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Original loading and Suzuki conditions for the solid-phase synthesis of biphenyltetrazoles. Application to the first solid-phase synthesis of irbesartan

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Abstract

Biphenyltetrazoles are recognized privileged structures. Among them, the therapeutically important class of sartans displays antagonistic activity on AT1 receptors. We have developed a method for anchoring tetrazole derivatives via the heterocycle on a hydroxylated resin using zinc triflate. New Suzuki–Miyaura cross-coupling conditions are developed for the quantitative formation of the phenyl–phenyl bond. Our straightforward synthesis scheme, starting from the conserved phenyltetrazole moiety and ending with the appending of the structurally variable moiety, is well suited to the preparation of sartans and their analogues at a laboratory scale. We thus describe here the first solid phase synthesis of irbesartan, a marketed AT1 antagonist.

Keywords: Tetrazoles; Solid-phase; Irbesartan; Zinc triflate

1. Introduction

Tetrazole is a widely used bioisostere of the carboxylic acid function.[1,2] This heterocycle displays a pK_a similar to the corresponding carboxylic acids, has good absorption properties, and metabolizes as a non electrophilic glucuronide.[2,3] Bearing a privileged biphenyl moiety, biphenyltetrazole is therefore a pharmaceutically relevant pharmacophore. Sartan AT1 antagonists are numerically important representatives of the biphenyltetrazole family in the pharmacopeia (Fig. 1).[4,5] For their synthesis, several solution-phase strategies have been described.[2,6] However, no synthesis of a commercially available sartan has yet been described on a solid support. This work is part of our on-going efforts to develop solid-phase syntheses of compounds bearing acidic heterocycles using common hydroxybenzyl resins.[7] Here, we first describe the development of (1) a method to anchor tetrazoles on such resins (2)

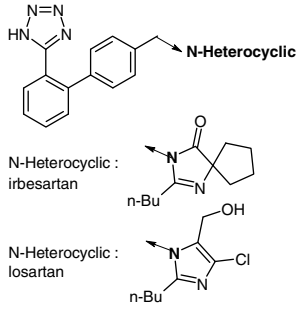

Fig. 1. Markush formula of sartans and structures of losartan and irbesartan.

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new aqueous Suzuki conditions on the solid support. Then, we illustrate this method by the facile solid-phase synthesis of irbesartan (Fig. 1).

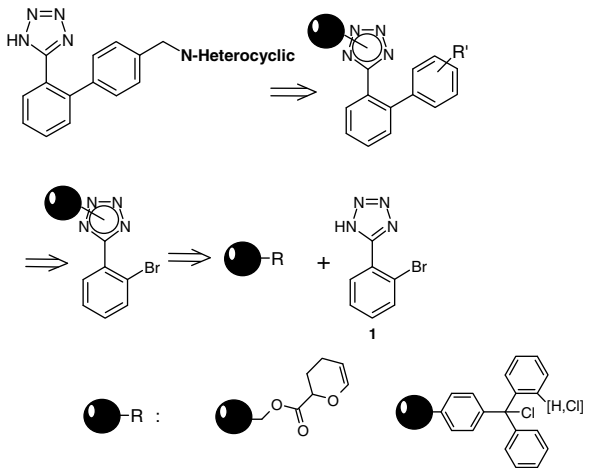
2. Choice of solid support and Lewis acid-catalyzed loading conditions for a new polymer-supported preparation of tetrazolic compounds

Because they are easily implemented at a laboratory scale, automatable, and applicable to large arrays of diverse reagents, polymer-supported syntheses of small molecules are of great interest in drug discovery. Indeed, solid-phase methods are genuine parts of the 'AMC' (automated medicinal chemistry) toolbox, and contribute to the acceleration of hit-to-lead and lead optimization stages of the drug discovery process.[8]

In that context, several polymer-supported methods have been described for the synthesis of compounds bearing a tetrazole ring. Most of them use the solid support as a protection of the tetrazole ring. Trityl chloride or 2-chlorotrityl chloride resins are often used to anchor tetrazoles in moderate to good yields (Scheme 1).[9,10] Vinyl ether resins such as THP, that are less convenient, have also been used (Scheme 1).[11] An elegant strategy that uses an isonitrile resin as a tetrazole precursor has been proposed by Chen et al.[12] Alternatively, some authors have described the terminal conversion of a nitrile function to a tetrazole on the solid support. In this case, another functional group must be found on the target molecule that serves as an anchoring group.[13]

