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2-CHLORO-4,6-DISUBSTITUTED-1,3,5-TRIAZINES A NOVEL GROUP OF CONDENSING REAGENTS

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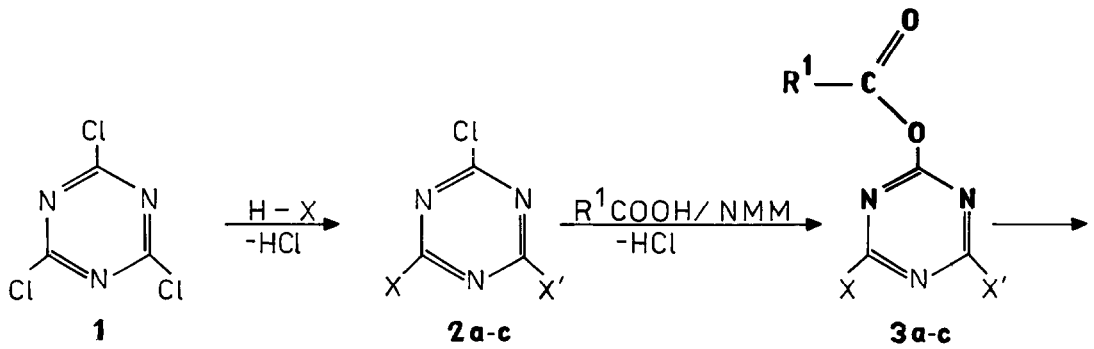
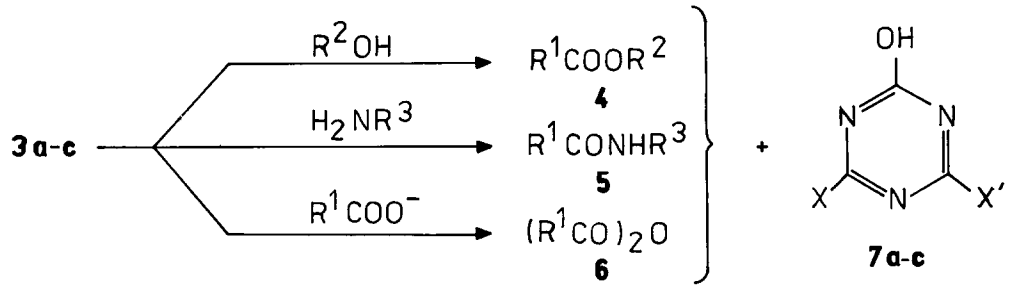
Abstract: The title, compounds form in reaction with carboxylic acids highly reactive intermediates, which are useful as acylating reagents in the preparation of esters, amides, acid anhydrides, and peptides in 64-98% yield.

Although it is generally accepted, that carbodiimides are the most efficient condensing agents, their side effects such as the formation of side products, racemization, and allergenic properties still give rise to the search for the new coupling reagents. In our research programme in this field we focused our attention on the derivatives of cyanuric chloride (1), which already has been applied for the preparation of acyl chlorides, amides, and peptides[1].

In this particular study indications have been found denoting that partial substitution of chlorine atoms of cyanuric chloride by methoxy or phenoxy groups changes the course of reaction with carboxylic acids. It is presumed that instead of expected acyl chlorides, the reaction between 2-chloro-4,6-disubstituted-1,3,5-triazines (2) and carboxylic acids gave highly reactive intermediates 3a-c, which under further treatment with alcohols, amines, and carboxylic acid anions, afforded appropriate esters (4) amides (5), and acid anhydrides (6), respectively.



1 2a-c 3a-c



a) X = Cl, X' = OCH_3; b) X, X' = OCH_3; c) X, X' = OC_6H_5

The proposed condensing reagents 2a-c are stable, crystalline compounds, easily accessible from commercialy available cyanuric chloride[2,3,4]. According to the preliminary observations, substituents attached to the triazinyl ring strongly affect the acylating ability of 2 in the following order: 2a (X=Cl, X'=OCH_3)[2] > 2b (X,X' = OCH_3)[3] > 2c (X,X'= OC_6H_5)[4]. This differentiated reactivity enables the choice of the most suitable reagent 2 for the particular synthetic purpose. The most reactive 2a gave amides, esters, and acid anhydrides in 74-98% yield. The scope of the application of 2c was found to be limited to the acylation of amines only.

The moderately reactive 2-chloro-4,6-dimethoxy-1,3,5-triazine has been found especially useful for the peptide synthesis. As evidenced by examples collected in the Table (entries 12-14) di-, and tripeptides were formed in 82-88% yield. The absence of the second chlorine atom and the slower rate of the acylation of alcohols and carboxylic acids by 2b, as compared with 2a, reduce the danger of the potential side reactions. This particular behavior of 2b offers an opportunity for coupling of amino-acids, such as serine, without protection of its hydroxyl group. Thus, for example, Boc-Ser-Val-OBzl, was obtained in 82% yield according to the following procedure: Boc-Ser-OH was activated at -5°C by treatment with equimolar amounts of 2b and N-methylmorpholine in methylene chloride solution for 2 hrs. The aminolysis of reactive intermediate by means of valine benzyl ester p-toluenesulphonate in the presence of equimolar amount of N-methylmorpholine was carried out first at -5°C for 2 hrs and then twelve hours at room temperature. Pure dipeptide was isolated after washing off the crude preparation with diluted hydrochloric acid, water, and aqueous sodium bicarbonate. This simple way of purification of the products demonstrates the another advantage of the use of 2a-c as a condensing reagents. The convenience in the purification is mainly due to weakly basic properties of 1,3,5-triazine ring. Thus, simple washing of the reaction mixture with diluted acids removes any side - and by - products, as well as an excess of coupling reagent. In this preliminary studies, the racemization accompanying the peptide bond formation was estimated by the model methods only. Under the typical coupling condition by means of 2b, no racemization was detected neither by Anderson[5] nor by Izumiya[6] test.

