[1,2]-Wittig Rearrangement of (Benzyloxy)acetamides

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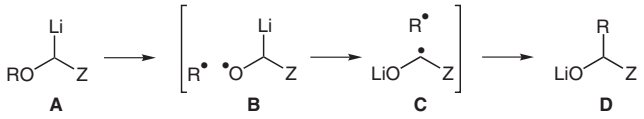
Abstract: [1,2]-Wittig rearrangement of (benzyloxy)acetamides can lead to substituted α-hydroxyamides in good yields and good diastereoselectivity.

Key words: [1,2]-Wittig rearrangement, amides, phase-transfer catalysis

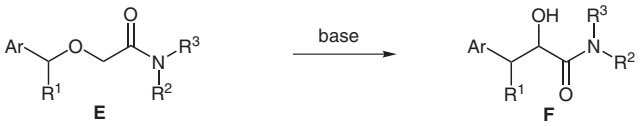
The [1,2]-Wittig rearrangement is the transformation of α-lithiated ethers of type **A** into lithium alkoxides of type **D** (Scheme 1).[1] This rearrangement has been reviewed many times[2] and due to intensive mechanistic studies since its discovery in 1942, it is now accepted that the rearrangement proceeds via an intramolecular radical dissociation–recombination process through species **B** and **C**.[3] During the reaction, the stereochemical information is essentially retained with retention of configuration at the migrating carbon and through inversion at the lithium-bearing terminus. Under chelated conditions, retention occurs at the two carbons.[4]

Applications of the [1,2]-Wittig rearrangement in synthesis have been limited because of the low yields in the rearranged product and the harsh conditions required.[5] [1,2]-Wittig rearrangements of substituted ethers of type **A** in which Z is an electron-withdrawing group, such as a ketone,[6] ester,[7] cyano,[8] imidazolium, or benzylimidazolium[9] group, have been reported. Furthermore, the rearrangements of (diarylmethoxy)acetamides,[10] α-alkoxycarbamides,[11] and α-benzyloxylactams[12] have been studied. We would like to report herein the [1,2]-Wittig rearrangement of (benzyloxy)acetamides of type **E** in order to have access to substituted α-hydroxyamides of type **F** (Scheme 2).

The synthesis of (benzyloxy)acetamides has been achieved by etherification of benzylic alcohols **1a–j** (1.1 equiv) by bromoacetylpyrrolidine (**2**, 1 equiv) under phase-transfer conditions using tetra-*n*-butylammonium hydrogenosulfate (20 mol%) in a heterogeneous mixture of 35% aqueous NaOH solution and toluene in a 1:1 ratio, at room temperature.[13,14] The corresponding ethers **3a–j** were obtained in 59–79% yield. The results are reported in Table 1.

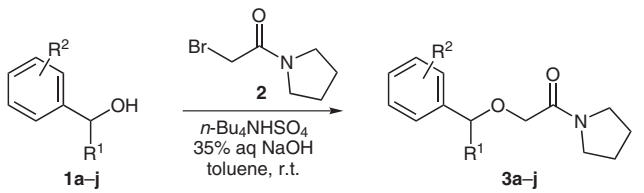


Scheme 1



Scheme 2

Table 1 Synthesis of (Benzyloxy)acetamides **3a–j**



Entry	R^1	R^2	3	Yield (%)
1	Me	H	**3a**	75
2	Me	4-Me	**3b**	73
3	Me	4-OMe	**3c**	69
4	Me	3,4-$(OMe)_2$	**3d**	65
5	Me	4-NO_2	**3e**	68
6	$CH_2CH{=}CH_2$	H	**3f**	79
7	$(CH_2)_2CH{=}CH_2$	H	**3g**	74
8	*n*-Bu	H	**3h**	59
9	cyclopropyl	H	**3i**	74
10	Ph	H	**3j**	65

(Benzyloxy)acetamides **3a–k** were deprotonated by treatment with LiHMDS (2.5 equiv) at –30 °C, and by raising up the temperature to 0 °C, the subsequent [1,2]-Wittig rearrangement of the resulting amide enolate proceeded smoothly to produce hydroxyamides **4a–k** in modest to good yields (35-67%), with modest to good diastereoselectivity in favor of the *syn* diastereomer (2.1:1 to 5.9:1, Table 2).[15] It is worth noting that the R^2 substituent present on the aromatic ring has no influence on the dia-

