtained benzoates **2a–i**, 2-ethylhexanoates **2j–m**, and trimethylacetate **2n** in 44–92% yield (see Table). Esters were purified by distillation or column chromatography. Purity was checked by GC and identity confirmed by comparison of physical parameters for known compounds with literature data and inspecting H NMR spectra.



R = Ph, 3-heptyl, *t*-Bu; R′OH see Table

Scheme

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Table Synthesis of Esters by Alcoholysis of 2-Acyloxy-4,6-dimethoxy-1,3,5-triazines

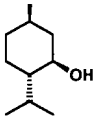
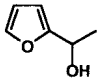
2	R	R′OH	Method/ Cat.	Time [d]	Yield[a] [%]	Bp (°C/Torr)	n_D^{20} or $[\alpha]_D$	Lit. bp or mp, n_D^{20} or $[\alpha]_D$	^{1}H NMR, ($CDCl_3$) δ, (ppm), *J* (Hz)
a	Ph	PrOH	A/$MgBr_2$	2	84	96–8/8	1.5006	113/14[8] 1.5003[9]	0.92 (t, 3H, *J* 7.5), 1.68 (sextet, 2H, *J* 7.5), 4.18 (t, 2H, *J* 7.5), 7.33 (m, 2H), 7.42 (m, 1H), 7.95 (m, 2H)
b	Ph	BuOH	A/$MgBr_2$	2	92	108–10/8	1.4995	108/10[10] 1.4975[11]	0.88 (t, 3H, *J* 7.25), 1.37 (m, 2H), 1.65 (m, 2H), 4.23, (t, 2H, *J* 6.5), 7.32 (m, 2H), 7.41 (m, 1H), 7.93 (m, 2H)
c	Ph	*i*BuOH	A/$MgBr_2$	3	85	105–8/8	1.4958	109/8[11] 1.4918[12]	1.02 (d, 6H, *J* 6.75), 2.08 (septet, 1H, *J* 6.75), 4.10 (d, 2H, *J* 6.75), 7.43 (m, 2H), 7.53 (m, 1H), 8.05 (m, 2H)
d	Ph	*i*PrOH	A/$MgBr_2$	4	82		1.4970	1.4948[13]	1.26 (d, 6H, *J* 6.25), 5.16 (septet, 1H, *J* 6.25), 7.31 (m, 2H), 7.43 (m, 1H), 7.94 (m, 2H)
e	Ph	*s*BuOH	A/$MgBr_2$	4	62	100–3/8	1.4959	114–7/20[14] 1.4948[15]	0.97 (t, 3H, *J* 7.25), 1.33 (d, 3H, *J* 6.25), 1.72 (m, 2H), 5.09 (sextet, 1H, *J* 6.25), 7.44 (m, 2H), 7.52 (m, 1H), 8.04 (m, 2H)
f	Ph		C/$MgBr_2$	5	85		1.4961	1.4887 (25°C)[20]	0.98, 1.08 (2d, 6H, *J* 6.8), 1.29 (d, 3H, *J* 6.8), 1.94 (octet, 1H, *J* 6.8), 5.0 (quintet, 1H, *J* 6.8), 7.46 (m, 2H), 7.54 (m, 1H), 8.05 (m, 2H)
g	Ph		A/DMAP	1	64	146–8/8	1.5215	144/8[10] 1.5223[10]	1.23–1.62 (m, 6H), 1.77 (m, 2H), 1.92 (m, 2H), 5.03 (m, 1H), 7.41 (m,2H), 7.51 (m, 1H), 8.06 (m, 2H)
			B/$MgBr_2$	11	43				
			C/$MgBr_2$	8	52				
h	Ph		C/$MgBr_2$	10	56	mp 54–55	$[\alpha]_D^{21}$ –94.2 (1.19, C_6H_6)	$[\alpha]_D^{20}$ –90.6 (0.953, C_6H_6)[16] mp 55[17]	0.80 (d, 3H, *J* 6.75), 0.91 (d, 3H, *J* 7.0), 0.94 (d, 3H, *J* 6.5), 1.12 (m, 3H), 1.56 (m, 2H), 1.73 (m, 2H), 1.96, 1.98 (d septet, 1H, *J* 7.0), 2.13 (m, 1H), 4.93, 4.95 (dt, 1H, J 11), 7.44 (m, 2H), 7.54 (m, 1H), 8.06 (m, 2H)
i	Ph		C/$MgBr_2$	6	44	124–6/1.4	1.5332		1.70 (d, 3H, *J* 6.75), 6.22 (q, 1H, *J* 6.75), 6.35 (m, 2H), 7.35–7.50 (m, 4H), 8.02 (m, 2H)
			B/$MgBr_2$	6	24				
j	3-heptyl		B/$MgBr_2$	6	41	102–4/1.2	1.4551		0.81–0.90 (2t, 6H), 1.20–1.30 (m, 4H), 1.48–1.60 (m, 4H), 1.57 (d, 3H, *J* 6.75), 2.24 (m, 1H), 6.0 (q, 1H, *J* 6.75), 6.31 (m, 2H), 7.36 (s,1H)

