New Practical Syntheses of 4′-Methylbiphenyl-2-carbonitrile and -2-carbaldehyde

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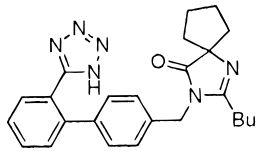
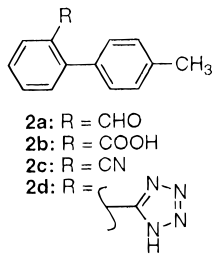
The discovery of orally active, nonpeptidic, angiotensin II receptor antagonists containing a biphenyl tetrazole moiety[1] led to the development of drugs for the treatment of hypertension such as irbesartan **1**.[2] Since that breakthrough, chemists have focused on the synthesis of key intermediates **2a**−**d** of this class of biphenyls, and several elegant synthetic methods have been published.[3−6]



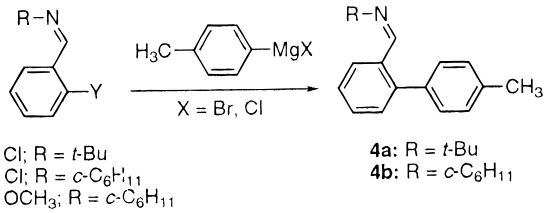
1 Irbesartan



2a: R = CHO
2b: R = COOH
2c: R = CN
2d: R =

However, the reported methods, which all involved a critical aromatic coupling, still suffer from various drawbacks such as the use of expensive starting materials, a lengthy scheme of reactions, the preparation of unstable synthetic intermediates, or a tedious purification procedure of the products. Herein, we report a simple, inexpensive, and efficient synthetic method for the preparation of **2a** and **2c**. This process gives very practical access to **2c** by entirely circumventing the use of chromatographic purification methods and is therefore readily applicable to industrial scale-up.

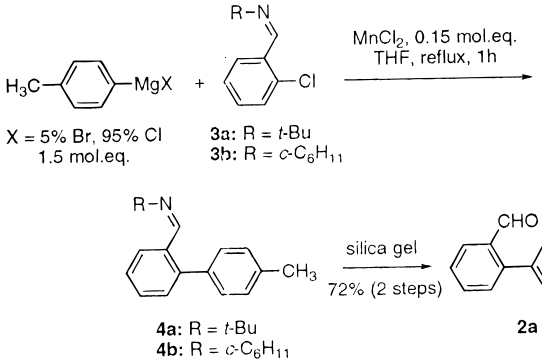
Scheme 1



3a: Y = Cl; R = *t*-Bu
3b: Y = Cl; R = *c*-C_6H_{11}
3c: Y = OCH_3; R = *c*-C_6H_{11}

4a: R = *t*-Bu
4b: R = *c*-C_6H_{11}

Scheme 2



X = 5% Br, 95% Cl
1.5 mol.eq.

3a: R = *t*-Bu
3b: R = *c*-C_6H_{11}

4a: R = *t*-Bu
4b: R = *c*-C_6H_{11}

2a

To develop an alternative to the expensive and time-consuming Meyers route involving an oxazoline,[1] we have investigated the nucleophilic aromatic substitution (S_NAr) of 2-chloro- and 2-methoxybenzaldimines **3a**−**c** with *p*-tolyl Grignard reagents (Scheme 1), taking into account the similarities between those structures.

The imines substrates **3a**−**c** were readily prepared in quantitative yield following standard procedures starting from commercially available materials. Equimolar treatment of the imines **3a**−**c** with the Grignard reagents in THF at room temperature for 2 days afforded very little coupling, as most of the nucleophilic reagent was consumed in the formation of 4,4′-dimethylbiphenyl byproduct. No nucleophilic addition reaction on the imine moiety was observed, certainly due to steric hindrance, and most of the chlorobenzaldimine was recovered unreacted. To improve the coupling procedure, we then turned our attention to the use of manganese salts which had already proved efficient as catalysts to perform similar aromatic cross-coupling reactions.[5d] Thus, addition of a catalytic amount of anhydrous $MnCl_2$ led to complete conversion of the starting chloro imines **3a,b** in 6 h (the methoxy imine **3c** was found much less reactive) to give, after neutral aqueous workup, the expected products **4a,b** in 80−84% yield together with a low amount of the Wurtz byproduct (5−8% yield) as determined by GC-MS. Higher temperatures considerably improved the kinetic rate of the coupling reaction while, surprisingly, the amount of byproduct formed remained almost constant. The crude biphenyl imines **4a,b** were then deprotected on silica gel to provide the corresponding aldehyde **2a** as a yellowish oil in 72% isolated yield for the two steps (Scheme 2).