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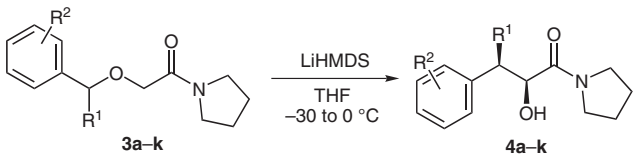
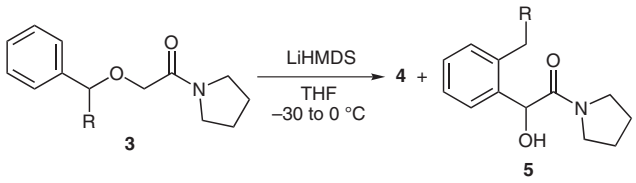
Table 2 Deprotonation of (Benzyloxy)acetamides **3a–k**

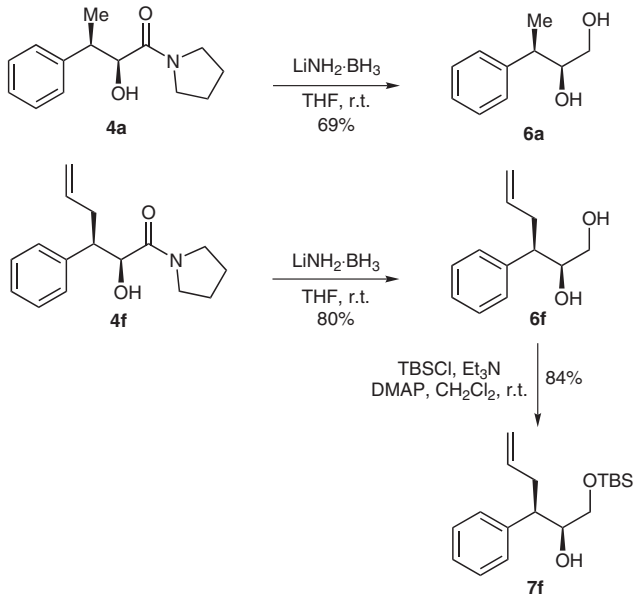


Entry	R^1	R^2	4	*syn*/*anti*	Yield (%)
1	Me	H	**4a**	2.7:1	63
2	Me	4-Me	**4b**	2.1:1	56
3	Me	4-OMe	**4c**	3:1	64
4	Me	3,4-$(OMe)_2$	**4d**	2.8:1	35
5	Me	4-NO_2		complex mixture of products	
6	$CH_2CH{=}CH_2$	H	**4f**	4.3:1	51
7	$(CH_2)_2CH{=}CH_2$	H	**4g**	5.2:1	63
8	*n*-Bu	H	**4h**	5.9:1	46
9	cyclopropyl	H	**4i**	5.7:1	62
10	Ph	H	**4j**	–	67
11	$(CH_2)_2OTBS$	H	**4k**	3:1	46

Table 3 Competitive *ortho*-[2,3]-Wittig Rearrangement



Entry	R	Yield of **4** (%)	Yield of **5** (%)
1	Me	63	15
2	$CH_2CH{=}CH_2$	51	26
3	$(CH_2)_2OTBS$	46	24



Scheme 3

stereoselectivity of the [1,2]-Wittig rearrangement. However, the presence of an aromatic nitro group (amide **3e**, Table 2, entry 5) led to a complex mixture of products. Furthermore, the diastereomeric ratio increased with the size of the R^1 group at the benzylic position (**4a–d** vs **4f–k**, Table 2).

The observed diastereomeric ratio for the products obtained after the rearrangement is the result of the rearrangement itself, as the treatment of *syn* compounds **4** with LiHMDS under the same conditions did not produce any modification of the diastereomeric ratio. The rearrangement proceeds via a diradical intermediate, and the recombination step is diastereoselective.[5b,e,11,16]

The modest yields obtained may be due to a competitive *ortho*-[2,3]-Wittig rearrangement, that led to compounds **5** in 15–25% yields (Table 3). The *ortho*-[2,3]-Wittig rearrangement has already been described as a side reaction of the [1,2]-Wittig rearrangement of (benzyloxy)ethers.[12,17] It could proceed via a concerted anionic [2,3]-rearrangement or via the delocalization of the benzylic radical into the aromatic ring before the recombination step.

