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Palladium-mediated synthesis of novel nimesulide derivatives

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Synthesis of a series of compounds structurally related to the anti-inflammatory agent nimesulide has been accomplished via Pd-catalyzed C–C bond forming reactions. Thus 4-iodo derivative, prepared from nimesulide, participated in Sonogashira (copper-free), Heck and Suzuki coupling reactions to afford the corresponding alkynyl, alkenyl and aryl substituted products. Some of the compounds synthesized were tested for anti-inflammatory activities *in vivo*.

Supporting information may be found in the online version of this article.

Keywords: nimesulide; anti-inflammatory; C–C bond; palladium; alkyne; alkene; boronic acid

Introduction

Nimesulide [N-(4-nitro-2-phenoxyphenyl)methanesulfonamide, **1,** Figure **1**], a non-steroidal anti-inflammatory drug (NSAID), is a moderately selective cyclooxygenase-2 (COX-2) inhibitor[1] which is presently in patient use, although concerns have been raised regarding its hepatotoxicity. Indeed because of the risk of hepatotoxicity, nimesulide has been withdrawn from market in many countries and restricted by the European Medicines Agency. The use of this drug has been reported to cause several types of liver damage,[2] ranging from mild abnormal function to severe organ injuries. These effects are usually reversible upon discontinuation of the drug but occasionally can progress to fatal hepatic failure.[3] The observed hepatotoxicity of **1** has often been linked to its uncoupling effects on mitochondria and study has shown that nimesulide exerts this effect via a protonopheretic mechanism as well as oxidation of mitochondrial NADH and NADPH.[4] The nitro group of nimesulide was thought to be responsible for its protonophoretic and NAD(P)H oxidizing properties as chemical reduction of -NO_2 to -NH_2 completely suppressed the above mitochondrial responses. It is therefore desirable to replace the nitro group of **1** by an appropriate unsaturated group or substituent without affecting its anti-inflammatory, analgesic and antipyretic properties. Accordingly, 4-cyano analog of nimesulide, i.e. compound **2** (Fig. 1) was synthesized and identified as a potent anti-inflammatory agent when tested in rats.[5]

In our effort[6,7] to develop novel anti-inflammatory agents derived from existing and well-known NSAIDs we have reported synthesis and COX-2 inhibitory properties of a series of diaryl ethers generated from nimesulide recently.[8] In further continuation of our previous work we now wish to report a palladium-mediated approach[9,10] to introduce unsaturated moieties at the C-4 position of **1** in place of the nitro group (Scheme 1). To the best of our knowledge preparation of nimesulide analogs via C–C bond forming reactions under palladium catalysis has not been reported earlier.

Experimental

General procedure for the preparation of *N*-(4-substituted-2-phenoxyphenyl)methanesulfonamide (4–6)

To a solution of *N*-(4-iodo-2-phenoxyphenyl)methanesulfonamide (1.0 mmol) in acetonitrile (10 ml) was added diisopropylethylamine (1.5–3.0 mmol) and $Pd(OAc)_2$ (0.10–0.19 mmol). The mixture was stirred for 15 min at room temperature and the appropriate coupling partner, e.g. a terminal alkyne or alkene or aryl boronic acid (1.0–8.0 mmol), was added. The mixture was then stirred for 10–30 h at 75–80 °C. After the usual workup followed by chromatographic purification the desired compound was obtained in 53–82% yield (see below and Supporting Information).

Results and Discussion

The key starting material, i.e. *N*-(4-iodo-2-phenoxyphenyl) methanesulfonamide (**3**), required for our synthesis was prepared from nimesulide **1** via reduction of the nitro group[5] followed by converting the resultant aryl amine to the iodo derivative under a Sandmayer reaction condition (Scheme 2).

