

Preparation of (Z)-1-(3-nitrophenyl)-4-phenylbut-1-ene and (Z)-1-(3-nitrophenyl)-5-phenylpent-1-ene by Pd(0)-catalyzed cross-coupling reaction

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Abstract

The two nitroolefins, (Z)-1-(3-nitrophenyl)-4-phenylbut-1-ene and (Z)-1-(3-nitrophenyl)-5-phenylpent-1-ene, were stereospecifically prepared by Pd(0)-catalyzed cross-coupling reaction between (Z)- β -bromo-3-nitrostyrene and 2-phenylethyl- or 3-phenylpropyl zinc chloride, respectively. The yield reached 60% in spite of the well-known tendency of aralkyl organometallic halides to undergo β -elimination during the catalytic reaction. Only Pd-complexes displayed a satisfactory catalytic activity, the presence of the nitro group destroying that of related Ni-derivatives.

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1. Introduction

As a part of our structure–reactivity studies of acid-catalyzed intramolecular cyclization of aryl olefins containing an azidophenyl group to macrocyclic compounds [1], we wished to develop a suitable general synthesis of the nitroolefins **1** and **2** having a definite stereochemistry (Fig. 1).

Reactions between organometallic reagents and vinyl halides catalyzed by nickel(0) or palladium(0)-complexes were considered by us as a promising tool to prepare the nitroaryl-olefins **1** and **2** [2]. In addition

to the unambiguousness of stereochemistry [3–6], mild reaction conditions and usually good to excellent yields, other advantages of this type of reaction are the easy preparation of both reaction partners and the expeditiousness of the experimental procedure.

For instance, Fauvarque and Jutand [7] and Sekiya and Ishikawa [8] described stereospecific transformations of (*E*)- or (*Z*)-bromostyrene into the corresponding olefins by cross-coupling reaction with benzylmagnesium bromides catalyzed by Pd(0)–triphenylphosphine complexes. More recently, also benzylzinc halides are reported to be selectively coupled with alkenyl halides giving generally the target products in high yields [9].

To our knowledge, the use of alkenyl halides containing nitroaryl groups in cross-coupling reactions is

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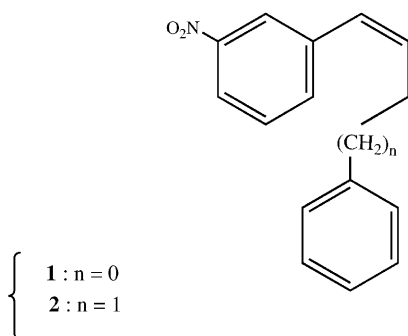


Fig. 1. 1: (Z)-1-(3-nitrophenyl)-4-phenylbut-1-ene (1) and (Z)-1-(3-nitrophenyl)-5-phenylpent-1-ene (2) prepared by cross-coupling reaction.

not reported in the literature; we could find only one example of preparation of a particular nitroolefin by coupling between the enol triflate of a *N*-Boc-protected 4-piperidinone with 3-nitrophenylboronic acid catalyzed by tetrakis(triphenylphosphine) palladium(0): 83% yield of the coupling product was reported [10].

2. Experimental section

All the cross-coupling experiments were carried out under a nitrogen atmosphere. THF was purified by distillation from sodium metal followed by a new distillation from LiAlH₄ under inert atmosphere before use. DMF was distilled from calcium hydride.

The ¹H and ¹³C NMR spectra were measured with a Bruker ARX (400 MHz) spectrometer, working at 400 MHz for ¹H and 100 MHz for ¹³C spectra (solvent, CDCl₃; TMS as an internal standard).

GLC analyses were performed with a Hewlett-Packard 5890 II PLUS gas chromatograph using fused silica capillary columns (HP5, 30 m). Flash-chromatography separations were carried out using CC-flash column packed with silica gel 60 (70–230 mesh ASTM).

GC–MS spectra were recorded using a HP 5971 series mass spectrometer.

