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Titanium-Promoted Acylation of Sulfonamides to *N*-Acylsulfonamide PPARα Antagonists

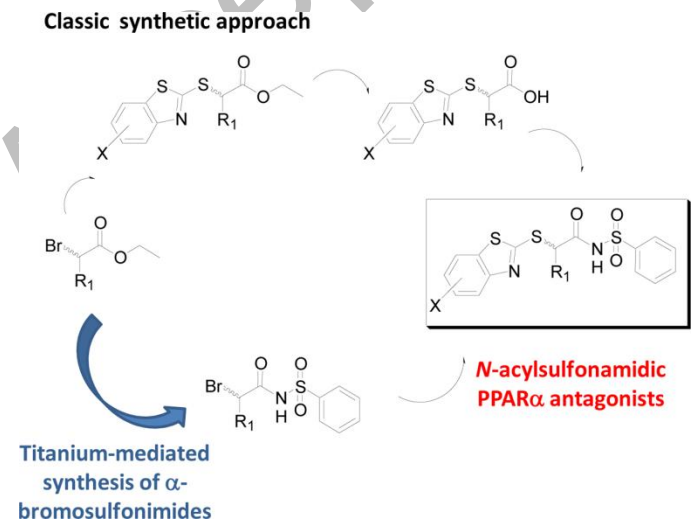
Alessandra Ammazzalorso[1], Maria Luisa Tricca[1], Isabella Bruno[1], Barbara De Filippis[1], Mauro Di Matteo[1], Marialuigia Fantacuzzi[1], Letizia Giampietro[1], Cristina Maccallini[1], Adriano Mollica[1], Rosa Amoroso[1]

[1]Dipartimento di Farmacia, Università G. d'Annunzio, 66100 Chieti, Italy

Corresponding Author to A. Ammazzalorso & R. Amoroso: Dipartimento di Farmacia, Università G. d'Annunzio, via dei Vestini 31, 66100 Chieti, Italy.
E-mail: aammazzalorso@unich.it (**A. Ammazzalorso**) Email: ramoroso@unich.it (**Rosa Amoroso**)

Abstract

The direct acylation of sulfonamides by esters represents an attractive strategy in organic chemistry, being an interesting alternative to classical approaches to *N*-acylsulfonamides. Here is described a simple and effective method to obtain *N*-acylsulfonamides of pharmaceutical interest, in a reaction promoted by titanium(IV) chloride. This strategy was successfully applied to the synthesis of a Peroxisome Proliferator-Activated Receptor α antagonist with a benzenesulfonimide moiety, ensuring an excellent yield of product. The reaction was further studied exploring the behaviour of different α-bromoesters and esters, and the effects of para-substitution in the benzenesulfonamide moiety.



KEYWORDS: PPARα antagonists, *N*-acylsulfonamides, Lewis acids, titanium tetrachloride, α-bromoesters

INTRODUCTION

Since the discovery in 1990s of Peroxisome Proliferator-Activated Receptors (PPARs), a large amount of work has been developed in the effort to clarify the biological role of three PPAR subtypes and their involvement in physiological and pathological conditions.[1-2] PPARα is highly expressed in metabolically active tissues and it is mainly implicated in lipid and lipoprotein metabolism;[3-4] the activation of PPAR improves insulin sensitivity and glucose homeostasis, in addition to anti-inflammatory properties.[5-6] PPAR interferes with lipid metabolism and cellular energetic homeostasis. [7] Potent and selective agonists, dual and pan-agonists were described and their important actions on lipid and glucose homeostasis were demonstrated.[8-10] In a parallel way, also PPAR inverse agonists and antagonists received great attention, because a reduced activation of these receptors ensured beneficial effects in energetic balance and glycemic control.[11-13] In recent years a number of PPAR antagonists has been described and their promising antitumoral effects have attracted research attention.[14] Blocking PPARα is emerging as a new interesting strategy to interfere with energetic metabolism of organisms, so potentially favourable in different cancer types, where metabolic pathways appear deregulated.[15-17] Also PPARγ and PPARδ antagonists could favourably interfere with survival and differentiation of cancer cells, determining apoptosis or arrest of cell growth.[18-19] In previous works we reported the identification of new *N*-acylsulfonamide PPARα antagonists, found to inhibit the nuclear receptor in low micromolar range.[20-21]

These compounds were developed starting from benzothiazole carboxylic acids, PPARα agonists at micromolar concentrations (Figure 1).[22]