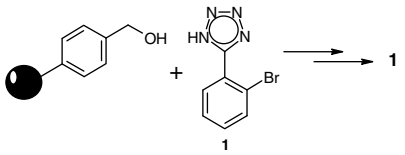
We investigated here the use of common benzylalcohol resins. N-Alkylation of the tetrazole ring by a tertiary alcohol using zinc triflate $Zn(OTf)_2$ as a catalyst has been previously reported for solution reactions.[14] We thus investigated the use of this catalyst to anchor 2-bromo-phenyl-tetrazole **1** on a Wang benzylalcohol resin (Table 1).

Various stoichiometries and concentrations of tetrazole and catalyst were compared. The best yield was obtained using condition **3**: 0.3 M tetrazole and 0.03 M of zinc triflate in refluxing dry acetonitrile.[15] However, because of the basic behavior of 1-alkyltetrazole, and the relative stability of its protonated form compared to the benzylic cation, the bond between the tetrazole and the benzylic carbon on the solid support is not easily cleaved in acidic conditions. Therefore, too harsh conditions (TFMSA/TFA) were needed to cleave the tetrazole from this resin. We thus moved to another resin: a 4-hydroxymethyl-3-methoxyphenoxybutyric acid benzhydrylamine resin (HMPB-BHA) that generates a more stable carbocation. Using this electron rich linker, we found TFA/DCM (50/50) to be a suitable cleavage mixture (Table 2). Different tetrazoles were used to validate the method. They were anchored and recovered in moderate to excellent yields (40–88%).[16,17] Interestingly, although Mitsunobu conditions are reported in the literature for N-benzylation of tetrazole, anchoring of tetrazole on benzylalcohol resins using these conditions was not successful (Table 2, entry 6).[7,18]



Scheme 1. Strategies used to synthesize biphenyltetrazoles on solid support, using tetrazole as the anchoring point.

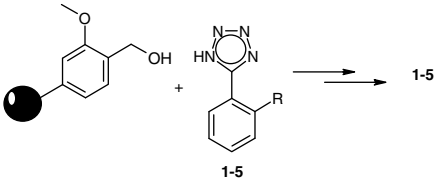
Table 1
Conditions to load 2-bromo-phenyl-tetrazole on Wang resin



	Tetrazole (M)	Catalyst (M)	Yield[a] (%)
1	0.15	0.03	35
3	0.30	0.03	58
4	0.30	0.06	43
5	0.30	0.09	46

[a] Two-step overall yield (loading-cleavage). Cleavage is performed using trifluoro-methylsulfonic acid (TFMSA) 10% in TFA 48 h.

Table 2
Loading of different tetrazoles on HMPB-BHA resin



	R-	Conditions	Yield[a] (%)
1	2-Br	$Zn(OTf)_2$[b]	63
2	3-Br	$Zn(OTf)_2$[b]	40
3	4-Br	$Zn(OTf)_2$[b]	47
4	H	$Zn(OTf)_2$[b]	40
5	4-CH_3–C_6H_4[d]	$Zn(OTf)_2$[b]	88
4	H	Mitsunobu[c]	<1

[a] Two-step overall yield (loading-cleavage). Cleavage is performed using TFA 50% in DCM during 4 h.
[b] Tetrazole 0.3 M; $Zn(OTf)_2$ 0.03 M; anhyd ACN; reflux, 24 h.
[c] Tetrazole; PPh_3; DIAD as described in Ref. 7.
[d] The synthesis of 5-(4′-methyl-biphenyl-2-yl)-1*H*-tetrazole **5** was performed as described in Ref. 17.