2.1. Chemical products and catalysts

1-Bromo-2-phenylethane, 1-bromo-3-phenylpropane, *trans*-cinnamic and 3-nitrocinnamic acid and 9-borabicyclo[3.3.1]nonane (9-BBN solution)

in THF were Aldrich products and used directly. (Z)-β-Bromostyrene was prepared by using the procedure of Mestdagh and Puechberty [11].

The catalytic precursors dichlorobis(dimethylphosphinoethane)nickel(II) [Ni(dmpe)Cl₂] [12] and dichlorobis[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) [Pd(dppf)Cl₂] [13] were prepared using the literature procedures. Tetrakis(triphenylphosphine)palladium(0) [Pd(PPh₃)₄] was a commercial product (Strem Chemicals).

2.1.1. (Z)-β-Bromo-3-nitrostyrene (3)

In a 100 ml flask 3-nitrocinnamic acid (11.0 g, 57.0 mmol) and CHCl₃ (50 ml) were introduced and a solution of Br₂ (3.2 ml, 62.7 mmol) in CHCl₃ was slowly added dropwise under stirring. The reaction mixture was further stirred for 2 h, then the solvent was removed under reduced pressure giving 2,3-dibromo-3-(*m*-nitrophenyl)propanoic acid (18.6 g) as a pale yellow solid. This product was used for the subsequent reaction without purification.

In a 250 ml flask the prepared 2,3-dibromo acid (18.6 g, 52.8 mmol), anhydrous K₂CO₃ (16 g) and acetone (100 ml) were placed. The mixture was heated at the reflux for 2 h, then the solvent was distilled off and the residue poured in 20 ml water. The organic phase was extracted with ethyl ether, the extracts dried over Na₂SO₄ and the solvent evaporated; (Z)-β-bromo-3-nitrostyrene was obtained as a deep-yellow oil and purified by flash-chromatography using hexane/ethyl acetate (10/1); yield 10.35 g (86%).

Gas chromatographic analysis showed a (Z)/(E) isomer molar ratio of about 98/2.

¹H-NMR: δ = 8.5 (m, 1H); 8.2 (m, 1H); 7.9 (d, 1H); 7.5 (t, 1H); 7.1 (d, 2H, *J* = 8 Hz); 6.6 ppm (d, 2H, *J* = 8 Hz). GC–MS (*m/z*): 228 (M⁺).

2.1.2. (Z)-1,4-Diphenylbut-1-ene

A three necked 50 ml flask, purged with nitrogen, was charged with (Z)-β-bromostyrene (1.0 g, 5.43 mmol), Ni(dmpe)Cl₂ (0.15 g, 0.5 mmol) and THF (10 ml). The mixture was then cooled at –78 °C under stirring, then a solution of 2-phenylethylmagnesium bromide (10.8 mmol) in THF (10 ml) was added dropwise and the reaction was continued for 2 h. The mixture was slowly warmed up to room temperature, and then cooled to 0 °C and treated with a saturated aqueous solution of NH₄Cl. THF was removed under

reduced pressure, the residue poured in 10 ml water and extracted with ethyl ether. The separated organic layer was dried over Na_2SO_4 , the solvent evaporated and the residue chromatographed on silica gel using hexane/ethyl acetate (10/1). 1,4-Diphenylbut-1-ene was obtained as a pale yellow oil; yield: 0.90 g (80%).

Gas chromatographic analysis showed a (Z)/(E) isomer molar ratio of about 98/2.

$^1\text{H-NMR}$: $\delta = 7.4\text{--}7.1$ (m, 10H); 6.4 (d, 1H, $J = 12$ Hz); 5.7–5.6 ppm (m, 1H, $J = 12$ Hz). GC–MS (m/z): 208 (M^+).

2.1.3. (Z)-1-(3-Nitrophenyl)-4-phenylbut-1-ene (1)

Procedure A. In a dry 50 ml flask equipped with a magnetic stirring bar, a reflux condenser and a dropping funnel and styrene flushed with nitrogen were placed (0.41 g, 3.9 mmol) in anhydrous THF (2.5 ml) and a solution of 9-BBN (0.48 g in 10 ml THF) at 0°C . The mixture was stirred at room temperature for 2 h giving a solution of B-2-phenylethyl-9-BBN. To this solution DMF (25 ml), $\text{Pd}(\text{PPh}_3)_4$ (0.12 g, 0.10 mmol), K_2CO_3 (0.85 g, 6.7 mmol) and (Z)- β -bromo-3-nitrostyrene (0.7 g, 3.34 mmol) were added. This mixture was stirred at 50°C for 6 h and, after the reaction was completed, was poured in water. The product was extracted with benzene, the organic phase washed with water, dried over Na_2SO_4 and concentrated.