The switch from a carboxylic acid to a sulfonimide moiety has been described as a chemical strategy to obtain PPARα antagonists, based on the hypothesis of the folding of helix 12, a substructure of ligand binding domain (LBD), responsible for the transcriptional activation of PPARs.[23] Sulfonimide group is often used in medicinal chemistry to replace carboxylic acid, being a bioisostere endowed with a comparable acidity (pK_a 4-5); its chemical and enzymatic stability to hydrolysis makes it amenable to being used as enzymatic inhibitor.[24-25] In the literature different synthetic approaches to *N*-acylsulfonamides have been described: in addition to coupling agents (carbodiimides, carbonyldiimidazole),[26-30] acylation of sulfonamides by acyl chlorides or anhydrides in basic or acidic conditions has been widely realized, also in the presence of catalysts.[31-36] Alternatively, *N*-acylbenzotriazoles were used as acylating agents in basic conditions.[37] Recently, the use of Lewis acid as catalyst in the preparation of sulfonimides has been described: a panel of Lewis acids were screened by using anhydrides or esters as acylating agents.[38-39] For the synthesis of our sulfonimide PPARα antagonists, we applied a classical synthetic route, by a direct coupling of carboxylic acids and sulfonamides in the presence of EDC as condensing agent.

In an attempt to explore a new synthetic route to *N*-acylsulfonamides, we decided to attempt a new strategy using esters as acylating agents; to this end, a recent work by *Fu et al* proposes the acylation of sulfonamides by esters in the presence of titanium chloride as

a promoter of the reaction. [40] This titanium-mediated strategy has been applied to a panel of esters, but in literature there are no examples of application to α-bromoesters, versatile and useful building blocks in medicinal chemistry. We decided to explore the applicability of this method to our compounds, starting from α-bromoesters, intermediates in our synthetic scheme (Figure 2).

To our knowledge, there are no previous examples of the transformation of α-bromoesters in α-bromosulfonimides; data from literature report the synthesis of α-bromosulfonimides by reacting sulfonamides with α-bromoacyl halides. [41-42]

In this paper we report the study of the applicability of titanium-mediated acylation of sulfonamides to our recently developed PPARα antagonists.

RESULTS AND DISCUSSION

Among the PPARα antagonists previously synthesized, we selected the isopropyl and phenyl derivatives (**1** and **2**, respectively) (Figure 3) as targets to tune up the new synthetic route. We chose the isopropyl derivative as an example of compound bearing an aliphatic substituent, endowed with a steric hindrance, and the phenyl derivative, that was the most promising compound due its biological profile. [20]

For the synthesis of the isopropyl derivative **1**, ethyl 2-bromo-3-methylbutanoate was reacted with benzenesulfonamides **3a-e** to obtain α-bromosulfonimide intermediates **4a-e**. The reactions were carried out in toluene or 1,1,2,2-tetrachloroethane (TCE) at 115 °C, in

a sealed tube, with a fixed $TiCl_4$ amount of 1.5 equivalents, found to be the best conditions in previous experiments (data not shown). Intermediate **4a** was reacted with 2-mercapto-5-chlorobenzothiazole, in basic conditions, to obtain target compound **1** in good yields (88%) (Scheme 1). In Table 1 data obtained for the synthesis of **4a-e** intermediates are reported.

Testing the ability of $TiCl_4$ in promoting the acylation of benzenesulfonamide, we observed a nearly quantitative yield of product in toluene at 115 °C for a time of reaction of 8 h (entry 1), whereas the yield drastically decreased by only changing the solvent (entry 2). When the same reaction was applied to a group of *p*-substituted benzenesulfonamides, we observed a general decrease of yields with respect to the unsubstituted derivatives. The reaction of *p*-toluensulfonamide in toluene afforded the product at 54-57% (entries 3-4), for reaction times of 8 and 24 h, respectively. By using TCE as solvent, a strong dependence on time of reaction was observed: yields of 31, 72, and 17% were obtained, respectively, after 8, 24, and 70 h of reaction (entries 5-7). The *p*-methoxy and *p*-chloro derivatives gave corresponding products with very similar yields (59 and 60%, entries 8-9); in this series, the best substitution was the *p*-nitro, with a recovery of product of 82% (entry 10), but changing the solvent the yield strongly decreased (37%, entry 11). These results clearly demonstrate the possibility to apply this strategy to our selected α-bromoester, with good to moderate yields depending on experimental conditions and differently substituted benzenesulfonamides. This procedure allowed us to strongly improve the way to prepare **1**, with a simplified synthetic route and excellent yield of reaction.

