Organic Syntheses

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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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1,4-FUNCTIONALIZATION OF 1,3-DIENES VIA PALLADIUM-CATALYZED CHLOROACETOXYLATION AND ALLYLIC AMINATION: 1-ACETOXY-4-DIETHYLAMINO-2-BUTENE AND 1-ACETOXY-4-BENZYLAMINO-2-BUTENE

[2-Buten-1-ol, 4-(diethylamino)-, acetate ester and 2-Buten-1-ol, 4-[(phenylmethyl) amino]-, acetate ester]
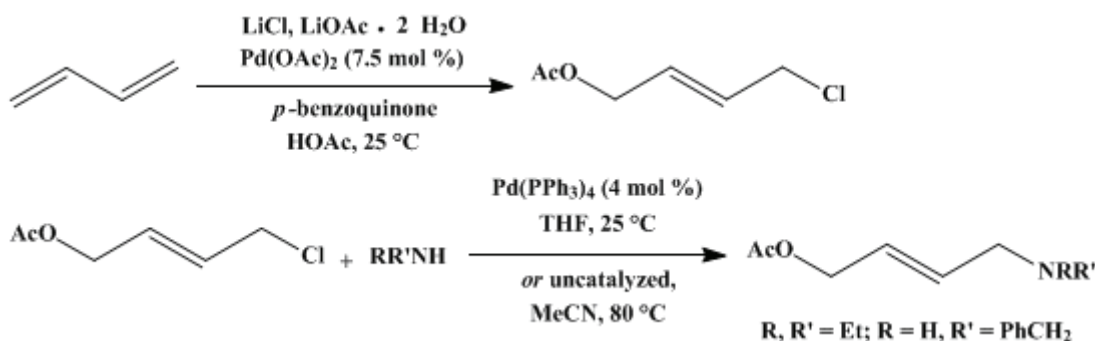
Submitted by J. E. Nyström, T. Rein, and J. E. Bäckvall[1].
Checked by Marvin M. Hansen and Clayton H. Heathcock.

1. Procedure

A. *1-Acetoxy-4-chloro-2-butene.* In a 2-L, two-necked, round-bottomed flask equipped with a 5-cm egg-shaped magnetic stirring bar and a pressure-reducing outlet (Note 1) is placed 800 mL of pentane (Note 2). The flask is cooled with an ice bath and 5.4 g (0.1 mol) of butadiene is dissolved with stirring (0–5°C) by addition through one of the inlets from a Fluka low-pressure bottle of butadiene (Note 3). The pressure-reducing outlet is removed and a freshly prepared solution of 1.68 g (7.5 mmol) of palladium acetate, Pd(OAc)₂, 8.4 g (0.2 mol) of lithium chloride, 20.4 g (0.2 mol) of lithium acetate dihydrate (LiOAc · 2H₂O), and 21.6 g (0.2 mol) of *p*-benzoquinone in 400 mL of acetic acid is added (Note 4). The cooling bath is removed and the two-phase system is stirred at a moderate rate (Note 5) at 25°C for 26 hr. A saturated sodium chloride solution (300 mL) is added and after the mixture is stirred for 5 min; it is filtered using a Büchner funnel with an intermediate paper filter using aspirator vacuum. The organic phase is separated and the aqueous phase is extracted with three 300-mL portions of pentane–ether (80 : 20). The combined organic phases are washed with two 75-mL portions of water, two 100-mL portions of saturated potassium carbonate solution, three 100-mL portions of 2 *M* sodium hydroxide solution, and finally with 50 mL of saturated sodium chloride solution. The organic phase is dried over anhydrous magnesium sulfate, filtered, and concentrated to a volume of 20–30 mL by distilling off the solvent at atmospheric pressure. The remaining solvent is removed with a rotary evaporator at aspirator vacuum to give 13–15 g of crude product, which is distilled (10 mm, 70–90°C) to yield 9.7–12.0 g (65–81%) of a light-yellow liquid consisting of 91% of 1-acetoxy-4-chloro-2-butene (*E/Z* = 90/10) and 9% of 4-acetoxy-3-chloro-1-butene. The chloroacetate is contaminated with approximately 1% of 5,8-dihydronaphthoquinone (Note 6).

Further purification is achieved by the following procedure. The chloroacetate from above is dissolved in 150 mL of ether. This solution is stirred together with a 10-mL aqueous solution saturated with sodium borohydride. The stirring is continued until the yellow color of the organic phase disappears (ca. 15 min). The organic phase is separated and washed with 5 mL of 2 *M* sodium hydroxide solution and 5 mL of a saturated sodium chloride solution, dried over magnesium sulfate, and concentrated by distilling off the solvent at atmospheric pressure. The solvent that remains is removed with a rotary evaporator to afford 9.5–10.5 g (64–70%) of chloroacetate, with the same composition as above, but which is now completely free from 5,8-dihydronaphthoquinone (Note 7).