The product was isolated by chromatography over silica gel 60 with hexane/ethyl acetate (10:1) as a pale yellow oil; yield 0.34 g (40%).

Gas chromatographic analysis showed a (Z)/(E) isomer molar ratio of about 9/1.

$^1\text{H-NMR}$: $\delta = 8.1$ (m, 2H); 7.4–7.5 (m, 2H); 7.1–7.3 (m, 7H); 6.45 (D, 1H); 5.7–5.9 (m, 1H); 2.7–2.8 (m, 2H); 2.5–2.6 ppm (m, 2H).

Procedure B. Using the same apparatus zinc chloride (1.79 g, 13 mmol) was added to a 1.3 M THF solution (10 ml) of 2-phenylethylmagnesium bromide and the mixture refluxed for 0.5 h. Then $\text{Pd}(\text{dppf})\text{Cl}_2$ (0.190 g, 0.26 mmol) was introduced and a solution of (Z)- β -bromo-3-nitrostyrene (1.2 g, 5.2 mmol) in THF (10 ml) added dropwise. After addition of THF (50 ml) the reaction mixture was refluxed for 4 h. After cooling at room temperature the solvent was evaporated, the residue treated with water and extracted with CH_2Cl_2 . The organic phase was dried over MgSO_4 and concentrated. Chromatography over

silica gel 60 with hexane/ethyl acetate (10:1) gave the product as a yellow oil; yield 0.79 g (60%).

Gas chromatographic analysis showed a (Z)/(E) isomer molar ratio of about 98/2.

2.1.4. (Z)-1-(3-Nitrophenyl)-5-phenylpent-1-ene (2)

Zinc chloride (3.5 g, 25 mmol) was added to a 4.3 M THF solution (6 ml) of 3-phenylpropylmagnesium bromide. Zinc chloride (3.5 g, 25 mmol) was added and the mixture refluxed for 0.5 h. Then $\text{Pd}(\text{dppf})\text{Cl}_2$ (0.47 g, 0.65 mmol) was introduced and (Z)- β -bromo-3-nitrostyrene (3.0 g, 13 mmol) in THF (10 ml) added dropwise. After addition of THF (40 ml) the reaction mixture was refluxed for 4 h. Usual working up gave the expected nitroaryl-olefin as a yellow oil; yield 1.98 g (57%).

Gas chromatographic analysis showed a (Z)/(E) isomer molar ratio of about 98/2. GC–MS (m/z): 267 (M^+).

$^1\text{H-NMR}$: $\delta = 8.1$ (s, 1H); 8.0 (d, 1H); 7.5 (m, 2H); 7.3 (m, 5H); 6.5 (d, 1H); 5.8 (m, 1H); 2.7 (t, 2H); 2.3 (q, 2H); 1.8 ppm (q, 2H).