By comparison, the direct coupling of proper carboxylic acid and benzenesulfonamide by EDC fournished **4a** in 69% yield.

With these good results, we tried to apply the same synthetic strategy to phenyl derivative **2**, starting from ethyl α-bromophenylacetate (Scheme 2, Table 2). The classical synthesis with EDC gave desired product in 30% yield.

Unfortunately, the *N*-acylation of benzenesulfonamides by ethyl α-bromophenylacetate did not afford the desired products, in the different experimental conditions tested (entries 1-10). The variation of solvent, temperature, reaction time and *p*-substitution of benzenesulfonamide had no effect in the outcome of the reactions: crude materials clearly showed the presence of unreacted sulfonamides and parts of starting □-bromoester. From these results it is evident that the substituent in α position to the bromoester strongly influences the reaction: whereas the isopropylic substituent allows the *N*-acylation of the substrate, the aromatic ring negatively affects the reaction.

In an attempt to clarify this result we applied the same synthetic strategy to the ethyl phenylacetate. Our aim was to verify if the presence of an aromatic ring in Cα to the ester could disallow the reaction, or if the failure has to be ascribed to the contemporary presence, in the starting, of a bromine atom and a phenyl ring on Cα. Results obtained in the reaction between ethyl phenylacetate and benzenesulfonamides **2a-e** (Scheme 3) are shown in Table 3.

Both solvents tested, toluene and TCE, allowed the transformation of ethyl phenylacetate in the corresponding benzenesulfonimide **5a**, at 115 °C; for a reaction time of 8 h in toluene, 72% yield was obtained (entry 1). The yield decreased by prolonging time of reaction (66% and 17% for 24 h and 70 h, respectively, entries 2 and 4). TCE allowed the transformation, with yields of 64 and 26%, for 24 and 70 h, respectively (entries 3 and 5). Testing *p*-substituted benzenesulfonamides, an overall decrease in yields was observed. The *p*-toluensulfonamide was reacted in different experimental conditions, producing moderate yields of product in TCE (45%, entry 9). The *p*-methoxy and *p*-chlorobenzenesulfonamides gave low yields (entries 11-12), whereas *p*-nitrobenzenesulfonamide afforded 43% of product (entry 13). These experiments show the titanium mediated approach as a valuable alternative in the synthesis of *N*-acylsulfonamides starting from proper esters and α-bromoesters.

In conclusion, the titanium-promoted acylation of sulfonamides by esters was studied and its applicability was tested to obtain sulfonimide PPARα antagonists. The reactions gave good yields of product with ethyl 2-bromo-3-methylbutanoate; the possibility to use α-bromoesters as acylating agents opens interesting views for organic and medicinal chemistry. This method was extended to *p*-substituted benzenesulfonamides, providing desired sulfonimides in moderate to good yields.

The study of titanium-mediated acylation of sulfonamides was further extended including ethyl α-bromophenylacetate and ethyl phenylacetate. Results of our experiments showed

no conversion in sulfonimides for the first α-bromoester, and yields of products good to moderate for ethyl phenylacetate.

EXPERIMENTAL

All the solvents and commercial reagents were used as received from Aldrich or Fluka. Reactions were monitored employing precoated silica gel 60 F_{254} plates (Merck). NMR spectra were run at 300 MHz on a Varian instrument with TMS as internal standard; chemical shifts (δ) are reported in ppm and coupling constants, *J*, are expressed in Hertz (Hz). Melting points were determined on a Büchi B-540 apparatus and are uncorrected. Infrared spectra were recorded on a FT-IR 1600 Perkin-Elmer spectrometer. Microanalyses were carried out with an Eurovector Euro EA 3000 model analyser and the analytical results were within 0.4% of the theoretical values.

General Procedure For Direct *N*-Acylation Of Benzenesulfonamides

Benzenesulfonamide (1.2 mmol), ethyl α-bromophenylacetate or ethyl phenylacetate (2.4 mmol), and toluene (4 mL) were combined in a sealed tube equipped with a stir bar. The mixture was stirred at 50 °C for 10 min, then $TiCl_4$ (1.8 mmol) was added and the reaction mixture was heated to 115 °C. After a variable period of time the mixture was diluted with H_2O (10 mL) to remove the excess of $TiCl_4$, filtered and extracted with AcOEt (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was evaporated *in vacuo*. Crude compounds were purified by flash column chromatography (silica gel; cyclohexane / AcOEt 8:2).