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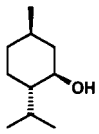
Table (continued)

2	R	R′OH	Method/ Cat.	Time [d]	Yield[a] [%]	Bp (°C/Torr)	n_D^{20} or $[\alpha]_D$	Lit. bp or mp, n_D^{20} or $[\alpha]_D$	^{1}H NMR, ($CDCl_3$) δ, (ppm), *J* (Hz)
k	3-heptyl-		C/$MgBr_2$	11	69	98–100/ 1.5	1.4492		0.86–0.92 (2t, 6H, *J* 6.8), 1.26–1.80 (m, 18H), 2.20 (m, 1H), 4.75–4.83 (m, 1H)
i	3-heptyl-	*i*PrOH	C/$MgBr_2$	4	73	88–90/19	1.4140		0.89 (2t, 6H, *J* 7.5), 1.24 (d, 6H, *J* 6), 1.22–1.29 (m, 4H), 1.48–1.61 (m, 4H), 2.20 (m, 1H), 5.03 (septet, 1H, *J* 6)
m	3-heptyl	*t*BuOH	C/$MgBr_2$	5	46		1.4170		0.89 (2t, 6H, *J* 7.5), 1.20–1.37 (m, 4H), 1.37–1.70 (m, 4H), 1.45 (s, 9H), 2.13 (m, 1H)
n	*t*Bu		C/none	1	60	126–8/17	1.4417 $[\alpha]_D^{20}$ –75.3 (2.49, MeOH)	124.5/ 13.5[18] 1.441 (25 °C)[19] $[\alpha]_D^{25}$ –83.1 (MeOH)[19]	0.75 (d, 3H, *J* 7), 0.85–0.91 (m, 8H), 1.19 (s, 9H), 1.20–1.55 (m,3H), 1.60–1.75 (m, 2H), 1.80–2.01 (m, 2H), 4.63 (double t, 1H, *J* 10,*J* 5)

[a] isolated yields of pure products

Although treatment of carboxylic acids with CDMT in the presence of *N*-methylmorpholine usually give high yield of numerous acyloxytriazines, it is always advantageous to avoid purification and handling these highly reactive derivatives **1**. Therefore, as proof of preparative utility of our method, esters **2f–i**, and **2k–n** were synthesized starting from corresponding carboxylic acids in a two-step procedure using crude triazinyl ester followed by immediate treatment with alcohol (Method C). We found crucial to wash out thoroughly the side products from the crude triazine ester, because alcoholysis carried out directly in the mixture obtained during activation procedure was slower, and hence the yields of esters went down (probably due to catalyst deactivation by the excess of *N*-methylmorpholine hydrochloride). Thus, the more convenient two-step "one pot" procedure without isolation of acyloxytriazine **1** (Method B), following standard workup and distillation or flash chromatography, gave esters **2g**, **2i**, and **2j** in moderate overall yield (24–43%).

In conclusion we established that carboxylic acids activated by 2-chloro-4,6-dimethoxy-1,3,5-triazine acylate primary, secondary, and tertiary alcohols. Acylation proceeds under mild reaction conditions, so the method is found to be useful for synthesis of esters of alcohols labile in acidic medium or at elevated temperature (1-(2-furyl)ethanol), as well as for esterification of α-branched carboxylic acids (2-ethylhexanoic, trimethylacetic acid). The general procedure C allows ester synthesis directly from appropriate carboxylic acid via crude triazinyl ester **1**.

The advantage of our method is also the convenient and efficient means for the purification of esters due to weak basicity of 1,3,5-triazine ring which simplifies the removal of co-product **3** simply by washing with acid solution. Hence in some cases it is possible to obtain esters of analytical purity (>98% by GC).