Having prepared the iodo compound **3** we then examined its reactivity under the conditions of Sonogashira,[11] Heck-Mizoroki[12] and Suzuki.[13] Although a wide variety of reaction conditions have been reported individually for each of these C–C bond forming methods we aimed to develop a common reaction

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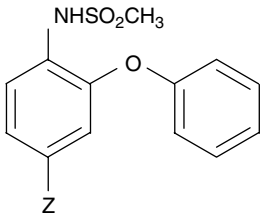


1. Z = NO_2 (Nimesulide)

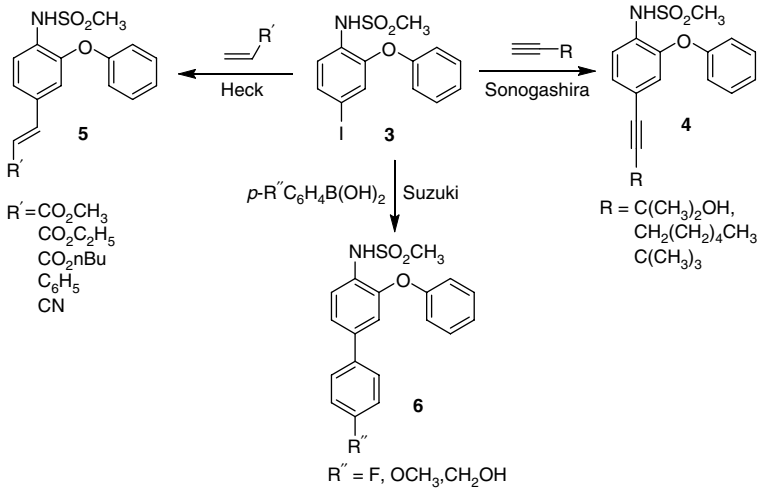
2. Z = CN

Figure 1. Nimesulide and its active analog.

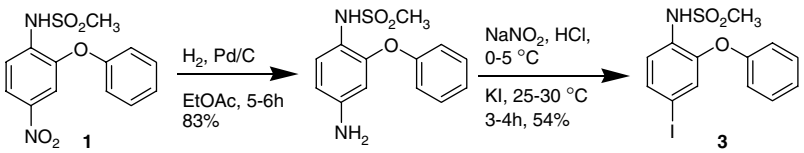
conditions for the synthesis of our target compounds. Accordingly, we conducted a preliminary study to establish the optimum reaction condition in order to obtain the best yields of desired products. The results of our palladium-catalyzed reaction leading to various compounds (**4–6**) structurally related to nimesulide are summarized in Table 1. The alkynyl derivatives **4a–c** were prepared in 75–82% yield via coupling of **3** with terminal alkynes under copper-free Sonogashira conditions (entries 1–5, Table 1). A copper-free method is advantageous as it precludes the dimerization of terminal alkynes (the Glaser coupling) leading to the formation of 1,3-diynes as side products and avoids the possibility of copper contamination with the product.[14] Thus, in a typical procedure to a solution of compound **3** (1.0 mmol) in acetonitrile (10 ml) was added diisopropylethylamine (1.5 mmol) and $Pd(OAc)_2$ (0.10 mmol). The mixture was stirred for 15 min at room temperature and the acetylenic compound (5.0 mmol) was added. The mixture was then stirred according to the time and temperature indicated in Table 1 and after the usual workup followed by chromatographic purification the pure product was isolated. Although the reaction was carried out in acetonitrile in the presence of diisopropylethylamine, the use of other solvents and bases was also examined. For example, the coupling reaction provided slightly inferior yield of product **4a** when triethylamine was used as a base (entry 1 vs 2, Table 1) or DMF was used as a solvent (entry 1 vs 3, Table 1) separately without changing the other reaction parameters.

Under the Heck reaction conditions compound **3** was coupled with a variety of alkenes in the presence of $Pd(OAc)_2$ and $^iPr_2NEt$ at 75–80 °C to afford the olefins (**5a–e**) in 53–66% yields (entries 6–10, Table 1). While acetonitrile was used a solvent in the present reaction, the use of other solvents, e.g. DMF (entry 2, Table 2), 1,4-dioxane (entry 3, Table 2) and toluene (entry 4, Table 2), were also examined for the coupling of methyl acrylate with **3**. The reaction proceeded well in these solvents except in toluene, where inferior yield (~40%) of product **5a** was obtained. An increase or decrease in reaction temperature from 75 to 80 °C also decreased the product yield (entries 5 and 6 vs 1, Table 2). We have chosen alkenes possessing an electron-withdrawing ester or cyano moiety in order to retain an electron-withdrawing effect similar to nitro group at the C-4 position of nimesulide ring. Based on the coupling constant of olefinic protons obtained from their ^1H NMR spectra (J = 15–16 Hz) all the olefins isolated were characterized as *E*-isomers.

