Unusual Detritylation of Tritylated Tetrazole in Sartan Molecules

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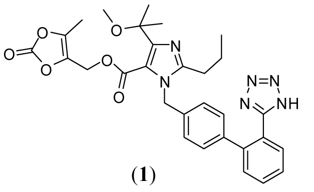
Tritylated tetrazole of 2a underwent unusual detritylation under basic reaction condition during the synthesis of methyl ether of olmesartan medoxomil 1. The unusual detritylation was found to be a common feature in the case of all tetrazole containing Sartan molecules (3—7).

Key words tritylamine; deprotection; detritylation; sartan molecule; tetrazole

Triphenylmethyl (Trityl) and related groups have been used extensively for *N*- and *O*-protection, where detritylation is accomplished employing acidic conditions, either with protonic acids[1] (*e.g.*, hydrochloric acid, acetic acid, CF_3COOH) or lewis acids[2] (*e.g.*, $ZnBr_2$, diisopropyl aluminium chloride, $Yb(OTf)_3$). Other methods reported for removal of trityl groups involve reductive protocols (*e.g.*, Li powder and a catalytic amount of naphthalene).[3] Trityl protected alcohols and amines are reported to exhibit good stability under basic reaction conditions and this property is made use in the total synthesis of various natural products and oligonucleotides.

Sartans are a class of drugs that are effective in treating hypertension and heart failure. These drugs block the renin-angiotensin system and represent one of the most significant therapeutic interventions available for the treatment of hypertension.[4—6] There are about seven sartans in clinical practice, of which five of them possess a tetrazole moiety in their structure. The protection and deprotection of the N-atom of the tetrazole moiety becomes essential during the synthesis of these sartan drugs. Olmesartan medoxomil (**3**) is a newest addition to the family of sartan drugs.[7,8] The multigram synthesis of (**3**) is always accompanied by the formation of corresponding methyl ether (**1**) as an impurity. For impurity profiling of an active pharmaceutical ingredient (API) we have synthesized and characterized this potential impurity (**1**). During the synthesis, it was observed that the tritylated tetrazole unusually underwent detritylation under basic reaction condition.[9]



(**1**)

In this communication, we have generalized this unusual detritylation under basic condition as a common feature in the case of tetrazole containing sartan molecules (**3**—**7**).

Results and Discussion

The tetrazole was protected with trityl group during the synthesis of **1** while the other protecting groups (*e.g.*, *N*-Boc) were unsuccessful. The synthetic route involves the hydrolysis of ethyl ester of **2a** under basic condition. On treatment of **2a** with saturated NaOH solution in aqueous methanol, unexpectedly hydrolysis of ester was accompanied by detritylation to **2** in 92% yield as shown in Chart 1.

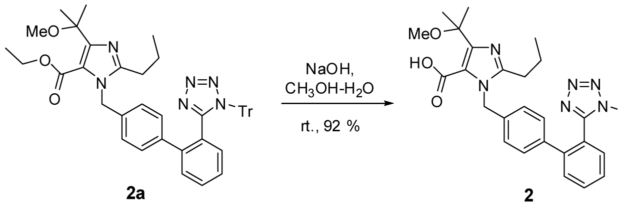
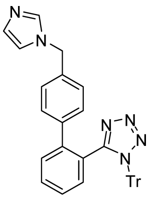


Chart 1

The unusual detritylation was interesting which prompted us to screen all the tetrazole containing sartan drugs. Accordingly, olmesartan medoxomil (**3**) was tritylated by the usual method and the tritylated olmesartan medoxomil (**3a**) was subjected to similar reaction condition as indicated in Chart 1. As expected, detritylation was effected forming **3** in 90% yield along with little hydrolysed product. In a similar way tritylated losartan (**4a**), valsartan (**5a**), candesartan (**6a**) and irbesartan (**7a**) were synthesized and subjected to deprotection using aqueous NaOH as shown in Chart 2. The results obtained are shown in Table 1.

The reaction times were around 2—3 h and the products were isolated without any side reactions in 84—90% yield.

Heterocyclic tritylamines other than sartan molecules were examined under same reaction condition to have a better insight on detritylation reaction. Simple tritylated pyrazole, imidazole and imidazole derivative **8** were found to be stable under basic reaction condition both at ambient temperature and also at reflux temperature. No detritylation however was observed in all the cases.