The mechanism of the cross-coupling reaction is still obscure, but a benzyne intermediate could be ruled out,

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(1) Carini, D. J.; Duncia, J. V.; Aldrich, P. E.; Chiu, A. T.; Johnson, A. L.; Pierce, M. E.; Price, W. A.; Santella, J. B., III; Wells, G. J.; Wexler, R. R.; Wong, P. C.; Yoo, S.-E.; Timmermans, P. B. M. W. M. *J. Med. Chem.* **1991**, *34*, 2525.

(2) Bernhart, C. A.; Perreault, P. M.; Ferrari, B. P.; Muneaux, Y. A.; Assens, J.-L. A.; Clément, J.; Haudricourt, F.; Muneaux, C. F.; Taillades, J. E.; Vignal, M.-A.; Gougat, J.; Guiraudou, P. R.; Lacour, C. A.; Roccon, A.; Cazaubon, C. F.; Brelière, J.-C.; Le Fur, G.; Nisato, D. *J. Med. Chem.* **1993**, *36*, 3371.

(3) **2a**: Rao, A. V. R.; Reddy, K. L.; Reddy, M. M. *Tetrahedron Lett.* **1994**, *35*, 5039.

(4) **2b**: (a)Schoen, W. R.; Pisano, J. M.; Prendergast, K.; Wyvratt, M. J., Jr.; Fisher, M. H.; Cheng, K.; Chan, W. W−S.; Butler, B.; Smith, R. G.; Ball, R. G. *J. Med. Chem.* **1994**, *37*, 897. (b) Kageyama, H.; Miyazaki, T.; Kimura, Y. *Synlett* **1994**, 371. (c) Hattori, T.; Hayashizaka, N.; Miyano, S. *Synthesis* **1995**, 41.

(5) **2c**: (a) Mantlo, N. B.; Chakravarty, P. K.; Ondeyka, D. L.; Siegl, P. K. S.; Chang, R. S.; Lotti, V. J.; Faust, K. A.; Chen, T.-B.; Schorn, T. W.; Sweet, C. S.; Emmert, S. E.; Patchett, A. A.; Greenlee, W. J. *J. Med. Chem.* **1991**, *34*, 2919. (b) Hatanaka, Y.; Goda, K.-I.; Okahara, Y.; Hiyama, T. *Tetrahedron* **1994**, *50*, 8301. (c) Reference 4b; (d) Bouisset M.; Boudin, A. Eur. Patent 0,566,468 A2, 1993. (e) Indolese, A. F. *Tetrahedron Lett.* **1997**, *38*, 3513.

(6) **2d**: Russell, R. K.; Murray, W. V. *J. Org. Chem.* **1993**, *58*, 5023.