Finally, the compound **3** was coupled with 4-subtituted arylboronic acids under Suzuki conditions to afford the aryl substituted products **6a-c** (entries 11–13, Table 1). Like earlier reactions, once again $Pd(OAc)_2$ was found to be an effective catalyst in this case when the reaction was carried out at 75–80 °C in acetonitrile. This catalyst was found to be equally effective when DMF (entry 2, Table 3) or dioxane (entry 3, Table 3) was used as a solvent. Although the reaction was carried out using diisopropylethylamine as a base the use of inorganic bases such as K_3PO_4 (entry 4, Table 3), Cs_2CO_3 (entry 5, Table 3) and K_2CO_3 (entry 6, Table 3) was also examined. However the isolated yield

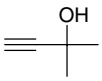
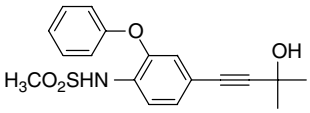
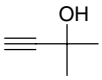
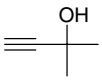
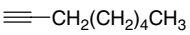
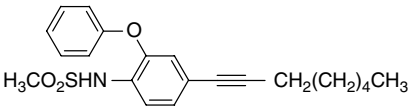
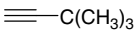
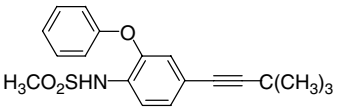
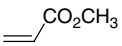
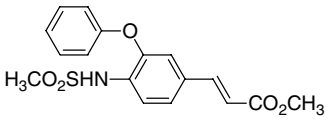
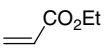
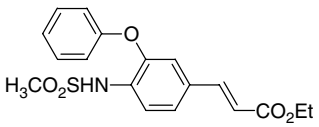
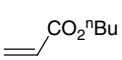
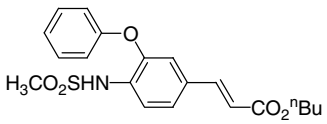
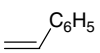
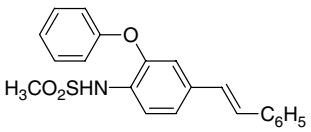
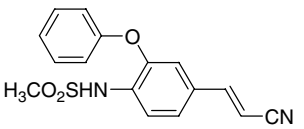
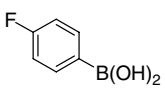
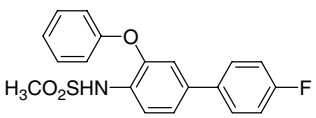
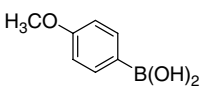
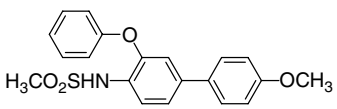
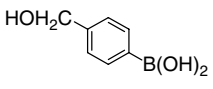
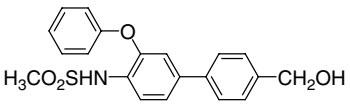


Scheme 1. Preparation of nimesulide analogs via Pd-mediated C–C bond-forming reactions.



Scheme 2. Preparation of *N*-(4-iodo-2-phenoxyphenyl)methanesulfonamide (**3**).

Table 1. Pd-mediated synthesis of alkynyl, alkenyl and aryl substituted compounds (**4–6**) structurally related to nimesulide from the iodo compound **3**[a]

Entry	Alkynes/alkenes/arylboronic acid	Products (**4–6**)		Reaction time (h)/temperature (°C)	Isolated yield (%)
1			**4a**	10/75–80	75
2			**4a**	10/75–80[b]	69
3			**4a**	10/75–80[c]	71
4			**4b**	10/75–80	79
5			**4c**	25/50–55	82
6			**5a**	30/75–80	66
7			**5b**	25/75–80	61
8			**5c**	25/75–80	60
9			**5d**	25/75–80	63
10			**5e**	25/75–80	53
11			**6a**	10.0/75–80	55
12			**6b**	10.0/75–80	67
13			**6c**	10.0/75–80	61

[a] All the reactions were carried out using $Pd(OAc)_2$, $^{i}Pr_2NEt$ in CH_3CN.
[b] Et_3N was used as a base in place of $^{i}Pr_2NEt$.
[c] DMF was used as a solvent in place of CH_3CN.