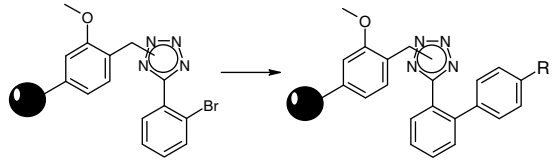
3. New Suzuki conditions

Only a few examples of Suzuki reactions between an anchored halogenated 5-phenyl-1*H*-tetrazole and an arylboronic acid have been reported.[11] Conditions tested for the Suzuki reaction between the anchored **1** are described in Table 3.

We used either anhydrous or aqueous conditions catalyzed by, respectively, $PdCl_2(P(Ph)_3)_2$ or $PdCl_2$(dppf) (Table 3). Applied to a HMPB-BHA resin, these conditions were not entirely satisfactory. Indeed either the formation rate of the desired product was low or a competitive dehalogenation of **1** occurred in significant proportion. Nevertheless, since aqueous conditions were encouraging and consistent with observations made in solution-phase synthesis,[19] we decided to use a PEG-grafted resin (Tentagel S AC) better swelled by aqueous solvents. Interestingly, in these optimized conditions, the Suzuki coupling went fast to completion (98%) and no dehalogenated product was observed (Table 3).[20]

The latter conditions were used for various boronic acids to evaluate the scope of the reaction. As can be seen in the reaction in Table 4, the conversion of the *o*-bromophenyltetrazole is quantitative. All compounds were obtained in good to excellent yield, with all substituents. The lower yield obtained for compound **10** bearing a pyridyl moiety is due to a difficult work-up owing to an amphoteric behavior and a poor solubility. Chloro compound **8** was obtained in a lower yield than its fluoro analogue because a second undesired Suzuki reaction took place at the chlorine atom.

Table 3
Different Suzuki conditions evaluated to load boronic acids[17a,b]



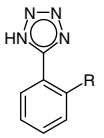
Catalyst	Base	Resin	Solvent	Relative proportions of A/B/C[c] (%)
$PdCl_2(P(Ph)_3)_2$	K_3PO_4	HMPB-BHA	Dioxane	30/70/0
$PdCl_2$(dppf)	Na_2CO_3	HMPB-BHA	DME/H_2O (2:1)	50/25/25
$PdCl_2$(dppf)	Na_2CO_3	Tentagel S AC	DME/H_2O (2:1)	98/2/0

[a] 4-Hydroxymethylphenylboronic acid R = $-CH_2OH$ (12 equiv, 0.3 M), Base (8 equiv, 0.2 M), catalyst (0.6 equiv, 0.015 M) in solvent and resin grafted with **1** (1 equiv), reflux, 24 h under argon.

[b] Cleavage is performed using TFA 50% in DCM during 4 h. Filtrate is analyzed by LCMS.

[c] % of A/B/C correspond, respectively, to expected biphenyl product/5-(2-bromophenyl)-1*H*-tetrazole/5-phenyl-1*H*-tetrazole byproduct (dehalogenated product).

Table 4
Scope of the Suzuki–Miyaura reaction



Compd	R	Conversion[a] (%)	Yield[b] (%)
6	$-C_6H_5$	100	70
5	$-C_6H_4-pCH_3$	100	78
7	$-C_6H_4-pCCH_3$	100	80
8	$-C_6H_4-m$Cl	78(12)[c]	69
9	$-C_6H_4-m$F	100	77
10	–4-Pyridyl	100	53
11	$-C_6H_4-pOCH_3$	100	62
12	$-C_6H_4-mOCH_3$	100	79
13	$-C_6H_4-oOCH_3$	100	68

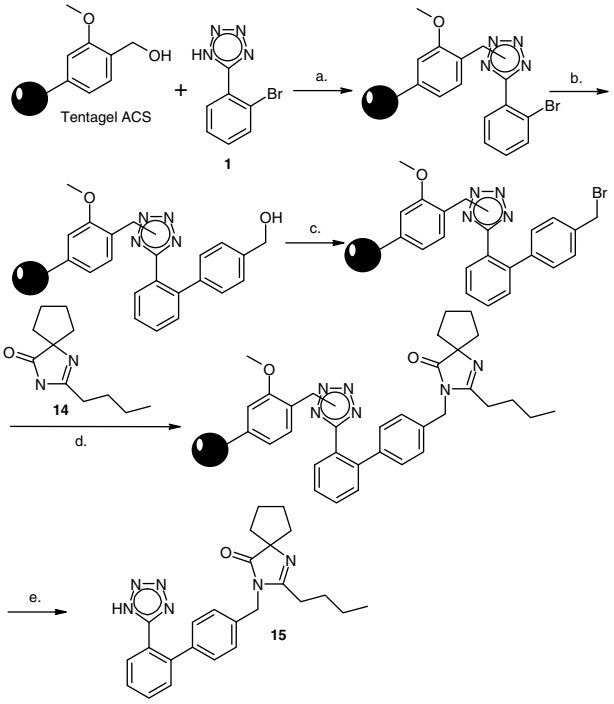
[a] 215 nm after.