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Scheme 3

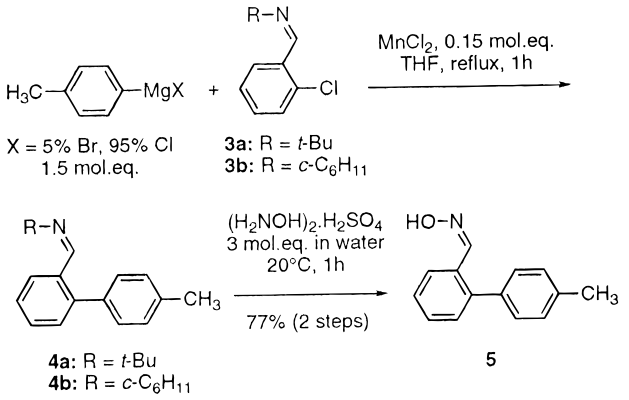


Table 1. Dehydration of 5 into 2c

entry	reagent	solvent	conditions	conversion of **5** (%)	purified yield of **2c** (%)
1	P_2O_5 (10eq.)	THF	20 °C, 1h	100	92
2	Zeolite HY 10, (3 mmol/g)	Toluene	120 °C, 16h	30	-
3	DCC (1 equiv)	THF	20 °C, 16h	5	-
4	DCC (1 equiv)	THF	90 °C, 4h	100	90
5	DCC (1 equiv)	CH_2Cl_2	20 °C, 24h	100	
6	*N*-methylpyrrolidinone		126 °C, 16h	40	-
7	formic acid, 99%		126 °C, 1h	100	91

as no *cine* substitution occurred. A more subtle directive effect, involving chelation at the nitrogen, is certainly operating, since 2-chlorobenzaldehyde dimethyl acetal and oxime were found unreactive under the same conditions. In the latter case, the nitrogen would not be available any longer for chelation following deprotonation of the oxime moiety.

Conversion of aldehyde **2a** into the corresponding nitrile **2c** was subsequently attempted following Streith's methodology.[7] Treatment of **2a** with 1.5 mol equiv of hydroxylamine-*O*-sulfonic acid in semiaqueous media (THF/water 1/1 or CH_3CN/water 1/1) at 65 °C for 2 h led to a mixture of the desired product **2c** with the corresponding oxime **5** and some unreacted aldehyde **2a** in a molar ratio (5/2/3) as determined by GC-MS.

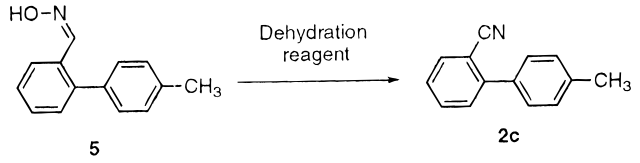
It is worth noting that the crude imines **4a,b**, on treatment with a 3-fold excess of hydroxylamine-*O*-sulfonic acid at reflux in THF/water 1/1 for 1 h, were quantitatively transformed into a mixture of **2c** and **5** in a 3/1 ratio. Since **5** gave **2c** only very slowly under such experimental conditions, the oxime must be considered more as a byproduct rather than as an intermediate of the reaction. The workup of the aromatic coupling was therefore modified to obtain the oxime **5** in a one-pot process (Scheme 3).

The crude crystalline mixture of **5** and bis-tolyl was then triturated in cold petroleum ether (fraction 30−40 °C) to provide after filtration the oxime as a white powder in 71% isolated yield for the three steps. Recrystallization from CH_2Cl_2/petroleum ether afforded **5** as white, sharp-melting needles, mp = 119−120 °C.

Various dehydration reagents listed in Table 1 proved to be efficient for conversion of **5** into **2c** (entries 1, 4, 5, and 7) (Scheme 4). As it only needs an aqueous workup, the one involving formic acid (entry 7) seems to be the most convenient for industrial scale-up.

In conclusion, nitrile **2c**, a key intermediate in angiotensin II antagonists synthesis, has been prepared in fair overall yield (ca. 60%) starting from inexpensive commercially available materials. Involvement of the oxime **5** in such a preparation opens up two possible pathways: (a) removing the byproducts of the aromatic coupling in a very simple manner followed by dehydration to the nitrile or (b) achieving the whole synthesis in a one-pot process and purification by distillation, which make the overall procedure a suitable candidate for industrial application.

Scheme 4



Experimental Section

All quantifications of reaction constituents were achieved on GC using a known quantity of dry dodecane as reference standard. Oven temperature rampings were chosen to obtain "baseline" separation of all components in a mixture. NMR spectra were run in $CDCl_3$ solutions. Proton spectra were recorded at 200 MHz and carbon spectra at 50 MHz. Chemicals shifts (δ) are reported in ppm. IR spectra were recorded in CCl_4 solutions. Solvents were purified and dried by standard techniques[8] before use. Solids were dried over P_2O_5 under vacuum.

