Application of (2E,4E)-5-Bromo-2,4-Pentadienal in Palladium Catalyzed Cross-Coupling: Easy Access to (2E,4E)-2,4-Dienals

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Abstract: Palladium catalyzed cross-coupling reactions of (2E,4E)-5bromo-2,4-pentadienal **1** with organozinc reagents gives an easy access to the corresponding (2E,4E)-2,4-dienals. The improved preparation of all trans **1** by isomerization of its (2E,4Z) isomer is reported.

In the course of our studies about convergent synthesis of polyenic compounds,¹ we recently reported the preparation² of (2E,4E)-5-bromo-2,5-pentadienal **1**. We² and others³ have taken advantage of the carbonyl group's potential through Wittig, Grignard or oxidation reactions. In this paper, we report the use of **1** as a brominated vinylic entity in palladium catalyzed cross-coupling⁴ without any protection of the aldehydic function⁵ (Scheme 1). Their high efficiency in such processes, their easy access and low reactivity with aldehydes,⁶ led us to select the mild organozinc reagents for this purpose.



Scheme 1

Aldehyde **1** was treated in standard conditions⁷ with various organozinc species **2a-h**, easily prepared *in situ* from corresponding bromomagnesium-(**2a,c** and **f**) or lithium-reagents (**2b,d,e,g** and **h**) and zinc bromide, in the presence of catalytic amounts of tetrakis(triphenylphoshine)palladium in THF. Results are reported in the table.

Table. Preparation of dienals by palladium catalyzed cross-coupling

Entry	R	RZnBr	product	yield (%) ^a
1	<i>n</i> -C ₅ H ₁₁	2 a	3 a	70
2	<i>s</i> -Butyl	2 b	3 b	83
3	Ph	2 c	3 c	89
4	2-Furyl	2 d	3 d	80
5	2-Thienyl	2 e	3 e	55
6	CH ₂ =CH	2 f	3 f	53
7	<i>n</i> -C ₅ H ₁₁ -C≡C	2 g	3 g	86
8	Me ₃ Si-C≡C	2 h	3 h	87

a) isolated yields after flash chromatography calculated from 1

In all cases, rapid reactions occurred (TLC analysis) at room temperature with alkyl, aryl, vinyl or alkynyl zinc reagents and corresponding (2E,4E) dienals **3a-h** were isolated as single isomers. We never observed any addition of the organometallic species on the carbonyl group. Yields were generally good after flash chromatography purification.

Dienals **2a-f** were already described.^{8,9} However, recent literature in this area shows that there is still a need for pratical synthetic methods.^{1,8,9}

Acetylenic aldehydes 3g and 3h are new.^{10,11} They are potential precursors of 2,4,6-trienals by simple selective reduction of the triple bond. Moreover, the synthesis of alkyne 3h, bearing the labile trimethylsilyl group,¹² shows that functionalized dienic aldehydes are in the reach of this methodology.

It is noteworthy that our strategy allows preparation of various (2E,4E) dienals in only one step from all trans aldehyde **1**. Access to large amounts of this starting material remained a drawback to this method. Actually, its preparation by bromination of glutaconaldehyde potassium salt **4** (Scheme 2) afforded a mixture of **1** and its (2E,4Z) isomer **5** which were separated by flash chromatography or crystallization.² Therefore, a stereoselective route to all trans **1** as a single isomer constituted a synthetic challenge. Advantage has been taken of the two following points: i) each pure isomeric form **1** or **5** could be converted into the thermodynamic 50/50 mixture of isomers, by standing at room temperature in hydrated chloroform; ii) the (2E,4E) isomer **1** preferentially crystallizes in diethyl ether.²



Scheme 2

So, to the oily mixture of isomers 1 and 5 (*ca.* 70/30) dissolved in diethyl ether was added a catalytic amount of *p*-toluenesulfonic acid. Slow vacuum removing of the solvent at room temperature afforded a solid product. 200 MHz ¹H NMR analysis demonstrated its high isomeric purity (1/5 = 98/2).¹³

We assume that the acid catalyzed thermodynamic equilibration between isomers 1 and 5 occurs rapidly in solution and that the preferential crystallization of all trans 1 transforms the whole initial mixture into this stereoisomer.