Melting points were measured on a Buchi capillary melting point apparatus and are uncorrected. Optical rotation was measured on Rudolph Autopol IV apparatus in 1 dm cell. Proton NMR spectra were run on Bruker 250 MHz in $CDCl_3$ using the residual solvent signal as the internal standard. All chemicals were reagent grade and were used without additional purification. Benzoic acid and CH_2Cl_2 were purchased from POCH-Gliwice, 2-ethylhexanoic acid and *N*-methylmorpholine from Fluka, anhyd magnesium bromide, 4-(*N*,*N*-dimethylamino)pyridine and 2-acetylfuran from Aldrich. 1-(2-Furyl)ethanol was obtained from 2-acetylfuran by reduction with $NaBH_4$ in MeOH at 0–5 °C. Kieselgel 60H (Merck) was used for flash chromatography and mixture of hexane and acetone in various proportions as eluent. TLC was performed on precoated silica gel plates (Merck) which were visualized with UV light or I_2 vapors.

Butyl Benzoate (2b); Typical Procedure
Alcoholysis of Acyloxytriazines (Method A)

To a solution of 2-benzoyloxy-4,6-dimethoxy-1,3,5-triazine (1.3 g, 5 mmol) in CH_2Cl_2 (10 mL), butanol (3.7 g, 50 mmol) and $MgBr_2$ (0.1 g, 0.5 mmol) were added at r.t. Progress of transesterification was followed by TLC. When the spot of benzoyloxytriazine disappeared, the mixture was diluted with CH_2Cl_2 (50 mL) and washed succesively with sat. $NaHSO_4$ (2 x 30 mL), $NaHCO_3$ (3 x 30 mL) and H_2O (1 x 50 mL). Extract was dried ($MgSO_4$) and solvent evaporated. Residue was distilled under reduced pressure (bp 108–110/ 8 Torr) yielding pure butyl benzoate (0.761 g, 92%).

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Two-Step Synthesis of Esters 2f–n; Typical Procedure
1-(2-Furyl)ethyl 2-Ethylhexanoate (2j) (Method B)
To a stirred solution of 2-chloro-4,6-dimethoxy-1,3,5-triazine (7.2 g, 50 mmol) in CH_2Cl_2 (70 mL) cooled to 0 °C, *N*-methylmorpholine (5.8 mL, 52 mmol) was added dropwise, followed by 2-ethylhexanoic acid (7.2 g, 50 mmol) dissolved in CH_2Cl_2 (30 mL). After 2 h stirring at 0–5 °C, 1-(2-furyl)ethanol (22.4 g, 200 mmol) and $MgBr_2$ (0.5 g, 2.5 mmol) were added. The mixture was left at r.t. After 6 days (the spot of 2-ethylhexanoyloxytriazine disappeared on TLC) the mixture was washed successively with $NaHSO_4$ (2 x 100 mL), $NaHCO_3$ (2 x 100 mL), H_2O (100 mL) and dried ($MgSO_4$). After solvent evaporation the residue was distilled under reduced pressure yielding 1-(2-furyl)ethyl 2-ethylhexanoate (4.9 g, 41%), bp 102–104 °C/ 1.2 Torr.

Isopropyl 2-Ethylhexanoate (2l) (Method C)
To a stirred solution of 2-chloro-4,6-dimethoxy-1,3,5-triazine (7.2 g, 50 mmol) in CH_2Cl_2 (70 mL) cooled to 0 °C, *N*-methylmorpholine (5.8 mL, 52 mmol) was added dropwise, followed by 2-ethylhexanoic acid (7.2 g, 50 mmol) dissolved in CH_2Cl_2 (30 mL). After 2 h stirring at 0–5 °C, the mixture was left at r.t. overnight, then washed successively with 10% solution of citric acid (1 x 50 mL), sat. $NaHCO_3$ (2 x 50 mL), H_2O (2 x 50 mL), and dried ($MgSO_4$). After solvent evaporation to crude triazinyl ester, isopropanol (30 g, 500 mmol), and $MgBr_2$ (0.5 g, 2.5 mmol) were added and the mixture left at r.t. After 4 days (small spot of triazinyl ester still present in TLC) the mixture was refluxed for 2.5 h, then H_2O (100 mL) and CH_2Cl_2 (100 mL) were added. The CH_2Cl_2 phase was separated, washed with $NaHSO_4$ (2 x 30 mL), $NaHCO_3$ (4 x 50 mL), H_2O (1 x 50 mL), and dried ($MgSO_4$). After solvent evaporation, residue was distilled under reduced pressure (bp 88–90 °C/19 Torr) yielding 6.8 g (73%) of isopropyl 2-ethylhexanoate.

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