The relative *syn* stereochemistry of the major isomers **4a** and **4f**, obtained, respectively, from the [1,2]-Wittig rearrangement of compounds **3a** and **3f**, was assigned after their conversion into known diols (Scheme 3). Compounds *syn*-**4a** and *syn*-**4f** were converted into 1,2-diols **6a** and **6f**, respectively, by treatment with $LiNH_2{\cdot}BH_3$.[18] Compound **6f** was transformed into the corresponding monosilylated ether **7f**, as this latter product was described in the literature.[19] By comparison of the NMR data of **6a** and **7f** with those described in the literature, the *syn* relative stereochemistry between the hydroxy and alkyl groups was attributed.[19,20]

Similarities between the different hydroxyamides **4** were observed by analysis of the ^{1}H NMR data in term of chemical shift,[21] and coupling constants between the benzylic proton and the proton at the α-position of the amide (major diastereomer $^3J = 4.6$–6.4 Hz, minor diastereomer $^3J = 3.1$–4.7 Hz, with $^3J_{major} > {}^3J_{minor}$).[22] On the basis of the chemical correlations obtained for compounds **6a** and **7f**, as well as the ^{1}H NMR observations, a *syn* stereochemistry for all the major isomers coming from the [1,2]-Wittig rearrangement, was assigned by analogy.

In conclusion, we have succeeded in the development of [1,2]-Wittig rearrangement of (benzyloxy)acetamides, which can produce substituted α-hydroxyamides with good diastereomeric ratio when a sterically hindered substituent is present at the benzylic position.

Acknowledgment

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(13) Barbazanges, M.; Meyer, C.; Cossy, J. *Org. Lett.* **2007**, *9*, 3245.
(14) **Representative Procedure for the Preparation of (Benzyloxy)acetamides 3**
To a solution of alcohol **1** (1.1 mmol) and bromoacetylpyrrolidine (**2**, 1 mmol) in toluene (15 mL), at r.t., was added *n*-Bu_4NHSO_4 (0.2 mmol) and a 35% aq NaOH solution (15 mL). The mixture was then stirred vigorously at r.t., and the reaction was monitored by TLC. After 3–4 h, H_2O (20 mL) and Et_2O (20 mL) were added at 0 °C. The aqueous layer was extracted with Et_2O (5 × 30 mL), and the combined organic layers were washed with sat. aq NH_4Cl soln (50 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified on SiO_2 (PE–EtOAc) to afford(benzyloxy)acetamide **3**. Amide **3k** with $R^1 = (CH_2)_2OTBS$ (Table 2, entry 11) was obtained from amide **3f** (Table 1, entry 6) by using the following sequence: 1) O_3, MeOH, –78 °C then Ph_3P, CH_2Cl_2, –78 °C to r.t.; 2) $NaBH_4$, EtOH, 0 °C; 3) TBSCl, Et_3N, DMAP, CH_2Cl_2, 0 °C (60% over 3 steps).
(15) **Representative Procedure for the [1,2]-Wittig Rearrangement of (Benzyloxy)acetamides 3**
To a solution of(benzyloxy)acetamide **3** (0.2 mmol) in THF (3 mL), at –30 °C, was added dropwise a 1 M solution of LiHMDS in THF (2.5 equiv). The reaction mixture was then warmed to 0 °C over 2–3 h, before being hydrolyzed with sat. aq NH_4Cl soln (10 mL). The aqueous layer was then extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified on SiO_2 (PE–EtOAc) to afford α-hydroxyamide **4**.
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(21) Similarities in term of chemical shift between the different hydroxyamides **4** were particularly relevant for the proton at the α-position of the amide, for which $\delta_{major} < \delta_{minor}$ in all cases.
(22) In all cases $^3J_{major} > {}^3J_{minor}$ except for hydroxyamide **4i** (Table 2, entry 9). For compound **4i**, $^3J_{major} = 4.3$ Hz and $^3J_{minor} = 5.0$ Hz. Therefore, the *syn* stereochemistry remained ambiguous in this latter case.