Tetrahedron 74 (2018) 2575–2583

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Catalyst-free Friedel-Crafts reaction of 1-(*N*-acylamino)alkyltriarylphosphonium salts with electron-rich arenes

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ARTICLE INFO

Article history:
Received 8 February 2018
Received in revised form
23 March 2018
Accepted 25 March 2018
Available online 7 April 2018

Keywords:
Friedel-Crafts-reaction
α-Amidoalkylation
α-Amidoalkylating agents
Phosphonium salts
Arenes
Amides

ABSTRACT

Friedel-Crafts reaction of 1-(*N*-acylamino)alkyltriarylphosphonium salts with arenes or heteroarenes without the need for any catalyst provided access to a wide range of biologically interesting *N*-(1-arylalkyl)amides or 1-arylalkylphosphonium salts which can be of great interest in the chemistry of ylides and phosphonium ionic liquids. Depending on reaction conditions and substrate structure, the reaction can be conducted selectively with high yields toward each of the above-mentioned products. Mechanistic aspects of the above transformations were also considered.

1. Introduction

Phosphonium salts are commonly used in chemistry as phase transfer catalysts or solvents (phosphonium ionic liquids),[1–4] but most of all as reagents in many reactions, especially as ylide precursors in the Wittig reaction, which is of great importance in the synthesis of biologically active substances.[5–8]

The specific types of phosphonium salts which have interesting chemical properties are 1-(*N*-acylamino)alkylphosphonium salts **1**. Individual structural features, including the presence of an acylamino group in the direct neighborhood of a positively charged phosphonium moiety, make the 1-(*N*-acylamino)alkylphosphonium salts **1** effective precursors of *N*-acyliminium cations **2** in α-amidoalkylation reactions (Scheme 1).[9–13]

One of the most important transformations, from the organic synthesis point of view, are reactions of carbon-carbon bond formation. The α-amidoalkylations of aromatics or heteroaromatics are examples with great potential of the synthetic methods available for C—C bond formation, which have developed and improved for a number of years.[14–24] α-Amidoalkylation of arenes was first performed by Einhorn at the beginning of the 20th century. The Einhorn method was based on Brønsted-acid-catalyst aromatic electrophilic alkylation (the Friedel-Crafts-type reaction) using (*N*-hydroxymethyl)amide as the alkylating reagent.[25] Over the past few decades, variations of this methodology include the use of a variety of catalysts and extension of the structure of α-amidoalkylating agents have been developed.[20,26–31] In 1991 Katritzky described α-amidoalkylation of active aromatic compounds with *N*-[1-(benzotriazol-1-yl)alkyl]amides in the presence of aluminum chloride (the classical course of the reaction, Scheme 2/a).[20] More recently, 1-(*N*-acylamino)alkyl sulfones were used as effective α-amidoalkylating agents in the Friedel-Crafts reaction. However, in the case of α-amido sulfones, the products differ depending upon reaction conditions and substrate structures. Petrini showed that *N*-[1-(phenylsulfonyl)alkyl]oxazolidin-2-ones in the presence of $TiCl_4$ at −78 °C react smoothly with aromatic compounds to give the expected adducts in good yields (the classical course of the reaction, Scheme 2/b).[26] On the other hand, at higher temperature and in the presence of an acidic catalyst (Lewis acid, amberlyst-15, montmorillonite K10) unusual reaction products have been obtained (the non-classical course of the reaction, Scheme 2/c).[27–30] Although the course of the α-amidoalkylation of

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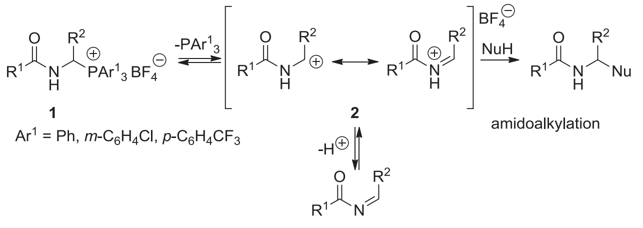
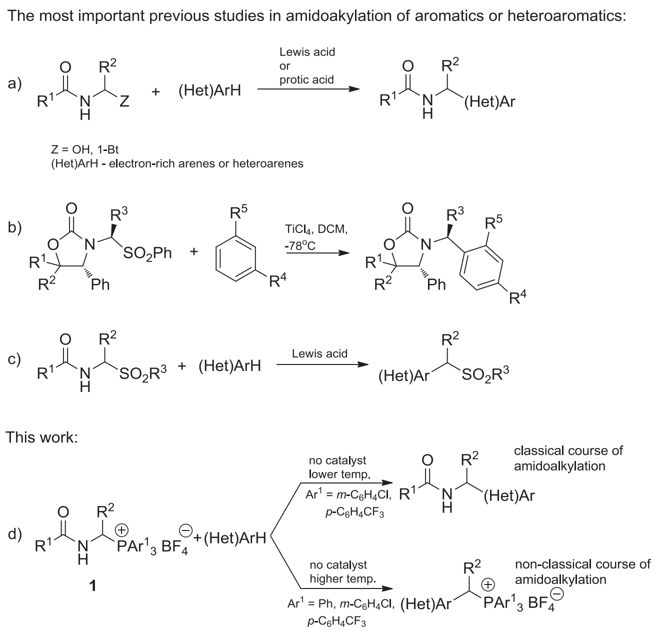
https://doi.org/10.1016/j.tet.2018.03.053



Scheme 1. 1-(*N*-acylamino)alkylphosphonium salts as an α-amidoalkylating agents.