Table 2. Effect of reaction conditions on the Pd-mediated coupling of methyl acrylate with iodo compound **3**

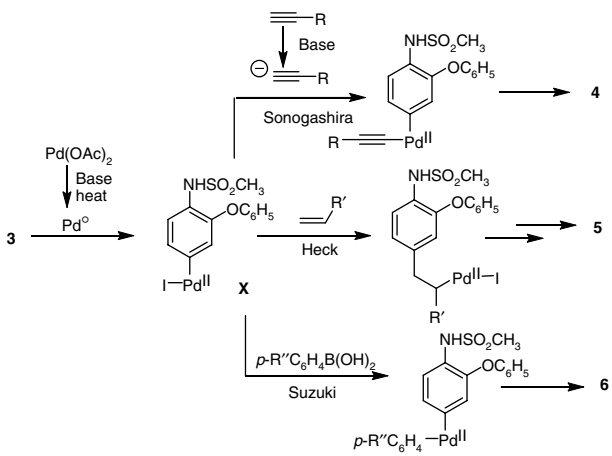
Entry	Solvent	Base	Reaction time (h)/temperature (°C)	Isolated yield (%)
1	CH_3CN	iPr_2NEt	30/75–80	66
2	DMF	iPr_2NEt	30/75–80	62
3	1,4-Dioxane	iPr_2NEt	30/75–80	59
4	Toluene	iPr_2NEt	30/75–80	40
5	CH_3CN	iPr_2NEt	30/50–55	56
6	DMF	iPr_2NEt	30/50–55	55

Table 3. Effect of reaction conditions on the Pd-mediated coupling of 4-flouropheylboronic acid with iodo compound **3**

Entry	Solvent	Base	Reaction time (h)/temperature (°C)	Isolated yield (%)
1	CH_3CN	iPr_2NEt	10/75–80	55
2	DMF	iPr_2NEt	30/75–80	54
3	1,4-Dioxane	iPr_2NEt	30/75–80	55
4	CH_3CN	K_3PO_4	30/75–80	48
5	CH_3CN	Cs_2CO_3	30/50–55	51
6	CH_3CN	K_2CO_3	30/50–55	49

of product was found to be marginally inferior in these cases. Similarly, increase or decrease in reaction temperature from 75–80 °C did not provide a better yield of product.

Mechanistically, all the coupling reactions (i.e. copper-free Sonogashira, Heck or Suzuki) proceed via generation of a common intermediate, e.g. aryl palladium complex **X** (Scheme 3), which formed as a result of oxidative addition of Pd^0 generated *in situ* with the iodo compound **3**. The organometallic intermediate then undergoes (i) displacement of the iodo group by a terminal alkyne in case of Sonogashira reaction, (ii) *syn* addition with an alkene in case of Heck reaction or (iii) trans-metallation with a boronic acid in case of Suzuki coupling. The copper-free Sonogashira coupling proceeds via generation of an acetylide anion in the presence of a base (Scheme 3) that eventually participates in the subsequent steps. Thus reductive elimination of Pd(0) from the alkynyl–aryl palladium(II)complex generated in the case of Sonogashira reaction afforded the product **4**. A *syn* elimination of H–Pd(II)–I from the suitably configured alkyl-palladium intermediate afforded the *E*-alkene **5** in case of Heck reaction. Like Sonogashira coupling, a reductive elimination of Pd(0) from di-aryl palladium(0) complex afforded the bi-aryl coupled product **6** in the case of Suzuki coupling. In all these cases the Pd(0) was regenerated to complete the catalytic cycle for each coupling reaction.



Scheme 3. Reaction mechanism of Pd-mediated C–C bond forming reactions leading to nimesulide derivatives.

