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SELECTIVE ACYLATIONS OF AMINOPHENOLS AND HYDROXYALKYLPHENOLS WITH 1-ACETYL-v-TRIAZOLO/4,5-b/PYRIDINE

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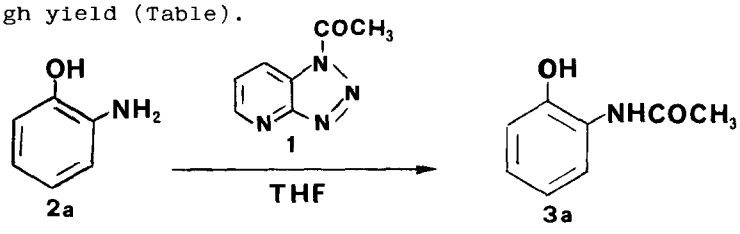
Abstract: The title triazolide serves as a convenient reagent for higly chemoselective acetylations of aminophenols and hydroxyalkylphenols.

The constant interest toward new acylating agents[1], and our recent results on the selective N-protection of hydroxyamino esters[2] with 1-alkoxycarbonyl- and 1-acyl-v-triazolo/4,5-b/pyridines, prompted us to extend the use of 1-acetyl-v-triazolo/4,5-b/pyridine (1)[2] to acetylations of aminophenols, hydroxyalkylphenols, and diols.

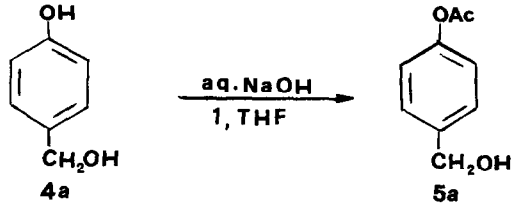
In the case of aminophenols (2a-c) the procedure is as follows. The mixture of the substrate (e. g. 2a) (0.5 mmol) and the triazolide 1 (0.5 mmol) in tetrahydrofuran (THF) (2 ml) was stirred at room temperature for 1 hour. Evaporation to dryness was followed by column chromatography on silica (1:50). Elution with dichloromethane-acetic acid (95:5 and 9:1) afforded pure N-acetyl derivative[3] (e. g. 3a) in high yield (Table).



As also previously observed[2], the hydroxyl function was unaffected in absence of basic catalysis.

On other hand selective acetylation of phenolic group of hydroxyalkylphenols (4a-e)[4] was performed by adding 1 (0.5 mmol), dissolved in THF (2 ml), to a solution of the substrate (e. g. 4a) (0.5 mmol) in 1N sodium hydroxide (0.5 ml). After stirring at room temperature for half an hour, 2N hydrochloric acid (2 ml) and ethyl ether (in excess) were added. The organic layers were washed with water, dried and evaporated under vacuum. Chromatography of the residue[5] on sil-

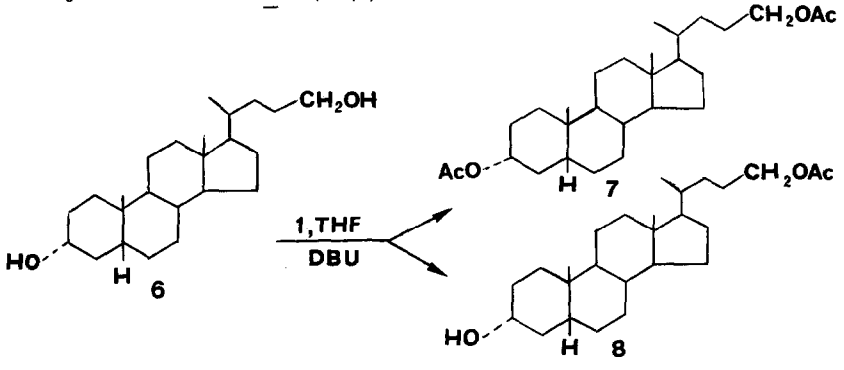
ica column[6] (1:50) [dichloromethane and dichloromethane-ether (9:1) as eluants] afforded pure phenolic acetate[3] (e. g. 5a) in good yield (Table).



The selectivity which can be achieved with our simple procedure is quite remarkable, even better than that exhibited by previous methods.

Mukaiyama and coworkers[1b] reported that acylation of 4a with 2,2'-bipyridyl-6-yl acetate proceeded smoothly (71% of phenyl ester) only in presence of cesium fluoride, while the procedure of Orazi[1a] for the esterification of a phenolic group in presence of a primary or secondary alcohol required more severe conditions.