TABLE

Acylation of alcohols, carboxylic acid salts, amino-acids, and amines by carboxylic acids activated with 2-chloro-4,6-disubstituted-1,3,5-triazines (2).

Entry	Product of acylation[7]	Condensing reagent	Yield %	m.p.(°C) n_{20}^{D}
1	$C_6H_5CO-OC_2H_5$	2a	74	1.5047
2	C_6H_5CO-Gly-OCH_3	2a	98	74-6
3	$CH_3CO-OC(CH_3)_3$	2a	78[8]	-
4	$C_6H_5CO-OC_2H_5$	2b	65[9]	1.5045
5	$(CH_3)_3CCO-NHC_6H_5$	2a	91	121-4
6	$(CH_3)_3CCO-NH$-⬡	2b	98	109-11
7	$C_6H_5CO-NHC_6H_5$	2b	92	157-60
8	$C_6H_5CO-NHC(CH_3)_3$	2b	84	134-5
9	C_6H_5CO-NH-⬡	2b	98	145-7
10	C_6H_5CO-NH-⬡	2c	64	140-5
11	$(C_6H_5CO)_2O$	2a	81	39-41
12	Boc-Ser-Val-OBzl	2b	82	53-5
13	Boc-Ala-Ser(Bzl)-Val-OBzl	2b	89	77-9
14	Z-Phe-Aib-OCH_3*	2b	88	123-5

*) Aib: 2-methylalanine.

The absence of racemization suggests that activation of carboxylic acids by 2-chloro-4,6-disubstituted-1,3,5-triazines proceeds on the different route than axpected formation of acyl chlorides.[10] Attempts to isolate the reactive intermediate in the condensation reaction mediated by 2a-c were successful only in the model experiment with sterically hindered 2,2-dimethylpropionic acid and 2b. Its structure, 2-(2,2-dimethylpropionyloxy)-4,6-dimethoxy-1,3,5-triazine (3b; m.p. 49-51°C) was confirmed by spectroscopic methods and elementary analysis.[11] IR absorption at 1775 cm^{-1} of 2,2-dimethylpropionyloxy group indicates the presence of carbonyl function of an active ester. Magnetically equivalent methoxyl substituents observed at

4,07 ppm.in ^{1}H-NMR ($CDCl_3$) and at 55.87 ppm. in ^{13}C-NMR ($CDCl_3$) spectra respectively, confirm the presence of the symmetrically substituted 1,3,5-triazine ring.[12] The structure 3b demonstrates several resemblances to the reactive intermediates formed in the reaction of carboxylic acids with carbodiimides[13,14] (viz. in fig. 3b by bold face typing). Interestingly, the only consequence of this analogy is the strong acylating ability of 3b. Neither O→N acyl group migration in 3b (corresponding to the formation of N-acyl urea, usually accompanying carbodiimide coupling), nor racemization in the cource of peptide syntesis via 3b were observed. Furthermore, all experimets involving the use of 2a-c have not caused in our laboratory any allergic effects even in these persons, who are otherwise sensitive towards carbodiimides.

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References and Notes

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6. Izumiya N., Muraoka M., J.Am.Chem.Soc., 91, 2391 (1969).
7. All products gave satisfactory ± 0,3% C,H,N analysis and their structures were confirmed by ^{1}H-NMR and IR spectroscopy.
8. Estimated by GLC analysis.
9. Alcoholysis of activated benzoic acid was carried out at room temperature for 10 days.
10. North M.B., Young G.T., Chem. and Ind. 1955, 1597 reported intensive racemization of acyl chlorides.
11. 2-(2,2-dimethylpropionyloxy)-4,6-dimethoxy-1,3,5-triazine (3b): $C_{10}H_{15}N_3O_4$ (241.25), calc. C 49,97%, H 6.27%, N 17.42%; found C 49.80%, H 6,57%, N 17.36%, ^{1}H-NMR ($COCl_3$) δ = 1.32 (s, 9H), 4,00 (s, 6H;) ^{13}C-NMR($CDCl_3$)δ = = 26.71 ($\underline{C}H_3$-C), 44,13($\underline{C}$-CO), 55.70(O-$\underline{C}H_3$), 171.35($\underline{C}$-OCO), 174.08, 174.34 (N=$\underline{C}$-O,O=$\underline{C}$-O).
12. In the case of less sterically hindered carboxylic acids the formation of unstable intermediates absorbing in JR spectrum at 1780-1810 cm^{-1} and showing in ^{1}H-NMR spectrum the presence of methoxyl or phenyl groups at 4.00-4.10 ppm or 7.00-7.60 ppm, respectively, were also observed.
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