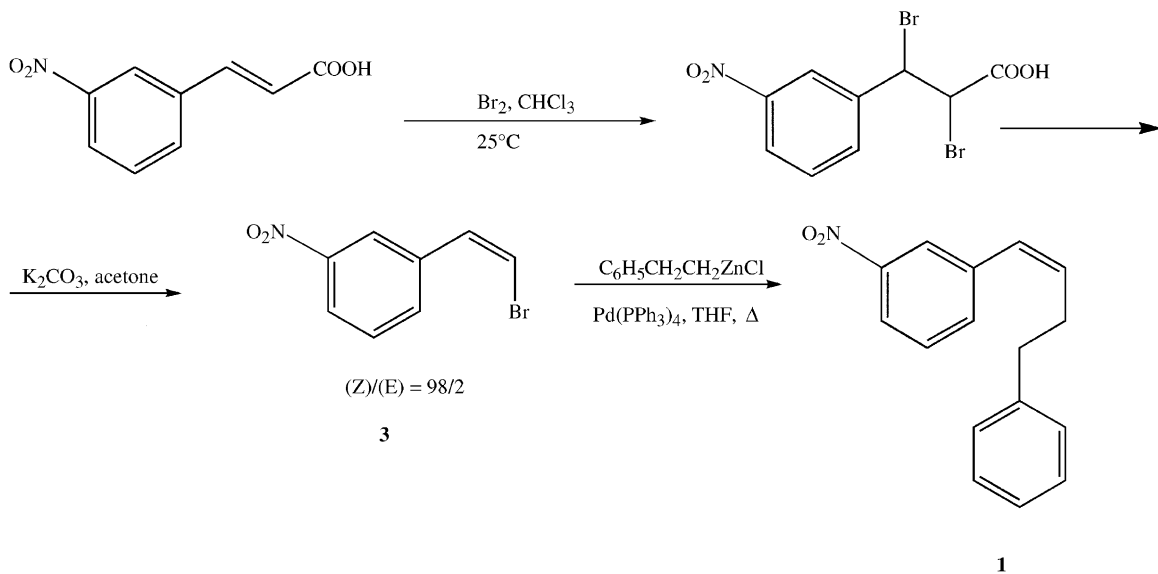
3. Results and discussion

The desired (Z)- β -bromo-3-nitrostyrene (**3**) was conveniently prepared from *trans*-3-nitrocinnamic acid by bromine addition to the olefinic double bond, followed by a stereoselective decarboxylative dehydrobromination reaction promoted by K_2CO_3 in acetone [11]; the bromide **3** was obtained in 86% yield and 98% stereoselectivity (Scheme 1).

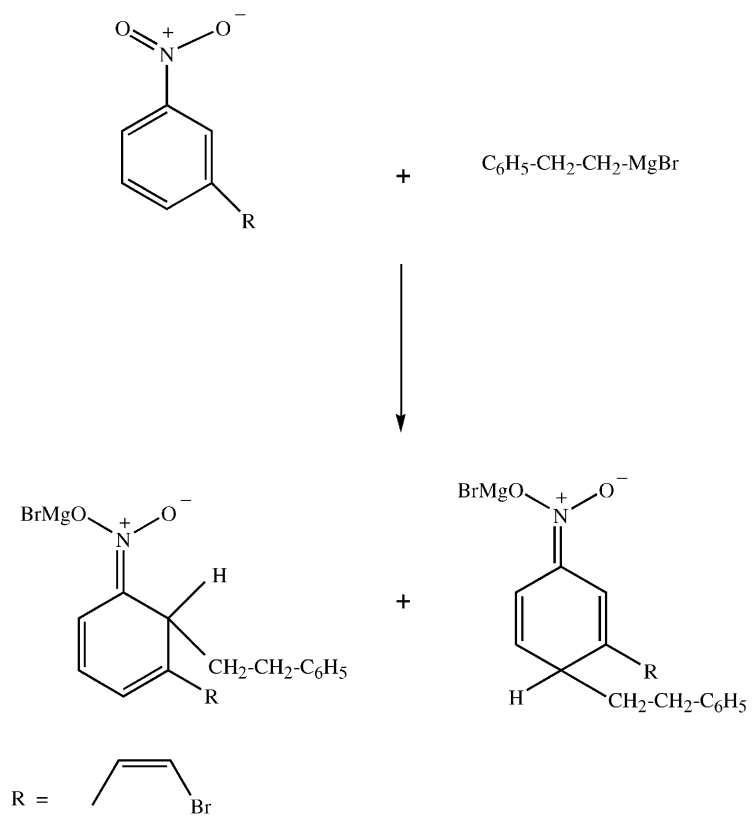
At this point various combinations of organometallic reagent/catalytic precursor were tested in performing the cross-coupling reaction between compound **3** and the 2-phenylethyl metal derivative. Thus, the reaction between 2-phenylethylmagnesium bromide and halide **3** using $\text{Ni}(\text{dmpe})\text{Cl}_2$ (9%) as catalyst in THF at 60°C gave quite disappointing results: a complex mixture of unidentified products was obtained, among which the expected coupling product **1** could not be detected.