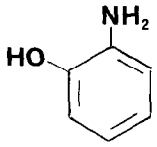
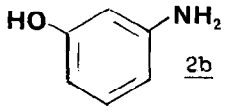
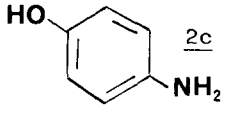
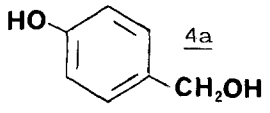
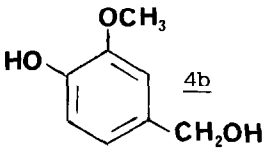
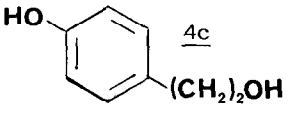
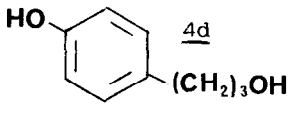
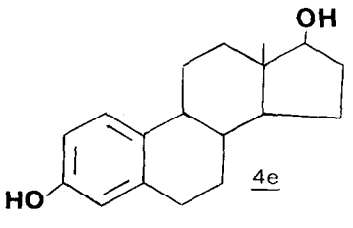
However only a moderate selectivity was observed when the application of the title triazolide was extended to acetylation of diols. Thus treatment of a THF (2 ml) solution of lithocholanyl alcohol (6) (0.5 mmol), containing 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.5 mmol) with 1 (0.5 mmol) gave[7] the diacetate 7[3] (14%) and primary monoacetate 8[3] (62%).



The following product[3] distribution was instead obtained after an analogous experiment carried out on 1-phenyl-1,2-ethanediol: diacetate (19%), primary monoacetate (37%), secondary monoacetate (8.3%).

It would not be unfair to point out that the activation of the phenolic group of a hydroxyalkylphenol as phenoxide ion, followed by the addition of 1, permits the nearly exclusive formation of a phenolic monoacetate. In this connection the acetylation of 17β-estradiol with 1 in presence of DBU, performed under the conditions adopted for the above diols, afforded a mixture of diacetate (10%) and of 3-acetate (64%). Finally a lower selectivity (diacetate 22%, phenolic

Table

Substrate	Monoacetyl derivative	Isolated yield (%)
 2a	N-acetyl derivative 3a	93
 2b	" 3b	100
 2c	" 3c	95
 4a	Phenyl ester 5a	80
 4b	" 5b	89
 4c	" 5c	90
 4d	" 5d	88
 4e	" 5e	98

monoacetate 36%) was observed after an analogous treatment of tyrosol (4c).

References and Notes

1. See for example: a) O. O. Orazi, R. A. Corral, and J. Zinczuk, Rev. Latinoamer. Quim., 9, 211 (1978); b) T. Mukaiyama, F.-C. Pai, M. Onaka, and K. Narasaka, Chem. Lett., 563 (1980); c) A. Saito and B. Shimizu, Bull. Chem. Soc. Jpn., 56, 2974 (1983); d) S. Kim, J. I. Lee, and K. Y. Yi, Bull. Chem. Soc. Jpn., 58, 3570 (1985); e) T. Kunieda, T. Mori, T. Higuchi, and M. Hirobe, Tetrahedron Lett., 1977 (1985) and references reported.
2. I. Torrini, G. Pagani Zecchini, F. Agrosì, and M. Paglialunga Paradisi, J. Heterocyclic Chem., in press.
3. The spectroscopic data (IR, ^{1}H-NMR) of all compounds were in agreement with the proposed structure and with literature data, when reported. Except for acetyl derivatives 5d and 8, the remaining products are known. Compound 5d (oil) had: IR (neat) 3389, 1757, 1196 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.87 (2H, m, CH_2-CH_2-CH_2), 2.25 (3H, s, OCOMe), 2.67 (2H, m, CH_2-Ar), 3.67 (2H, t, J=6.5 Hz, CH_2-OH), 7.00 (2H, m, AA' of Ar), 7.21 (2H, m, BB' of Ar). Microanalysis found: C, 68.09; H, 7.17. $C_{11}H_{14}O_3$ requires: C, 68.02; H, 7.26. Compound 8 had: mp 73-74° (from n-hexane), $[\alpha]_D^{20}$ +29° (c,1 in $CHCl_3$); IR (KBr) 3314, 1745, 1236 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.65 (3H, s, 13-Me), 0.92 [6H, m, 10-Me (s) superimposed on 20-Me (d)], 2.03 (3H, s, OCOMe), 3.64 (1H, m, 3ß-H), 4.05 (2H, apparent t, CH_2OCO). Microanalysis found: C, 76.95; H, 10.90. $C_{26}H_{44}O_3$ requires: C, 77.17; H, 10.96.
4. In the case of 4e, a solution of 1 (0.75 mmol) in THF (1.5 ml) was added to the steroid (0.5 mmol) dissolved in a mixture of 1N NaOH (0.5 ml) and THF (0.5 ml). After stirring at room temperature for 1 hour, work up and purification of 5e on silica were conducted as detailed for the other hydroxyalkylphenols.
5. Traces of alkyl esters were detected by ^{1}H-NMR preliminary analysis of the reaction residues arising from 4a-d.
6. Compound 5b was purified on preparative layer chromatography [Merck F_{254} silica gel; dichloromethane-methanol (95:5) as eluant].
7. The mixture was stirred at room temperature for 1 hour. Work up as described for 4a-e and chromatography on silica (1:30) (dichloromethane as eluant) afforded 7 and 8.

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