B1. *1-Acetoxy-4-diethylamino-2-butene. Method 1.* In a 500-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, nitrogen-vacuum inlet, and a rubber septum, is placed 2.77 g (2.4 mmol) of tetrakis(triphenylphosphine)palladium, Pd(PPh$_3$)$_4$ (Note 8). The flask is closed, evacuated, and filled with nitrogen. This flushing procedure is repeated twice (Note 9). A solution of 8.91 g (0.06 mol) of the chloroacetate from Procedure A in 180 mL of dry tetrahydrofuran (Note 10) is added through the membrane with the aid of a 50-mL syringe. With the same syringe 21.9 g (0.30 mol) of diethylamine (Note 11) in 120 mL of dry tetrahydrofuran is added. The mixture is stirred at ambient temperature and the reaction is followed by gas chromatography. When the starting material has been consumed, which takes approximately 4 hr (Note 12), 600 mL of ice-cooled ether and 600 mL of ice-cooled saturated aqueous sodium carbonate solution are added and the mixture is shaken in a separatory funnel (Note 13). The aqueous phase is extracted with ether (2 × 300 mL).

The combined organic phases are washed with 50 mL of saturated potassium carbonate solution and dried over solid potassium carbonate. Evaporation with a rotary evaporator affords 13.7 g of crude product. The residue is put on a column (silica, 3 × 10 cm) and eluted with 600 mL of ether–pentane–triethylamine (47.5 : 47.5 : 5) (Note 14). The main fractions are collected to give 8.15 g (73%) of essentially pure *E*-1-acetoxy-4-diethylamino-2-butene (>94% *E*). No 1,2-isomer could be detected. The product is further purified by Kugelrohr distillation to afford 7.81–8.21 g (70–74%) (Note 15).

B2. *1-Acetoxy-4-benzylamino-2-butene. Method 2.* In a 250-mL, one-necked, round-bottomed flask are placed in order 8.91 g (0.06 mol) of the chloroacetate from Method A, 100 mL of acetonitrile, and 19.3 g (0.18 mol) of benzylamine (Note 6). The flask is equipped with a reflux condenser and the solution is refluxed for 2 hr using an oil bath at 100–110°C. The reaction mixture is cooled and 150 mL of ether and 100 mL of a saturated sodium carbonate solution are added. The mixture is shaken in a separatory funnel and the organic phase is collected. The aqueous phase is extracted with 50 mL of ether. The combined organic phases are dried over potassium carbonate. The solvent and excess benzylamine are removed by rotary evaporation and Kugelrohr distillation at 50°C (1 mm). Kugelrohr distillation of the crude product gives 9.1–9.9 g (70–76%) of 1-acetoxy-4-benzylamino-2-butene as a 90 : 10 mixture of the *E* and *Z* isomers (Note 17).

2. Notes

1. The pressure-reducing outlet can be a U-shaped tube filled with oil or a thick-walled rubber balloon.
2. Light petroleum, boiling point 40°C, can also be used.
3. The amount of butadiene added is determined by weighing the Fluka bottle and double-checked by weighing the reaction flask before and after addition. The checkers purchased butadiene from Matheson and measured it by condensation into a 25-mL flask cooled to −10°C. The cooled material was then transferred by cannula into the reaction vessel containing the pentane, cooled to 0–5°C.
4. *p*-Benzoquinone, 200 mol%, is needed for a rapid and efficient reaction.
5. A stirring rate of approximately 5 rps (revolutions per second) is used. The reaction tolerates a variation of 3–10 rps, which gives essentially the same result.
6. 5,8-Dihydronaphthoquinone is the oxidized Diels–Alder adduct between butadiene and benzoquinone.
7. The spectral properties are as follows: ^{1}H NMR (CDCl$_3$, 250 MHz) δ: 2.09 (s, 3 H), 4.06 (m, 2 H), 4.59 (m, 2 H), 5.90 (m, 2 H).
8. Tetrakis(triphenylphosphine)palladium, Pd(PPh$_3$)$_4$, is commercially available but is readily prepared according to [2] (or [3]). Palladium acetylacetonate, Pd(acac)$_2$, together with 4 PPh$_3$, can be used in place of Pd(PPh$_3$)$_4$ and gives essentially the same result.
9. A manifold system connected to a vacuum line and a nitrogen line is used.
10. Tetrahydrofuran is distilled under nitrogen from potassium benzophenone.
11. Commercial diethylamine (BDH) is used without further purification.
12. The rate of the reaction varies slightly depending on the quality of the catalyst.
13. The solution is kept cold to avoid hydrolysis of the acetoxy group.
14. The checkers observed that, on placing the crude product on the top of the silica gel column, the residual Pd(PPh$_3$)$_4$ precipitates. However, the presence of this solid residue does not interfere with the progress of the chromatography or affect the yield of product.
15. The spectral properties are as follows: ^{1}H NMR (CDCl$_3$, 250 MHz) δ: 1.03 (t, 6 H, *J* = 7.2), 2.07 (s,