In conclusion, we report a significant improvement to the preparation of (2E,4E)-5-bromo-2,4-pentadienal **1**. We have also established that this bromo-aldehyde could be converted into (2E,4E) dienals by simple palladium catalyzed cross-coupling with organozinc reagents, without any protection of the carbonyl group, providing a new synthetic application of this versatile reagent.^{2,3} Extension to other nucleophiles, especially functionalized ones, and application of this last methodology to natural product synthesis is currently under way and will be reported elsewhere.

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References and Notes

- a) Duhamel, L.; Plé, G.; Ramondenc, Y. *Tetrahedron Lett.* **1989**, 30, 7372-7380. b) Contreras, B.; Duhamel, L.; Plé, G. *Synth. Commun.* **1990**, 20, 2983-2990. c) Duhamel, L.; Guillemont, J.; Le Gallic, Y.; PLé, G.; Poirier, J.M.; Ramondenc, Y.; Chabardes, P. *Tetrahedron Lett.* **1990**, 31, 3129-3133. d) Ramondenc, Y.; Plé, G. *Tetrahedron* **1993**, 49, 10855-10876.
- (2) a) Soullez, D. Ph. D. Thesis, Rouen, 1994. b) Soullez, D.; Plé, G.; Duhamel, L.; Duhamel, P. J. Chem. Soc., Chem. Commun. 1995, 563-564. c) Soullez, D.; Plé, G.; Duhamel, L. J. Chem. Soc., Perkin Trans. 1 1997, 1639-1645.
- (3) Macdonald, G.; Lewis, N.J.; Taylor, R.J.K. J. Chem. Soc., Chem. Commun. 1996, 2647-2648.
- (4) a) Heck, R.F. Palladium Reagents in Organic Syntheses; Academic Press: London, 1985. b) Tsuji, J. Palladium Reagents and Catalysts. Innovation in Organic Synthesis; John Wiley and Sons: Chichester, 1995.
- (5) Only a few examples of palladium catalyzed cross-coupling of halogenated vinylic or aromatic aldehydes have been reported so far in the literature: a) Watanabe, T.; Miyaura, N.; Suzuki, A. *J. Organomet. Chem.* **1993**, *444*, C1-C3. b) Gilchrist, T.L.; Healy, M.A.M. *Tetrahedron* **1993**, *49*, 2543-2556. c) Gao, Y.; Harada, K.; Hata, T.; Urabe, H.; Sato, F. *J. Org. Chem.* **1995**, *60*, 290-291. d) Shi, G-Q.; Huang, X-H.; Hong, F. *J. Org. Chem.* **1996**, *61*, 3200-3204.
- (6) a) Erdik, E. *Tetrahedron* 1992, 48, 9577-9648. b) Knochel, P.;
 Singer, D. *Chem. Rev.* 1993, 93, 2117-2188. c) Rieke, R.D.;
 Hanson, M.V. *Tetrahedron* 1997, 53, 1925-1956.
- (7) Typical procedure for palladium catalyzed cross-coupling experiments: preparation of dienal 3i:
 a) Preparation of the alkynyl zinc bromide 2i:

n-Butyllithium (0.520 ml, 2.5 M in hexanes, 1.30 mmol) was added to a solution of trimethylsilylacetylene (0.185 ml, 1.30 mmol) in THF (2mL) at 0° C under argon. The mixture was stirred at room temperature for 1 hour, then cooled to -50 °C and ZnBr₂ (0.337 g, 1.50 mmol) dissolved in THF (3 ml) was added *via* a canula. The resulting solution was then allowed to warm up to room temperature.