We synthesized a range of alkynyl, alkenyl and aryl substituted novel compounds (**4–6**) structurally related to the anti-inflammatory agent nimesulide. We then examined anti-inflammatory activities of some of the compounds synthesized. The anti-inflammatory activity was evaluated in a carrageenan-induced rat model of inflammation[15] using indomethacin as a reference compound. At a dose of 10 mg/kg (i.p.) compound **4a** showed 15, 20, 35 and 48% inhibition of edema after 1, 2, 3 and 4 h when indomethacin showed 24, 43, 66 and 93% inhibition at 10 mg/kg at the same time points. Similarly, compounds **4b** and **4c** showed 32 and 37% inhibition after 4 h at a dose of 10 mg/kg.

Spectral data of selected compounds

*Compound **5a***

White solid, m.p. 154–155 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.02 (s, 3H, CH_3), 3.69 (s, 3H, CH_3), 6.49 (d, J = 16.1 Hz, 1H, –CH═), 7.02 (d, J = 7.8 Hz, 2H, 2 × *CH* arom), 7.15 (t, J = 7.0 Hz, 1H, 1 × *CH* arom), 7.29 (s, 1H, 1 × *CH* arom), 7.38–7.49 (m, 2H, 2 × *CH* arom), 7.51–7.53 (m, 2H, 2 × *CH* arom), 7.56 (d, J = 16.1 Hz, 1H, –CH═), 9.53 (bs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 38.2 (CH_3), 51.3 (CH_3), 117.7, 118.1, 119.2, 123.4, 123.9, 124.2, 129.8, 131.1, 131.5, 143.2, 148.2, 156.3, 166.4 (C═O); IR (KBr, cm^{-1}) 3251 (NH), 1724 (C═O); MS (ES): *m/z*, 348.0 (M^+, 100%). Elemental analysis found: C, 58.52; H, 4.90; N, 4.20 $C_{17}H_{17}NO_5S$ requires C, 58.78; H, 4.93; N, 4.03.

*Compound **5c***

White solid; m.p. 138–139 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.89 (t, J = 7.3 Hz, 3H, CH_3), 1.32–1.38 (m, 2H, CH_2), 1.56–1.61 (m, 2H, CH_2), 3.0 (s, 3H, CH_3), 4.11 (t, J = 6.5 Hz, 2H, CH_2), 6.48 (d, J = 15.6 Hz, 1H, –CH═), 7.02 (d, J = 7.8 Hz, 2H, 2 × *CH* arom), 7.10 (t, J = 7.3 Hz, 1H, 1 × *CH* arom), 7.30 (s, 1H, 1 × *CH* arom), 7.38–7.49 (m, 2H, 2 × *CH* arom), 7.51–7.58 (m, 3H, 2 × *CH* arom and –CH═), 9.6 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.5 (CH_3), 18.6 (CH_2), 30.2 (CH_2), 40.6 (CH_3), 63.6 (CH_2), 118.1, 118.2, 119.2, 123.4, 123.9, 124.2, 129.8, 131.0, 131.6, 143.1, 148.2, 156.4, 166.0 (C═O) IR (KBr, cm^{-1}) 3248 (NH), 1730 (C═O); MS (ES): *m/z* 390.0 (M^+, 100%). Elemental analysis found: C, 61.75; H, 5.90; N, 3.53 $C_{20}H_{23}NO_5S$ requires C, 61.68, H, 5.95, N, 3.60.

Conclusions

In conclusion, we have shown for the first time that the 4-iodo analog of nimesulide participates in palladium-mediated C–C bond forming reaction smoothly under Sonogashira (copper-free), Heck or Suzuki[16–18] reaction conditions. This study yielded a number of compounds of potential pharmacological interest. $Pd(OAc)_2$ and $^iPr_2NEt$ were found to be a common and effective

catalyst and base, respectively, for these coupling reactions. Our study provides easy access to the novel and diversity-based compounds structurally related to nimesulide, synthesis of which otherwise may be difficult or cumbersome via other conventional methods.

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Supporting information

Supporting information may be found in the online version of this article.

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