ACKNOWLEDGEMENTS

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SUPPLEMENTAL MATERIAL

Full experimental detail, ^{1}H and ^{13}C NMR spectra for this article can be accessed on the publisher's website.

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Table 1. *N*-acylation of benzenesulfonamides **3a-e** by ethyl 2-bromo-3-methylbutanoate [a]

Entry	R	Solvent	Time (h)	Yield % [b]
1	H	toluene	8	98 (**4a**)
2	H	TCE	8	23 (**4a**)
3	CH_3	toluene	8	54 (**4b**)
4	CH_3	toluene	24	57 (**4b**)
5	CH_3	TCE	8	31 (**4b**)
6	CH_3	TCE	24	72 (**4b**)
7	CH_3	TCE	70	17 (**4b**)
8	OCH_3	toluene	24	59 (**4c**)
9	Cl	toluene	24	60 (**4d**)
10	NO_2	toluene	24	82 (**4e**)
11	NO_2	TCE	24	37 (**4e**)

[a] Reaction conditions: ester (2.4 mmol), benzenesulfonamide (1.2 mmol), $TiCl_4$ (1.8 mmol), solvent (4 mL). Reactions were carried out in a sealed tube. [b] Isolated yield obtained after chromatographic purification.

Table 2. Experimental conditions tested to *N*-acylation of benzenesulfonamides **3a-e** by ethyl α-bromophenylacetate.[a]

Entry	**R**	**Solvent**	**Temperature (°C)**	**Time (h)**
1	H	toluene	115	24
2	H	TCE	115	24
3	H	TCE	145	70
4	CH_3	toluene	115	36
5	CH_3	TCE	110	20
6	CH_3	TCE	115	24
7	CH_3	TCE	130	70
8	OCH_3	toluene	115	24
9	Cl	toluene	115	24
10	NO_2	toluene	115	24

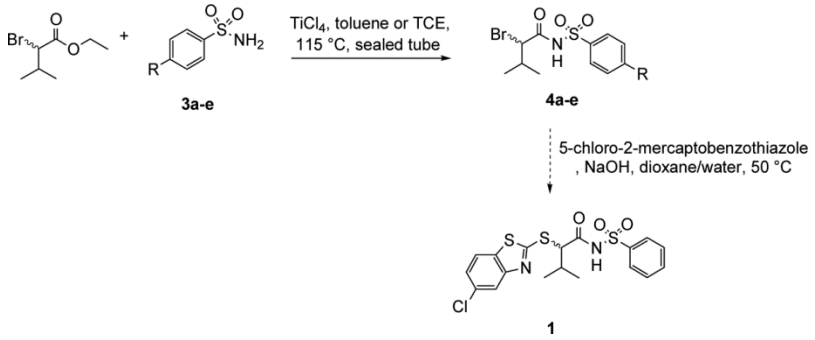
[a] Reaction conditions: ester (2.4 mmol), benzenesulfonamide (1.2 mmol), $TiCl_4$ (1.8 mmol), solvent (4 mL). Reactions were carried out in a sealed tube.

Table 3. *N*-acylation of benzenesulfonamides **3a-e** by ethyl phenylacetate.[a]

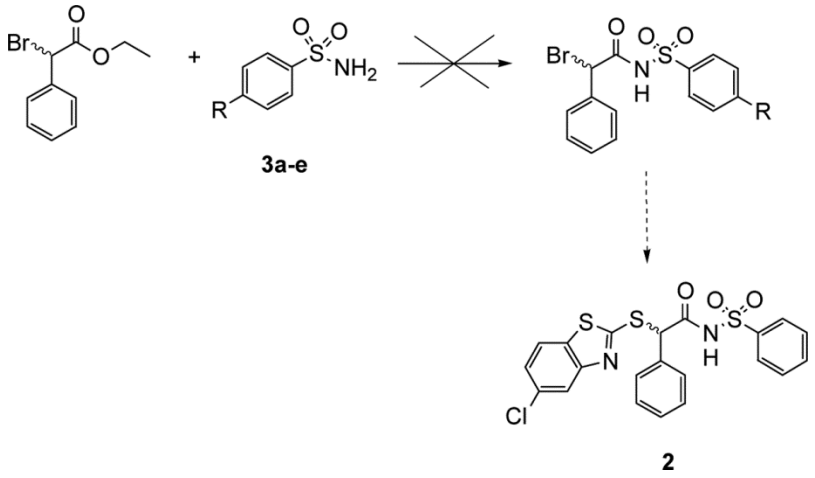
Entry	R	Solvent	Time (h)	Yield %[b]
1	H	toluene	8	72 (**5a**)
2	H	toluene	24	66 (**5a**)
3	H	TCE	24	64 (**5a**)
4	H	toluene	70	17 (**5a**)
5	H	TCE	70	26 (**5a**)
6	CH_3	toluene	8	18 (**5b**)
7	CH_3	TCE	8	35 (**5b**)
8	CH_3	toluene	24	23 (**5b**)
9	CH_3	TCE	24	45 (**5b**)
10	CH_3	TCE	70	19 (**5b**)
11	OCH_3	toluene	24	21 (**5c**)
12	Cl	toluene	24	22 (**5d**)
13	NO_2	toluene	24	43 (**5e**)