Scheme 2. α-Amidoalkylation of electron-rich arenes and heteroarenes – various synthetic routes.

aromatics has been the subject of many studies, the literature gives no information on factors, excluding the influence of temperature and the substrate structures, deciding on the classical or non-classical direction of the reaction.

In this paper, we present attempts to conduct the α-amidoalkylation reaction of aromatics or heteroaromatics using 1-(*N*-acylamino)alkylphosphonium salts — a new class of effective α-amidoalkylating agents recently introduced into organic chemistry.[9–13] The course of the reaction was investigated, its plausible mechanism was proposed, but above all the criteria to control the direction of a reaction either in the classical or non-classical manner were evaluated.

2. Results and discussion

Although 1-(*N*-acylamino)alkylphosphonium salts are very reactive α-amidoalkylating reagents, the possibility of their α-amidoalkylation of aromatics or heteroaromatics has not been investigated so far. Therefore, we studied whether such reactions can be performed. The reactivity of phosphonium salts toward aromatic systems was conducted based on a reaction of 1-(*N*-pivaloylamino)ethyltriphenylphosphonium tetrafluoroborate **1a** with 1,3,5-trimethoxybenzene. The progress of the reaction was monitored based on NMR spectroscopy. Surprisingly, the analysis of NMR spectra of the reaction mixture indicated that the amidoalkylation product **3g** was not formed at all. The main reaction product was another phosphonium salt: 1-(2,4,6-trimethoxyphenyl)ethyltriphenylphosphonium tetrafluoroborate **4f** (see Scheme 3). Other triphenylphosphonium salts **1** react with 1,3,5-trimethoxybenzene in a similar way (entries 10, 11, 13 and 14, Table 1). The use of different aromatics or heteroaromatics affected the reaction conditions. For comparison, reactions of 1-(*N*-pivaloylamino)ethyltriphenylphosphonium tetrafluoroborate **1a** with 1,3,5-trimethoxybenzene, 1,3-dimethoxybenzene and indole occur at 80 °C, 100 °C and 80 °C, respectively but reactions with less active anisole or thiophene require much higher temperatures: 150 °C or even 180 °C in the case of the latter (entries 7, 2, 15, 1 and 16, Table 1).

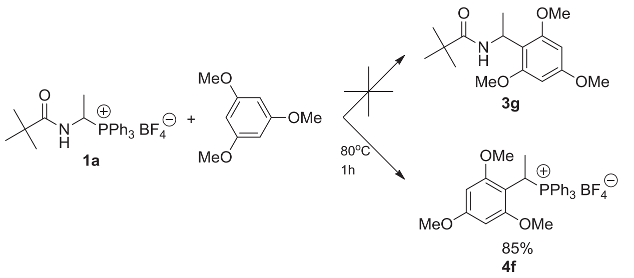
However, in each example, the main reaction products were 1-arylalkylphosphonium salts **4 -** products of the non-classical course of the reaction. Attempts to perform the reaction with non-activated or deactivated arenes such as toluene, benzene or chlorobenzene failed.

Recently, we have demonstrated that $C_α$-P^+ bond strength can be reduced by replacing the triphenylphosphonium moiety by more electron-withdrawing tris[(*p*-trifluoromethyl)phenyl]phosphonium or tris(*m*-chlorophenyl)phosphonium groups.[31] Such a reduction makes the generation of *N*-acyliminium cations easier, which facilitates the reaction with aromatics and allows it to be carried out under milder conditions.

To this end, we synthesized and tested 1-(*N*-acylamino)alkylphosphonium salts **1** derived from tris(*m*-chlorophenyl)phosphine or tris[*p*-(trifluoromethyl)phenyl]phosphine. First, we performed the reaction of 1-(*N*-pivaloylamino)ethyltris(*m*-chlorophenyl)phosphonium tetrafluoroborate **1f** with 1,3,5-dimethoxybenzene. The progress of the reaction was monitored by NMR spectroscopy. As we expected, the reaction occurs in milder conditions, even at room temperature. This time, both possible compounds **3g** and **4g** were detected in the reaction mixture. Changes in the concentration of substrate **1f**, classical **3g** and non-classical product **4g** as a function of time were measured and these are shown in Fig. 1.

The concentration of the classical product **3g** quickly reaches its maximum and then recedes, while the concentration of the non-classical product **4g** at the beginning of the reaction is low and then rapidly grows. The induction period, which is characteristic for the formation of the final product in the consecutive-type reaction, is very clearly visible. Furthermore, it can be seen that the reaction rate constant k_1 for the formation of the classical product **3g** is higher than the reaction rate constant k_2 for the transformation of the classical product to the non-classical product **4g**. A favorable ratio of the rate constants k_1/k_2 seems to be crucial for the possibility of separating the classical reaction product.

A plausible mechanism, which explains described kinetic facts, is shown in Scheme 4. In the first step, there is a typical electrophilic aromatic substitution S_EAr. *N*-Acyliminium cation **5** generated from 1-(*N*-acylamino)alkylphosphonium salt **1** reacts smoothly with activated arene (Friedel-Crafts type reaction). In the next step, the protonation of amide **3** occurs, which initiates its



Scheme 3. Reaction of 1-(*N*-pivaloylamino)ethyltriphenylphosphonium tetrafluoroborate **1a** with 1,3,5-trimethoxybenzene.