[b] Cleavage and purification.

[c] % in brackets corresponds to obtention of 5-[1,1′;3′,1″]terphenyl-2″-yl-1*H*-tetrazole after cleavage.

4. Synthesis of irbesartan

To illustrate the usefulness of our method, we went on with the synthesis of irbesartan, a marketed AT1 antagonist. Irbesartan was chosen as an example, because it bears



Scheme 2. Reagents and conditions: (a) Tentagel S AC resin, **1** (0.15 M), $Zn(OTf)_2$ (1.5 mM) dry acetonitrile, under argon, reflux, 24 h; (b) resin, Boronic acid (0.3 M), Na_2CO_3 (0.2 M), $PdCl_2$(dppf) (15 mM), in DME/H_2O (2:1), under argon, reflux, 24 h; (c) resin, dry diisopropylethylamine (0.03 M), $P(C_6H_5)_3Br_2$ (0.15 M), in dry DCM, under argon, room temperature, 18 h; (d) (i) **14** (0.6 M), sodium hydride (0.8 M) in dry DMF, under argon, 40 °C, 1 h, (ii) TBAI (0.8 mM), resin, 45 °C, 20 h; (e) TFA 50% in DCM.

an imidazoline head for which a regioselective alkylation is possible (unlike for losartan, bearing an ambident imidazole ring).[6] Imidazolinone **14** was thus synthesized in three steps as previously reported.[21,22] Using our optimized conditions, the synthesis of irbesartan was performed in five steps as described in Scheme 2.[23] First, anchoring of tetrazole **1** using $Zn(OTf)_2$ was performed on a 4-hydroxymethyl-3-methoxyphenoxy Tentagel® resin. Then, the arylation of 2-bromophenyltetrazole was achieved using our aqueous Suzuki conditions, and dehydrohalogenation of the benzylalcohol was performed with $P(C_6H_5)_3Br_2$.[24] Noteworthy, dichloromethane was carefully dried, to avoid the cleavage of the product from the resin. Finally, bromide was displaced by **14** in the presence of tetrabutylammonium iodide, and irbesartan **15** was released from the resin using TFA 50% in dichloromethane. Irbesartan was obtained in excellent purity and an overall yield of 64% after five reaction steps, corresponding to an average yield of 91% per synthesis step, including the arylation step.

We have developed an efficient anchoring of tetrazoles on 4-hydroxymethyl-3-methoxyphenoxy resins. The use of a water-compatible resin allowed maximizing the yield of the Suzuki arylation step. The method was then successfully applied to the synthesis of irbesartan. Thanks to the use of a polymer-supported technology, this linear scheme is nonetheless very efficient and readily applicable to parallel synthesis of biaryltetrazoles. Our method could thus be extended to other bioactive series.

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Supplementary data

Experimental details and characterization biphenyltetrazoles **6–13**, heterocycle **14** and irbesartan **15** are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.02.147.

