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Regioselective alkylations of optically active 4,5-dihydro-1,2,4-triazin-6(1*H*)-ones

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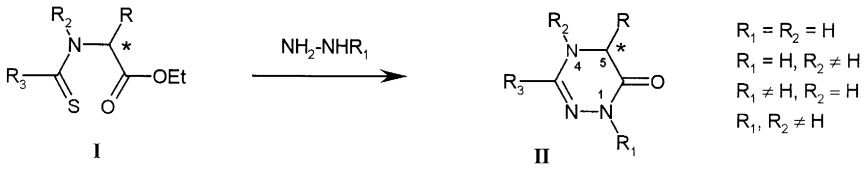
Abstract

Regiocontrolled alkylations of chiral 4,5-dihydrotriazin-6-ones using sodium hydride in DMF are reported. By this approach different N1-alkyl, N1,N4-dialkyl and N4-alkyl dihydrotriazinones could be obtained in good yields with conservation of their optical activity.

Among the different 1,2,4-triazinones described in the literature, only a few are 4,5-dihydro-1,2,4-triazin-6-ones **II**.[1,2] They constitute valuable heterocycles as scaffolds for combinatorial chemistry. For this goal, an efficient control of different substituents within the heterocycle is needed to generate the largest molecular diversity. Their preparation often involves reaction of an *N*-acyl α-amino acid derivative **I** with hydrazine.[2] In particular starting from either an *N*-alkyl *N*-acyl α-aminoester **I**,[3] or an *N*-alkyl hydrazine,[4] it is formally possible to prepare, respectively, N4 or N1 substituted dihydrotriazinones (Scheme 1). However, yields are generally poor, and the methods lead to significant racemisation. In addition specific starting materials have to be available or synthesised for each selected dihydrotriazinone.



Scheme 1.

The work reported here describes an easy and versatile method of regioselective alkylation of either the amide or the amidine moieties present in the structure of the corresponding *N*-unsubstituted dihydrotriazinones. The optically pure (*S*)-5-methyl-3-phenyl-4,5-dihydrotriazin-6-one **1a**, chosen as the reference compound, was prepared according to literature procedures, starting from (L)-*N*-thiobenzoyl alanine ethylester and hydrazine.[2] When **1a** was reacted with methyl iodide in THF degassed with a

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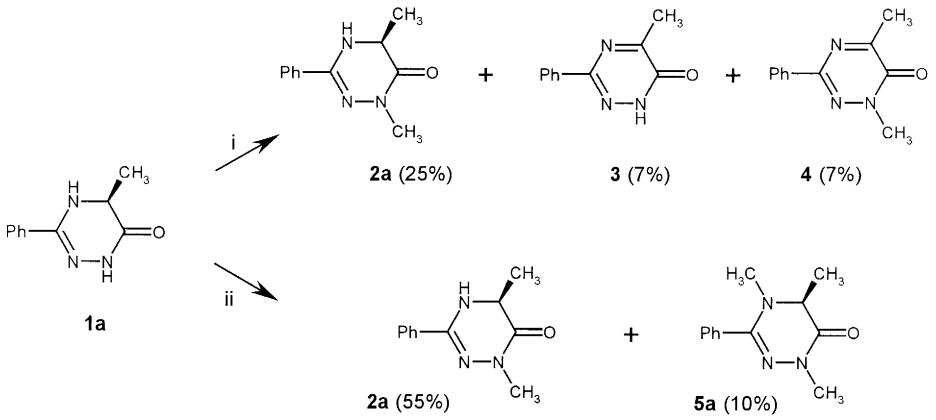
stream of nitrogen, in the presence of sodium hydride as a base, besides important amounts of starting material (40%) and the expected N1-methyl derivative **2a** (25%), two unexpected triazinones **3** and **4** were isolated from the reaction mixture (Scheme 2). They result from the dehydrogenation of the starting dihydrotriazinone **1a** facilitated in our experimental conditions.



Scheme 2. (i) MeI (1.2 equiv.), NaH (1.2 equiv.), THF, N_2 atm., rt; (ii) MeI (1.2 equiv.), NaH (1.2 equiv.), DMF, N_2 atm. 0°C or rt

In order to increase the yield of alkylation and to avoid the formation of other side-products, the procedure was reinvestigated. Several results could be summarised as follows:

(i) when starting from **1a** in the presence of sodium hydride in THF degassed with a stream of nitrogen, but in the absence of alkylating agent, dehydrogenation occurred and the corresponding triazinone **3** was obtained nearly quantitatively.[5]

(ii) temperature (rt or 0°C) did not strongly influence the reaction: a mixture of dihydrotriazinones **1a**, **2a** and unsubstituted triazinone **3** was recovered in similar ratios.

(iii) when the reaction was carried out in DMF, increasing amounts (55%) of N1-methyl derivative **2a** were obtained. Surprisingly in DMF, no dehydrogenation reaction took place at 0°C, or at room temperature. As a result of the higher reactivity of nucleophilic substitution reactions performed in DMF, a significant amount (10%) of N1,N4-dimethyl dihydrotriazinone **5a** was also isolated from the reaction mixture (Scheme 2).

(iv) replacement of sodium hydride by potassium *tert*-butoxide did not significantly modify the course of the reaction, whereas in absence of base no reaction occurred, even with heating (80°C). As expected the deprotonation is the key step for alkylation.

According to pathway ii (Scheme 2), several N1-alkyl 4,5-dihydrotriazin-6-ones were prepared[6,7] using various alkyl halides (Scheme 3, entries 1–5).