Synthesis of 4′-Methylbiphenyl-2-carbaldehyde (2a). To a solution of **3a** (15.7 g, 70.8 mmol) in dry refluxing THF (79 mL) under nitrogen, containing 1.34 g of $MnCl_2$ (10.6 mmol, 0.15 mol equiv), was slowly added 66 mL of a 1.6 M solution of Grignard reagent in anhydrous THF (106 mmol, 1.5 mol equiv). After completion of the addition, reflux was maintained for 1 h, and the brown mixture then carefully quenched into an ice−water bath (200 mL) containing 3 mL of 2-(diethylamino)ethanol (2.7 g, 22.6 mmol). The mixture was extracted with 3 × 100 mL of dichloromethane, and the combined organic layers were dried with anhydrous magnesium sulfate, filtered, and evaporated in vacuo to give 16.3 g of a viscous brown oil. The oil was eluted on silica with petroleum ether/dichloromethane to provide pure **2a** as a pale yellow oil (10.1 g, 51.3 mmol, 72% yield): MS: *m/e* 196 ($M^{\bullet+}$). IR: 1697 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.44 (s, 3H), 7.26−7.28 (m, 4H), 7.42−7.52 (m, 2H), 7.59−7.64 (m, 1H), 8.00−8.05 (m, 1H), 10.00 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.21, 127.56, 128.95, 129.19, 129.87, 130.06, 130.81, 133.53, 133.80, 134.84, 138.04, 146.01, 192.51.

Synthesis of 4′-Methylbiphenyl-2-carboxime (5). To a solution of **3a** (15.7 g, 70.8 mmol) in dry refluxing THF (79 mL) under nitrogen, containing 1.34 g of $MnCl_2$ (10,6 mmol, 0.15 molar equivalent), was slowly added 66 mL of a 1.6 M solution of Grignard reagent in anhydrous THF (106 mmol, 1.5 mol equiv). After completion of the addition, reflux was maintained for 1 h, and the brown mixture then carefully quenched into 150 mL of an ice-cold solution of hydroxylamine sulfate (23.4 g, 0.14 mol) containing 3 mL of 2-(diethylamino)ethanol (2.7 g, 22.6 mmol). The biphasic mixture was then vigorously stirred at room temperature for 1 h. Workup as above gave 11.0 g of white needles. Trituration in cold petroleum ether and filtration provided **5** (10.6 g, 50.2 mmol, 71% yield) as white needles which were recrystallized from dichloromethane/petroleum ether. mp: 119−120 °C. MS: *m/e* 211 ($M^{\bullet+}$). IR: 3596 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.45 (s, 3H), 7.28 (large m, 4H), 7.43 (large m, 3H), 7.95 (m, 1H), 8.22 (large s, 1H), 9.27 (large s,1H); ^{13}C NMR ($CDCl_3$) δ 21.22, 126.20, 127.53, 129.15, 129.59, 129.69, 129.84, 130.37, 136.56, 137.42, 142.36, 149.85. Anal. Calcd for $C_{14}H_{13}NO$: C, 79.58; H, 6.20; N, 6.63. Found: C, 79.69; H, 6.29; N, 6.71.

Synthesis of 4′-Methylbiphenyl-2-carbonitrile (2c). A suspension of **5** (0.54 g, 2.56 mmol) in formic acid (5 mL) was refluxed for 1 h. The solution was then cooled to room temper-

(7) Streith, J.; Fizet, C.; Fritz, H. *Helv. Chim. Acta* **1976**, *59*, 2786.

(8) *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Longman, London, 1989; pp 395−413.

ature, quenched into water (5 mL), and extracted with ether. The ethereal layer was separated and washed with a 0.5 M sodium hydroxide solution until washings were slightly basic (pH around 9) and then with water until the washings were neutral. The organic layer was then dried with anhydrous magnesium sulfate, filtered, and evaporated in vacuo to afford **2c** as an oil (0.45 g, 2.33 mmol, 91%), which hardened on standing and was recrystallized from heptane, mp: 48−49 °C (lit.,[1] mp: 48−49.5 °C). Its structure and purity were assigned by comparison with an authentical sample provided by the Sanofi Chimie.

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Supporting Information Available: ^{1}H and ^{13}C NMR, IR, and mass spectrometry data of **2a** and **5** as well as mass spectrometry data of imines **4a** and **4b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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