[a] Reaction conditions: ester (2.4 mmol), benzenesulfonamide (1.2 mmol), $TiCl_4$ (1.8 mmol), solvent (4 mL). Reactions were carried out in sealed tube. [b] Isolated yield obtained after chromatographic purification.

Scheme 1. Synthetic route to compound **1** via α-bromosulfonimide intermediates **4a-e**.



Scheme 2. Synthetic route to compound **2** via α-bromosulfonimide intermediates.



Scheme 3. Synthetic route to sulfonimides **5a-e**

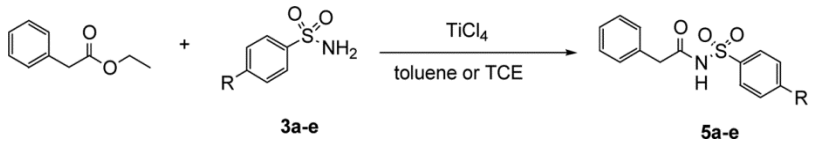
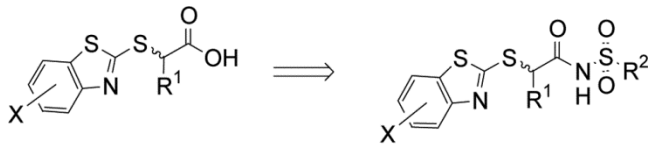


Figure 1. From carboxylic PPARα agonists to sulfonimide PPARα antagonists.



X= Cl, OEt
R^1= Alk, Ph

X= Cl, OEt
R^1= Alk, Ph
R^2 = Ph, Me

Figure 2. Classical and titanium-mediated synthetic approach to the synthesis of sulfonimide PPARα antagonists.

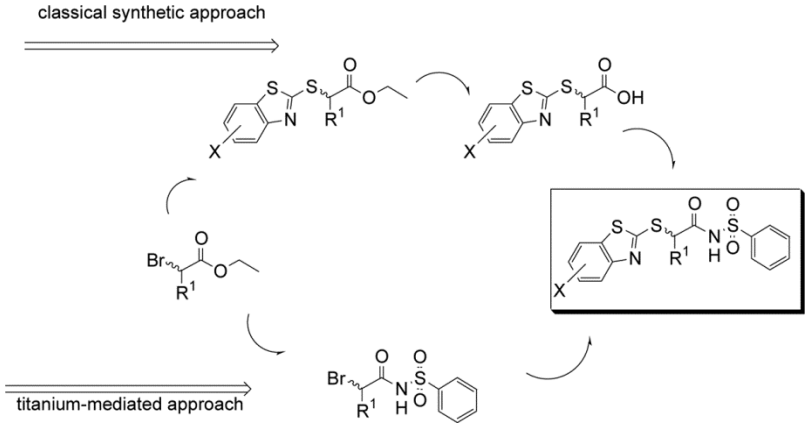
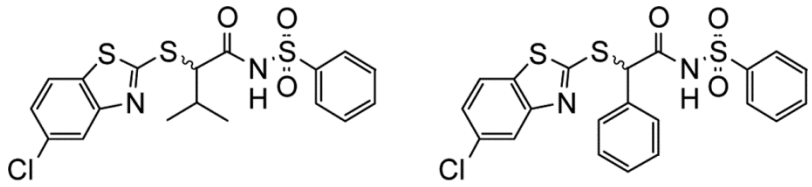


Figure 3. Target compounds **1** and **2**.



1 **2**