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Nafion®-catalyzed microwave-assisted Ritter reaction: an atom-economic solvent-free synthesis of amides

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Abstract

An atom-economic solvent-free synthesis of amides by the Ritter reaction of alcohols and nitriles under microwave irradiation is reported. This green protocol is catalyzed by solid-supported Nafion®NR50 with improved efficiency and reduced waste production.

Keywords: Ritter reaction; Amides; Nafion®NR50; Solvent-free reaction; Microwave irradiation

Amides are common moieties in naturally occurring substances like peptides and proteins and are also found in various synthetic materials.[1,2] This makes the amide functionality an important building block in synthetic chemistry and many methods for its synthesis were reported in the literature.[1] In general, amides are formed by the condensation of carboxylic acid and amines, using various coupling agents.[3] Although good results were obtained using this protocol, the reaction conditions were very harsh. In 1948, Ritter reported the efficient synthesis of amide by the reaction of alkenes with nitriles,[4] in which alcohols can also be used instead of alkenes.[5,6] In recent years, several alternative methodologies have been developed for Ritter reaction using sulfuric and other acid catalysts,[7–10] metal complexes,[11] trifluoromethanesulfonic anhydride,[12] and boron trifluoride etherate.[13] The main disadvantages of these methods are the use of toxic catalysts or corrosive acids.

Use of solid-supported acids, such as silica-sulfuric acid, P_2O_5/SiO_2,[10] and $Cs_{2.5}H_{0.5}PW_{12}O_{40}$, was also made for this reaction;[14] however, reuse of these catalysts is not possible. Olah et al. in 1987 reported the use of Nafion-H as an efficient catalyst for the Ritter reaction.[15] This is an excellent protocol in terms of catalyst reusability and product yield; however, harsh reaction conditions, longer reaction time, and the use of excessive nitrile make this method non-sustainable. In view of the emerging interest in microwave chemistry,[16,17] and in keeping with our emphasis on the development of green synthetic methods,[17,18] we revisited this protocol. The primary objective of this project was to find an economical and greener method for the conversion of nitrile into the corresponding N-monosubstituted amide, and herein we report Nafion®NR50[18a,19]-catalyzed atom-economic solvent-free Ritter reaction under microwave (MW) irradiation (Scheme 1).

After screening a range of MW power, reaction temperature, and time, and exploring the scope of various solvents, we found that the solid-supported Nafion®NR50 was the most efficient catalyst for Ritter protocol at 130 °C under MW irradiation (200 W), in the absence of any solvent. The efficiency of this protocol was then studied for the synthesis of various amides, and the results are summarized in Table 1.

Various alcohols reacted efficiently with nitriles to afford the corresponding amides in good yields (entries 1–15). The generality and scope of this protocol was evaluated for a wide range of alcohols, bearing both electron withdrawing

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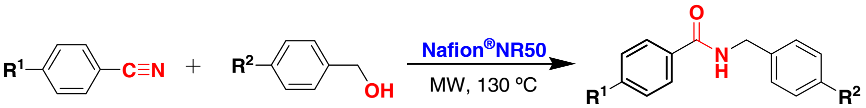


R^1 = H, OMe, Cl
R^2 = H, Me, OMe, Cl, naphthyl,
adamantyl etc

Scheme 1. Nafion®NR50-catalyzed solvent-free Ritter reaction under MW irradiation.

Table 1
Nafion®NR50-catalyzed Ritter synthesis of amides under MW irradiation[a]

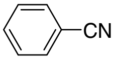
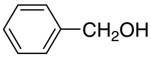
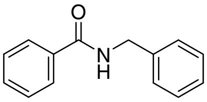
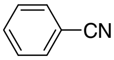
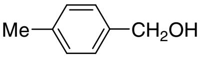
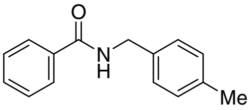
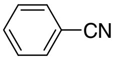
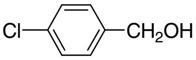
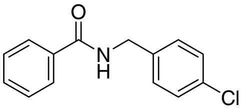
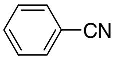
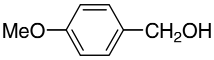
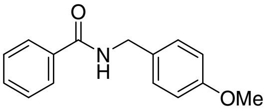
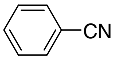
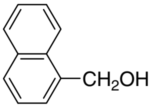
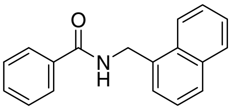
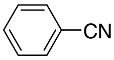
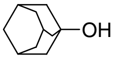
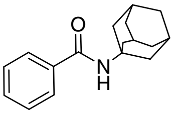
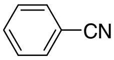
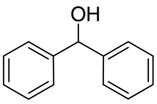
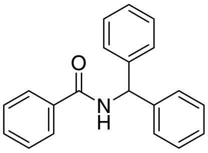
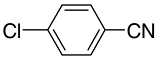
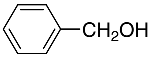
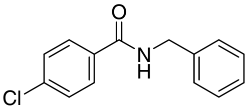
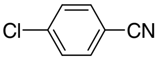
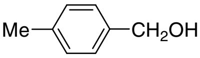
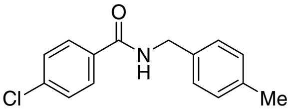
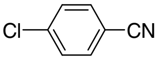
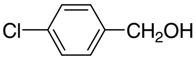
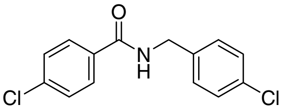
Entry	Nitrile	Alcohol	Product	Yield[b] (%)
1				92
2				88
3				86
4				86
5				82
6				90
7				72
8				88
9				86
10				85