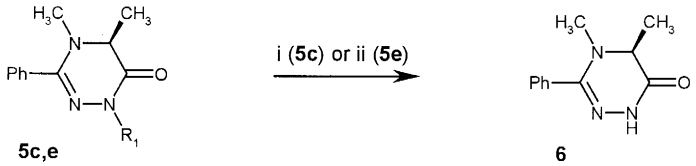
Moreover, further alkylation reactions could be performed on the amidine moiety of N1-substituted dihydrotriazinones **2** using the same experimental conditions as above (a second alkyl halide/NaH/DMF/0°C). The corresponding N1,N4-dialkyl derivatives were prepared[7] in good yields (Scheme 3, entries 6–9).

This approach may constitute an efficient way for introducing various substituents on N4-position in a regioselective manner. Indeed the removal of the N1-substituent of N1,N4-dialkyl compounds **5** would lead to derivatives **6** substituted only on N4-position (Scheme 4). The N1-benzyl group of **5c** was not a satisfactory protective group, as it could not be removed by catalytic hydrogenation using various catalysts. In addition, debenzylation using aluminium trichloride in toluene[8] gave only low yields. However, the benzyloxymethyl group was found to be an advantageous protective group of N1-nitrogen:

Entry	R	R_1X	R_2X	Compound	R_1	R_2	Yield (%)
1	Me	MeI	/	**2a**	Me	H	55
2	Bn	MeI	/	**2b**	Me	H	65
3	Me	BnBr	/	**2c**	Bn	H	50
4	Me	BuI	/	**2d**	Bu	H	72
5	Me	$BnOCH_2Cl$	/	**2e**	$BnOCH_2$-	H	50
6	Bn	MeI	BnBr	**5b**	Me	Bn	55
7	Me	BnBr	MeI	**5c**	Bn	Me	80
8	Me	BnBr	BnBr	**5d**	Bn	Bn	60
9	Me	$BnOCH_2Cl$	MeI	**5e**	$BnOCH_2$-	Me	80

Scheme 3.

alkylation yields were similar to N1-benzyl derivatives but cleavage of benzyloxymethyl group of **5e** using boron tribromide led to the N4-substituted 4,5-dihydrotriazin-6-one **6** in good yields (70%).



Scheme 4. (i) $AlCl_3$, toluene, 60°C, 24 h, 35%; (ii) BBr_3, CH_2Cl_2, rt, 1 h, 70%

As part of the validation of our synthetic approach to build libraries of novel heterocycles, it was important to check whether racemisation occurred during the different alkylation steps performed in basic medium (presence of a strong base in DMF). As a model of the novel substituted dihydrotriazinones, the optical purity of **2a** was determined by ^{1}H NMR using europium tris-[3-(heptafluoropropylhydroxymethylene-(+)-camphorate] as the chiral lanthanide shift reagent (LSR)[9]. The efficacy of the method was first tested with a mixture of racemates ((*R*,*S*)-**2a**). After addition of $Eu(hfc)_3$ ([$Eu(hfc)_3$]/[substrate]=0.5), the signals of the N1-methyl group (s, 3.39 ppm) and C5-methyl group (d, 1.48 ppm, J=7 Hz) were fully resolved into two diastereomeric singlets (6.38 and 6.48 ppm) and two diastereomeric doublets (3.76 and 3.88 ppm, J=9 Hz), respectively. No trace of such splitting signals were found for (*S*)-**2a** prepared in our conditions, even at higher concentrations of $Eu(hfc)_3$. In a similar manner, the synthesised (*S*)-**6** was found optically pure by the LSR method. These results strongly support that in our experimental alkylation conditions, no racemisation occurred.

In conclusion, we have described here an easy and general method of preparation of mono (N1 or N4) and dialkyl (N1 and N4) chiral 4,5-dihydrotriazin-6-ones with control of regioselectivity (N1 versus N4) and retention of optical activity. These works involved alanine for building substituted triazinones,

but could be extended to other α-aminoacids (Phe, see Scheme 3, entries 2 and 6) and therefore will be useful to prepare original libraries of peptidomimetics.[10]

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6. Preparation of **2a**: 150 mg (0.8 mmol) of **1a** in dry DMF (5 ml), under nitrogen atmosphere was cooled at 0°C. Methyl iodide (135 mg, 0.95 mmol) and a dispersion of sodium hydride in mineral oil (w/w 60%, 38 mg, 0.95 mmol) were added successively to the mixture, which was kept at 10°C for 4 h. The mixture was diluted with 50 ml of water, extracted with ethyl acetate. The organic layer was evaporated in vacuo, and the residue was chromatographed on silica gel (hexane:ethyl acetate, 1:1) to provide 90 mg (55%) of a white solid, mp 108–110°C. ^{1}H NMR (300 MHz): 1.49 (d, 3H, $J_{CH–CH_3}$=7 Hz, CH-C*H*$_3$), 3.39 (s, 3H, N-C*H*$_3$), 4.21 (qd, 1H, $J_{CH–CH_3}$=7 Hz, $J_{CH–NH}$=1 Hz, -C*H*), 5.10–5.20 (m, 1H, N*H*), 7.40–7.50 (m, 3H, H arom), 7.60–7.75 (m, 2H, H arom).
7. Authentic samples of **2c** and **5c** were also prepared by unambiguous synthetic methods, as introduced previously,[3,4] and compared with our reaction products in order to ascertain the structure of different regioisomers.
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