ORGANIC LETTERS

2003
Vol. 5, No. 7
987−989

Activation of Glycoyl Trihaloacetimidates with Acid-Washed Molecular Sieves in the Glycosidation Reaction

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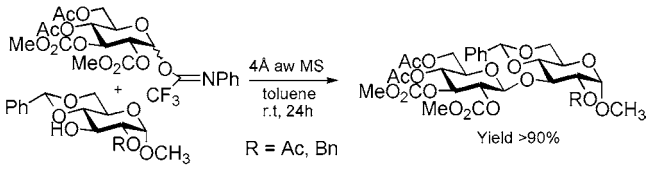
Received November 26, 2002

ABSTRACT



Commercially available 4 Å acid washed molecular sieves (4 Å AW 300 MS) are efficient activators of glycosyl trichloro- and *N*-phenyltrifluoroacetimidates. These promoters allow glycosidation of primary and secondary saccharidic acceptors to be performed in high yield, under very mild conditions and by an experimentally simple procedure. In addition, the recyclability of such promoters also has been demonstrated.

In the course of our recent investigations aimed at developing novel moisture-stable activators of glycosyl trichloro-[1] and *N*-phenyltrifluoroacetimidates,[2] we observed with two different systems, iodine/triethylsilane[3] and ytterbium triflate,[4] respectively, the beneficial effect of the use of 4 Å acid-washed molecular sieves (AW 300 MS) in place of ordinary molecular sieves. As a matter of fact, in the case of the first system, the use of these drying reagents allowed glycosidations to be completed in shorter times at room temperature, while with the lanthanide promoter, reactions could be effected at much lower temperatures and with a higher yield than previously reported,[5] especially with disarmed[6] donors.

In both cases, we postulated that ordinary molecular sieves could interfere with glycosidation due to their ability to act as proton scavengers. In the case of ytterbium triflate activation, glycosidations with the disarmed trifluoroacetimidate donor **1** were efficiently promoted at room temperature with AW 300 MS rather than at 60 °C with ordinary molecular sieves.[4] This led us to investigate the viable use of acid-washed molecular sieves as promoters as well as drying agents. As a matter of fact, we found that only acid-washed molecular sieves 4 Å AW 300 MS could promote the coupling between donor **1** (1.3 equiv) and acceptor **5** (1 equiv) (Table 1, entry 1). However, to achieve good yields within a few hours a higher temperature was required than when using $Yb(OTf)_3$ and AW 300 MS (70 °C instead of room temperature).[4]

Acid-washed molecular sieves were also found to activate disarmed trichloroacetimidate donors **2**, **3**, and **4** efficiently, and the expected[4,7] higher reactivity of trichloro- vs. *N*-phenyltrifluoroacetimidate donors was evidenced by the

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10.1021/ol027353i CCC: $25.00
Published on Web 03/11/2003