Table 1 (*continued*)

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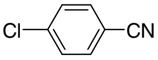
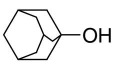
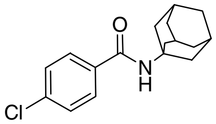
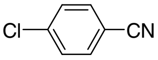
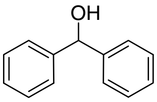
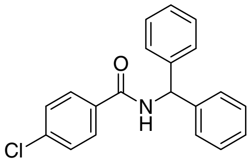
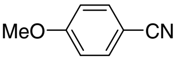
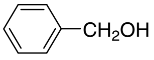
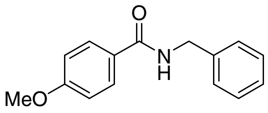
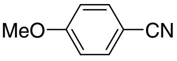
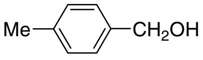
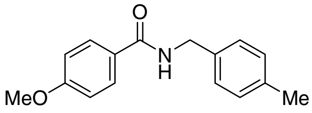
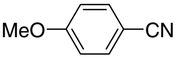
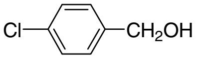
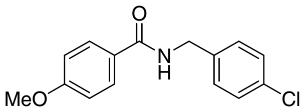
11				89
12				70
13				88
14				85
15				86

[a] Reaction temperature 130 °C, time 30 min, and no solvent.

[b] GC yields.

(entries 3, 4, 10, 15) and donating (entries 2, 9, 14) substituents, and a variety of aryl nitriles. In all the cases, the Ritter reaction proceeded efficiently and yielded the desired amides in good to excellent yields, under solvent-free conditions. It is noteworthy to mention that these reactions proceeded efficiently without any solvent, even though they involved the use of heterogeneous solid-supported catalyst. This is due to the selective absorption of microwaves by reactants, polar intermediates, and Nafion, which accelerated the reaction rate.[20] These reactions also get completed under conventional heating in an oil bath in a sealed tube but require an extended period of time, 6–8 h.

As compared to Olah's protocol,[15] which requires longer reaction time (18–48 h) and an excess amount of nitrile, the present method needs only 30 min for the completion of the reaction, with stoichiometric amounts of nitrile and alcohol. This protocol is also superior to the recently reported P_2O_5/SiO_2 method,[10] in which handling and reuse of the catalyst is difficult. However, the salient feature of this procedure is the ease of handling the catalyst Nafion®NR50, as it involves the simple addition of solid Nafion beads (like a glass bead) in a reaction vessel, which can be physically removed by forceps after the completion of the reaction.

For practical applications of the catalyst Nafion®NR50, the lifetime of the catalyst and its level of reusability are important factors. The catalyst showed excellent recyclability in this Ritter condensation of alcohols with nitriles. The reactions were conducted under similar conditions (130 °C/30 min) without any solvent. After the completion of the first reaction to afford the corresponding amide, the catalyst was recovered by forceps, washed with acetone, and dried. The catalyst was then used in a new reaction with fresh reactants under the same conditions; Nafion®NR50 could be used at least 6 times without any change in activity.

In conclusion, we have demonstrated an atom-economic Ritter approach for the synthesis of amides, which may find useful application in sustainable synthetic chemistry. Also, the use of solid-supported, relatively low toxic, and inexpensive Nafion®NR50 as a catalyst and the solvent-free reaction conditions are additional eco-friendly attributes of this synthetic protocol.

Experimental: The alcohol (1 mmol), nitrile (1.1 mmol), and Nafion®NR50 (50 mg) were placed in a 10 mL crimp-sealed thick-walled glass tube equipped with a pressure sensor and a magnetic stirrer. The contents were mixed on a rota-mixer and the reaction tube was placed inside the cavity of a CEM Discover focused microwave synthesis system, operated at 130 ± 5 °C (temperature monitored by a built-in infrared sensor), power 20–200 W, and pressure 5–30 psi for 30 min (Table 1). After the completion of the reaction, the solid catalyst was physically removed by forceps, to isolate crude amides, which were further purified by crystallization/column chromatography.

Acknowledgment

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