b) <u>Palladium catalyzed cross-coupling</u>: Solid **1** (0.160 g, 1.00 mmol) and Pd(PPh₃)₄ (0.058 g, 0.05 mmol) were flushed under argon for 5 min. THF (2 ml) was added and the resulting yellow solution was stirred at room temperature. The preceding solution of zinc reagent **2h** was then added dropwise. At the end of the

addition (10 min), all the starting aldehyde **1** was consumed as demonstrated by TLC analysis (light petroleum ether / $Et_2O = 80 / 20$). The final red mixture was diluted with Et_2O (20 ml) and washed with water (20 ml). The aqueous phase was extracted with Et_2O (3 x 20 ml). The organic layers were combined, washed with brine (20 ml), dried on MgSO₄, and evaporated. Purification by flash chromatography on silica gel (light petroleum ether / $Et_2O = 95 / 5$) afforded pure dienal **3h** (0.155g). Yield: 87 %.

- (8) For examples in polyenic natural product synthesis see: a) Nozoe, S.; Kikuchi, K.; Ishii, N.; Ohta, T. *Tetrahedron Lett.* **1992**, *33*, 7551-7552. b) Ripoche, I.; Bennis, K.; Canet, J-L.; Gelas, J.; Troin, Y. *Tetrahedron Lett.* **1996**, *37*, 3991-3992. c) Peng, Z-H.; Li, Y-L.; Wu, W-L.; Liu, C-X.; Wu, Y-L. J. Chem. Soc., Perkin Trans. 1 **1996**, 1057-1066. d) Gonzàlez, A.; Aiguadé, J.; Urpi, F.; Vilarrasa, J. *Tetrahedron Lett.* **1996**, *37*, 8949-8952.
- (9) For other preparations of dienals and spectral data examples see:
 a) Bellassoued, M.; Salemkour, M. *Tetrahedron*, **1996**, *52*, 4607-4624.
 b) Friedli, A.C.; Yang, E.; Marder, S.R. *Tetrahedron* **1997**, *53*, 2717-2730 and references cited therein. See also Ref. 8c.
- (10) New compounds gave satisfactory ¹H and ¹³C NMR, IR and MS analysis.
- (11) For cross-coupling reactions of acetylenic and selective reduction see: Crousse, B.; Alami, M.; Linstrumelle, G. *Synlett* 1997, 992-994 and references cited therein.
- (12) For an example of the use of trimethylsilylated alkyne as vinylic anion equivalent in polyene synthesis, see: Lipshutz, B.H.; Lindsley, C. J. Am. Chem. Soc. **1997**, *119*, 4555-4559.
- (13) Typical procedure: Bromine (3.15g, 19.7 mmol) in CH₂Cl₂ (20 ml) was added dropwise to triphenylphosphine (5.37g, 20.4 mmol) in CH2Cl2 (80 ml) under argon at 0 °C. Glutaconaldehyde potassium salt 414 (2.27 g, 14.2 mmol) was immediately added in one portion and this suspension was stirred at room temperature for four hours. The final black solution was filtered through a small pad (c.a. 50g) of Merck silica gel 60 (40-63 µm), to eliminate the resulting triphenylphosphine oxide and potassium bromide, and evaporated. The residue was chromatographed on silica gel (light petroleum ether / Et₂O : 90/10) affording a mixture of bromopentadienals (1/5 = 70/30) with an overall yield of 84%. To 1.28 g (8.00 mmol) of this mixture in anhydrous Et₂O (20 ml) para-toluenesulfonic acid (0.10 g, 0.52 mmol) was added. After stirring for 5 min under argon, the solvent was slowly removed in vacuo at room temperature and a grey solid was recovered. It was then dissolved in Et₂O (10 mL) and the solution was forced through silica gel, affording pure (2E,4E)-5-bromo-2,4-pentadienal 1 80 % yield from glutaconaldehyde potassium salt 4.
- (14) Becher, J. Org. Synth. 1980, 59, 79-84.