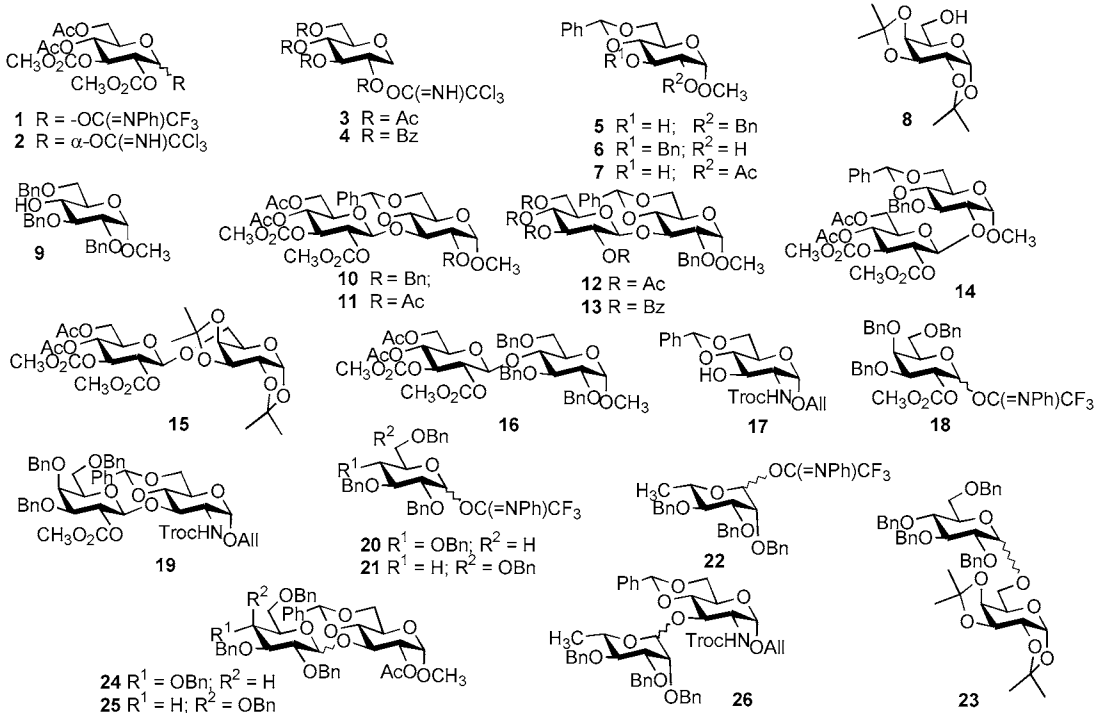

Figure 1. Compounds **1**−**26**.

lower temperatures required for glycosidations to be completed in short times (entries 3−5). Interestingly, use of the more unusual 2-*O*-methoxycarbonylated donor **2** yielded better results than with the usual peracetylated and benzoylated donors **3** and **4**. An analogous behavior had been previously observed in the investigations on the iodine/triethylsilane promoter.[3]

This mild activation system proved also effective with other secondary and primary acceptors (entries 6, 8, 9, and 10). Entries 7 and 8 show the feasible activation of the trifluoro disarmed donor **1** even at room temperature, although much longer reaction times are required for the completion of glycosidations. However, under these conditions remarkably high yields were registered. Interestingly,

Table 1. Glycosidation of Saccharidic Acceptors (1 equiv) with Trichloro- and *N*-Phenyltrifluoroacetimidate Donors (1.3−1.4 equiv) under the Activation of 4 Å AW 300 Molecular Sieves

entry	donor	acceptor	product	solvent	temp, °C	time, h	yield[b]
1	**1**	**5**	**10**	toluene	70	2	88
2[a]	**1**	**5**	no reaction	toluene	70	7	-
3	**2**	**5**	**10**	toluene	rt	6	85
4	**3**	**5**	**12**	toluene	rt	2	68
5	**4**	**5**	**13**	toluene	40	3	65
6	**1**	**6**	**14**	toluene	75	4	84
7	**1**	**5**	**10**	toluene	rt	24	91
8	**1**	**7**	**11**	toluene	rt	24	95
9	**1**	**8**	**15**	toluene	60	4	71
10	**1**	**9**	**16**	toluene	60−70	3	82
11	**18**	**17**	**19**	dichloroethane	rt	48	68
12	**20**	**8**	**23**	toluene	rt	2	89 (0.8)
13[c]	**20**	**8**	**23**	toluene	−10	1	90 (1.7)
14	**20**	**7**	**24**	toluene	rt	2	75 (1.7)
15[c]	**20**	**7**	**24**	toluene	−10	1	81 (1.6)
16	**21**	**7**	**25**	toluene	rt	3	73 (1.1)
17[d]	**22**	**17**	**26**	dichloroethane	−10 to rt	6	78 (1.7)

[a] Ordinary molecular sieves were used. Both the donor and the acceptor were recovered unaltered. [b] Isolated yields (α/β ratios). [c] TMSOTf (0.05 equiv) was used as the promoter. [d] 2 equiv of the donor were used.

the glycosidation outcome was strongly influenced by the nature of the solvent, the best results being obtained with toluene or dichloroethane (experiments in more polar solvents such as dioxane or acetonitrile led to low yields). These observations confirm that $Yb(OTf)_3$ is the actual promoter in the glycosidation conditions we recently reported,[4] where ether and nitrile solvents were used in the activation of both armed and disarmed donors. Under these latter conditions the activating power of AW 300 MS is negligible and they essentially act as drying agents devoid of proton scavenging properties.

The proposed protocol was also successfully tested in the srereocontrolled synthesis of the disaccharide **19**, performed in a scale of hundreds of milligrams (entry 11).