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Conclusion

An unusual *N*-detritylation in sartan molecules under basic condition was identified and explored. This can be regarded as an exclusive method of detritylation for sartan molecules and not for other heterocyclic compounds. This should be a

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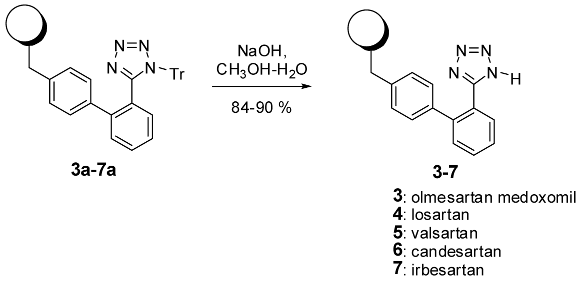

3: olmesartan medoxomil
4: losartan
5: valsartan
6: candesartan
7: irbesartan

Chart 2

useful addition to synthetic methodology and valuable information to the process chemistry for multigram scale synthesis of sartan molecules.

Experimental

General Experimental Procedure for the Detritylation of Sartan Molecules To a solution of **3a** (1.0 g, 1.25 mmol) in methanol (10 ml) was slowly added a saturated solution of sodium hydroxide (0.4 g, 10 mmol) at room temperature and the mixture was allowed to stir for 12 h. The completion of the reaction was monitored by TLC and the solvents were removed under reduced pressure. The residue is dissolved in water (6 ml) and washed twice with ethyl acetate (2×10 ml). The aqueous layer was cooled to 5—10 °C, acidified to pH 3—4 with dilute hydrochloric acid and extracted with ethyl acetate (2×10 ml). The organic layer was separated, dried over anhydrous sodium sulphate, filtered and the solvent was evaporated *in vacuo* to give **3** in 90% yield.

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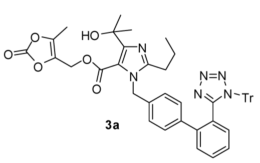
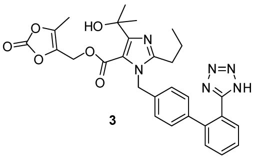
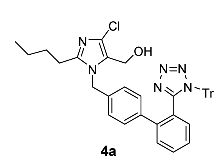
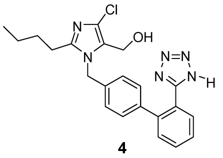
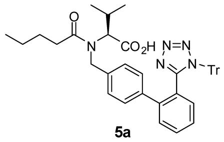
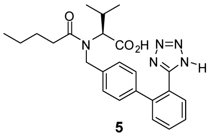
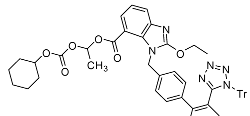
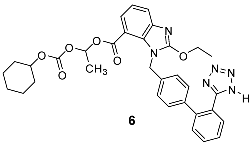
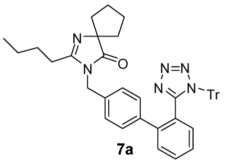
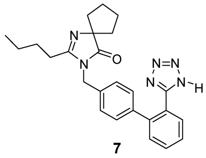
Table 1

Entry	Reactant	Product	Yield (%)
1	 **3a**	 **3**	90
2	 **4a**	 **4**	87
3	 **5a**	 **5**	84
4	 **6a**	 **6**	86
5	 **7a**	 **7**	87

References and Notes

1) Takatani M., Nakama T., Kubo K., Manabe S., Nakahara Y., Ito Y., NakaharaY., *Glycoconjugate J.*, **17**, 361—375 (2000).
2) Borkow G., Vijayabaskar V., A. Lapidot A., U.S. Patent 10831224 (2007).
3) Ma M., Zhang X., Peng L., Wang J., *Tetrahedron Lett.*, **48**, 1095—1097 (2007).
4) Whittaker A., *Br. J. Cardiol.*, **12**, 125—129 (2005).
5) Elliot H. L., *J. Hypertens.*, **12**, 271—274 (1998).
6) Burnier M., Brunner H. R., *J. Am. Soc. Nephrol.*, **10**, S278—S282 (1999).
7) Birkenhager W. H., de Leeuw P. W., *J. Hypertens.*, **17**, 873—881 (1999).
8) Ball K. J., Williams P. A., Stumpe K. O., *J. Hypertens.*, **19**, S49—S56 (2001).
9) Pati H. N., Lahiri S., Rameshkumar S., Vijaya Bhaskar V., Boobalan R., Hiriyanna S. G., Bose P., *J. Heterocycl. Chem.*, (2008) (in press).