In our opinion, two main factors are responsible for the failure of this catalytic process:

- (i) The concurrent irreversible nucleophilic attack of the 2-phenylethyl group to the aromatic system according to Scheme 2 [14,15].



Scheme 1.



Scheme 2.

- (ii) The strong poisoning effect of the nitro group, which destroys the catalytic ability of Ni(0)-complexes [16].

The negative effect of the nitro group on the chemoselectivity of the Ni(0)-catalyzed cross-coupling reaction was confirmed by the following result: (*Z*)- β -bromostyrene reacted smoothly with 2-phenylethylmagnesium bromide in the presence of Ni(dmpe)Cl₂ under the same reaction conditions giving (*Z*)-1,4-diphenylbut-1-ene [(*Z*)/(*E*) = 97/3] in about 80% yield.

To improve the chemoselectivity of the catalytic step giving nitroolefin **1** we devised to use organoborane or organozinc reagents, which contain an alkyl group of reduced nucleophilicity with respect to the corresponding Grignard reagent, and Pd(0)-complexes, which are known to be compatible with strongly electron withdrawing groups [4,17].

The reaction between β -(2-phenylethyl)-9-borabicyclo[3.3.1]nonane, readily accessible by addition of 9-BBN to styrene [18], and the bromide **3** in the presence of Pd(dppf)Cl₂ (5%) and 3 M NaOH(aq) or K₂CO₃/DMF [19] gave only traces of the coupling product **1**. Better results were achieved using Pd(PPh₃)₄ (3%) as catalyst precursor in the presence of K₂CO₃/DMF; the nitroolefin **1** was isolated from the reaction mixture in about 40% yield after 6 h at 50 °C. GC- and NMR-analyses showed a (*Z*)/(*E*) isomer molar ratio of about 9/1 for the olefin **1**.

Finally, taking into account the highly satisfactory results obtained with organozinc reagents in a wide variety of cross-coupling processes [17], we used 2-phenylethylzinc chloride as the organometallic partner for the reaction with the bromide **3** under the aforementioned experimental conditions: in this case the yield of the nitroolefin **1** reached about 60% and the process showed to be again highly stereoselective [(*Z*)/(*E*) = 98/2].

Comparable results were obtained in the parent cross-coupling reaction between 3-phenylethylzinc chloride and (*Z*)- β -bromo-3-nitrostyrene (**3**) in the presence of Pd(PPh₃)₄ using the same experimental procedure; the expected (*Z*)-1-(3-nitrophenyl)-5-phenylpent-1-ene (**2**) was isolated in 57% yield and showed a (*Z*)/(*E*) = 98/2 molar ratio.

The fact that an aromatic nitro derivative destroys the catalytic activity of Ni(0)-phosphine complexes,

in contrast with the behavior with the related Pd(0) species, can be reasonably ascribed to the more pronounced tendency of nickel to be oxidized by the nitro group; it has to be pointed out that only metal(0) species are able to promote the catalytic cycle of the cross-coupling reaction [20].

In repeated cross-coupling experiments we were not able to improve the yields of the nitroolefins **1** and **2**; they are however among the highest ever achieved in the Pd(0)-catalyzed processes involving alkyl groups with sp³ carbon atoms containing β -hydrogen atoms [21]. On the other hand, it is well known that σ -organopalladium species formed during the catalytic process can easily undergo, under the experimental conditions employed, β -hydride elimination, which strongly competes with the reductive elimination leading to the desired cross-coupling products [22].

It has to be pointed out that the presence of a nitro group in an aromatic system offers the possibility of introducing a large number of other functionalities. Thus, the nitroolefins **1** and **2** are easily transformed into the corresponding azidoolefins by selective reduction of the nitro group to amino group, for instance, with the Zn/CaCl₂ system in aqueous ethanol [23], diazotation and nucleophilic substitution with sodium azide [24]; the overall yield of these three steps ranging between 50 and 60%.

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