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15. *General procedure for anchoring tetrazoles on hydroxyl resin using Zn(OTf)$_2$*: A reactor was loaded with tetrazole (10 equiv, 0.3 M) and zinc triflate (0.1 equiv, 0.003 M) in dry acetonitrile and hydroxyl resin (1 equiv). The mixture was refluxed under argon during 24 h. Resin was filtered and washed with acetonitrile (3 × 5 mL), methanol (3 × 5 mL), DMF (5 × 3 mL), DCM (5 × 3 mL), and diethyl ether (5 × 3 mL). This protocol was validated for the following quantities of resin: 75, 150 or 300 μmol, either using SynPhase Lanterns (Mimotopes, Pty, Clayton, Australia) or classical resins.
16. While the procedure described in Ref. 14 was successful for the attachment of 5-phenyltetrazoles on the HMPB-BHA resin, it was not suitable for anchoring 5-phenyl-1,2,4-oxadiazole-5-one, another classical acidic heterocycle: 7% overall yield.
17. The synthesis of 5-(4′-methyl-biphenyl-2-yl)-1*H*-tetrazole **5** was performed using conditions described in Wittenberger, S. J., Donner, B. G. *J. Org. Chem.* **1993**, *58*, 4139. 4′-Methyl-biphenyl-2-carbonitrile (1 equiv, 22 mmoL; 4.28 g) and $(CH_3)_3SiN_3$ (5.45 equiv, 120 mmol, 16.8 mL) are dissolved in toluene (44 mL). $(nC_4H_9)_2SnO$ (0.18 equiv, 4 mmol, 996 mg) is then added and the reaction mixture is refluxed for 72 h. ^{1}H NMR (DMSO-d_6) 300 MHz δ 2.27 (s, 3H); 7.05 (d; $J = 8.1$ Hz, 2H); 7.15 (d, $J = 8.2$ Hz, 2H); 7.50–7.70 (m, 4H); mp: 148–149 °C; LCMS (EI): $m/z = 237$ [MH^+].
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20. *General procedure for Suzuki conditions to load 4-hydroxymethylphenylboronic acid*: A reactor was loaded with boronic acid (12 equiv, 0.3 M), Na_2CO_3 (8 equiv, 0.2 M), $PdCl_2$(dppf) (0.6 equiv, 0.015 M) in DME/H_2O (2:1), and Tentagel S AC resin grafted with 1 (1 equiv). The mixture was refluxed during 24 h under argon. Resin was filtrated and washed with DME (3 × 5 mL), methanol (3 × 5 mL), DMF (5 × 3 mL), DCM (5 × 3 mL) and diethyl ether (5 × 3 mL). This protocol was validated for the following quantities of resin 30 or 300 μmol.
21. See supporting information section: Bernhart, C. A.; Perreaut, P. M.; Ferrari, B. P.; Muneaux, Y. A.; Assens, J. L. A.; Clement, J.; Haudricourt, F.; Muneaux, C. F.; Taillades, J. E., et al. *J. Med. Chem.* **1993**, *36*, 3371–3380.

22. *Butyl-1,3-diaza-spiro[4.4]non-1-en-4-one* **14**: Colorless oil (yield: 55%). ^{1}H NMR: (300 MHz, DMSO-d_6, ppm): $\delta = 3.34$ (sl, 1H, CONHR); 2.28 (t, 2H, $J = 7.5$ Hz, CH_2); 1.59 (m, 10H, CH_2); 1.30 (m, 2H, CH_2); 0.88 (t, 3H, $J = 7.2$ Hz, CH_3); LCMS (EI): $m/z = 195$ [MH^+] (base peak).
23. *Solid-phase synthesis of irbesartan* **15** *as the TFA salt (white powder)*: overall yield 64%, purity 98% ^{1}H NMR (CH_3OH-d_4) δ ppm: 0.88 (t, 3H, $J = 3.6$ Hz), 1.34 (m, 2H), 1.52 (m, 2H), 2.1–1.8 (m, 8H), 3.63 (s, 2H), 4.8 (s, 2H), 7.10–7.20 (m, 4H), 7.54 (d, $J = 6.6$ Hz, 2H), 7.65 (d, $J = 6.6$ Hz, 2H). ^{13}C NMR (CH_3OH-d_4) δ ppm: 13.9, 23.1, 26.9, 28.3, 38.3, 44.3, 71.4, 76.4, 124.8, 128, 129.1, 130.8, 131.6, 131.7, 132.3, 136.8, 140.7, 142.9, 155.7 (Cq Tetrazol), 166.6 (C=N), 184.3 (C=O); Lcms (EI): $m/z = 429$ [M−TFA+H^+] (base peak); mp: 161–163 °C.
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