While the stereoselectivity of glycosidations with disarmed donors was controlled by the neighboring participation of their 2-*O*-protecting groups, in the case of armed donors the stereoselectivity was not satisfying, although equally good yields could be achieved with three different perbenzylated *N*-phenyltrifluoroacetimidates as shown in entries 12, 14, 16, and 17. Attempts to overcome this problem by the use of solvents such as acetonitrile or dioxane, able to direct the stereoselectivity of the glycosidation in the absence of a participating group in the donor,[4,8,9] resulted in low yields, similarly to disarmed donors. For comparison purposes, glycosidations in entries 12 and 14, involving an armed glucosyl donor with a primary and a secondary acceptor, respectively, were also performed in the same solvent (toluene) under the activation of the standard TMSOTf promoter (entries 13 and 15). In the case of the secondary acceptor, comparable α:β ratios were observed (entries 14 and 15), while with the primary acceptor a pronounced difference in the stereoselectivity was found (entries 12 and 13). However, in no case was a high control of stereoselectivity attained.

Some experiments have been performed to clarify the reasons for the efficiency of the commercial AW 300 MS as promoters. First, ordinary 4 Å molecular sieves were found totally ineffective in promoting glycosidation (entry 2),[10] both coupling partners being quantitatively recovered. In the second place, the reactions were reproducible when acid-washed molecular sieves from two different commercial batches were used. Furthermore, we have considered the presence of residual traces of acids (possibly introduced in the acid-washing procedure) as the actual promoter. However, thorough washing of commercial AW 300 MS with distilled water prior to the drying procedure (overnight heating at 200 °C under vacuum) did not result in any loss in efficiency. These results suggest that the activation process occurs on the surface of the sieves, whose acidic sites could favor the approach of the activated donor and the acceptor.[11] Very interestingly, acid-washed molecular sieves turned out to be recoverable promoters. The coupling of entry 7 was performed three times with the same sieves. The yield of the second and third experiment was higher than 80% (^{1}H NMR).[12]

In conclusion, the activation procedure described here looks particularly attractive due to the noteworthy simplification of the experimental procedure,[13] the avoidance of more acidic promoters, and the mildness of the reaction conditions. Although this activation protocol implies higher reaction temperatures or longer reaction times than those with more common acidic promoters (including the recently reported lanthanide triflates), the resulting yields are often competitive. In addition, to the best of our knowledge this appears to be the first report on the use of recoverable activators for commonly used glycosyl imidate donors.

Acknowledgment. This work was supported by MIUR (Programmi di Ricerca di Interesse Nazionale 2001-2) and by a grant (to M.S.) from Università Federico II di Napoli (Progetto Giovani Ricercatori).

Supporting Information Available: ^{1}H and ^{13}C NMR data for all disaccharides. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Typical procedure: donor **1** (23.0 mg, 0.042 mmol) and acceptor **5** (12.1 mg, 0.032 mmol) were dissolved under argon in toluene (1 mL) in the presence of freshly activated acid-washed 4 Å molecular sieves AW MS 300 (600 mg, purchased from Fluka, $^1/_8$ in. rods). After being stirred for 30 min at room temperature, the mixture was heated at 70 °C for 2 h, and then a few drops of triethylamine was added. The mixture was filtered and concentrated and the residue chromatographed on a short silica gel column eluted with 7:3 hexane/ethyl acetate to afford disaccharide **10** (21.7 mg, yield 91%). The procedure was upscaled for the synthesis of **19**: acceptor **17** (228 mg, 0.48 mmol) and donor **18** (426 mg, 0.62 mmol) were azeotroped three times with anhydrous toluene. The mixture was then dissolved at 0 °C (ice bath) under argon in anhydrous dichloroethane (10 mL) in the presence of 4 Å AW 300 MS (2.4 g). After 30 min the ice bath was removed, and the mixture was left under stirring for 24 h at room temperature. An additional aliquot of AW MS (2.4 g) was then added. After a further 24 h, a few drops of triethylamine was added and the mixture was filtered and concentrated. Silica gel chromatography of the residue (eluent 85:15 hexane−AcOEt) yielded 312 mg (68%) of disaccharide **19**. The recovered sieves were dehydrated and reactivated by overnight heating at 200 °C under vacuum.