3 H), 2.51 (q, 4 H, $J = 7.2$), 3.10 (br d, 2 H), 4.55 (br d, 2 H), 5.64–5.90 (m, 2 H).
16. Benzylamine (Fluka) is dried over NaOH and distilled over sodium. The three-fold excess of benzylamine is used to depress the dialkylation product.
17. The spectral properties are as follows: ^{1}H NMR (CDCl$_3$, 250 MHz) δ: 1.20–1.60 (br s, 1 H), 2.06 (s, 3 H), 3.28 (br d, 2 H, $J = 5.7$), 3.78 (s, 2 H), 4.55 (br d, 2 H, $J = 5.8$), 5.74 (dt, 1 H, $J = 15.5$, 5.8), 5.88 (dt, 1 H, $J = 15.7$, 5.7), 7.20–7.45 (m, 5 H).
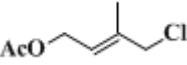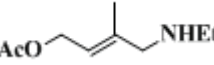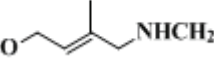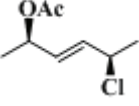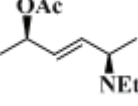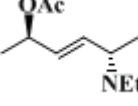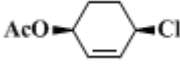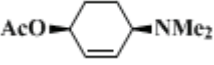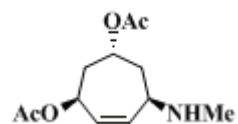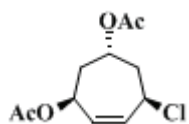
3. Discussion

The procedure reported here provides an efficient method for the preparation of 4-amino-2-alken-1-ol derivatives. It is based on the palladium-catalyzed 1,4-acetoxy-chlorination of 1,3-dienes[4,3] and palladium-catalyzed amination of allylic substrates.[5] Compared to other methods,[6] this method is more convenient and more general. It allows complete control of the 1,4-relative configuration when the carbons bearing nitrogen and oxygen are stereogenic. In these cases the chloride is replaced with *retention* according to Procedure B1 but with *inversion* according to Procedure B2.[3,7]

Procedure A is very effective for a range of acyclic and cyclic conjugated dienes.[4,3] The major side reaction in the chloroacetoxylation is Diels–Alder addition of *p*-benzoquinone to the diene. The purpose of the pentane phase is to ensure a low concentration of diene in the acetic acid phase, which represses the Diels–Alder reaction. The reaction can also be performed without the pentane phase with slow addition of the diene using a syringe pump.

Some representative examples of the amination reaction according to Procedure B are shown in Table I.

TABLE I

Chloroacetate[a]	Amine	Procedure	Aminoacetate	Yield(%)
	Et$_2$NH	B1 B2		87[b] 75
	EtNH$_2$	B2		89
	Me$_2$NH	B2		76
	PhCH$_2$NH$_2$	B2		89
	Et$_2$NH	B1		80
		B2		70
	Me$_2$NH	B1		95
		B2		93
	MeNH$_2$	B1		87

References and Notes

1. Department of Organic Chemistry, Royal Institute of Technology, S-100 44 Stockholm, Sweden.
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5. Genêt. J. P.; Balabane, M.; Bäckvall, J. E.; Nyström, J. E. *Tetrahedron Lett.* **1983**, *24*, 2745.
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

Palladium acetylacetonate

potassium benzophenone

potassium carbonate (584-08-7)

acetic acid (64-19-7)

ether (60-29-7)

acetonitrile (75-05-8)

sodium hydroxide,
NaOH (1310-73-2)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

oxygen (7782-44-7)

nitrogen (7727-37-9)

chloroacetate (79-11-8)

sodium (13966-32-0)

diethylamine (109-89-7)

Pentane (109-66-0)

benzoquinone,
p-benzoquinone (106-51-4)

magnesium sulfate (7487-88-9)

benzylamine (100-46-9)

butadiene (106-99-0)

Tetrahydrofuran (109-99-9)

Lithium chloride (7447-41-8)

triethylamine (121-44-8)

sodium borohydride (16940-66-2)

acetoxy

lithium acetate dihydrate (6108-17-4)

1-Acetoxy-4-diethylamino-2-butene,
2-Buten-1-ol, 4-(diethylamino)-, acetate ester (82736-47-8)

1-Acetoxy-4-benzylamino-2-butene,
2-Buten-1-ol, 4-[(phenylmethyl)amino]-, acetate ester (130892-14-7)

4-acetoxy-3-chloro-1-butene (96039-67-7)

5,8-dihydronaphthoquinone

palladium acetate (3375-31-3)

Tetrakis(triphenylphosphine)palladium (14221-01-3)

E-1-acetoxy-4-diethylamino-2-butene

1-Acetoxy-4-chloro-2-butene (34414-28-3)