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Microwave-Assisted Synthesis of Isonitriles: A General Simple Methodology

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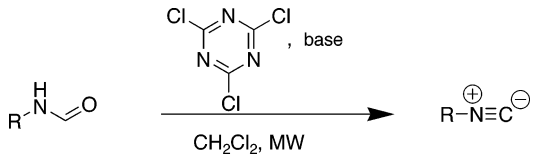

A facile conversion of formamides to isonitriles under very mild conditions and microwave irradiation is described. This simple and efficient method has been applied for the synthesis of both aliphatic and aromatic isonitriles in high yields.

Multicomponent reactions have become an important component of the combinatorial chemist's library, as a great number of compounds can be produced in a rapid parallel synthetic program.[1] Thus, the Passerini[2] and Ugi[3] reactions, for example, have become well-established procedures in library synthesis.

One of the most important and recurring reagents of these reactions, although very limited in accessibility, is the isonitrile. Isonitriles are versatile intermediates, with a extraordinary functional group, owing to their unusual reactivity, acting as both nucleophiles and electrophiles in the course of the reaction. Many natural isonitriles are known to have a strong antibiotic, fungicidal, or antineoplastic effect. Isonitriles are also used as versatile building blocks for the synthesis of heterocyclic systems.[4] Recently a series of terpene isonitriles have been reported to show significant antimalarial activity in vitro.[5]

There are several methods reported for isonitrile synthesis, by dehydration of formamides with various reagents,[6] using chlorodimethylformiminium chloride,[7] phosphoryl chloride,[8] phosgene[9] or diphosgene,[10] DABCO,[11] aryl chlorothionoformate,[12] and supported sulfonyl chlorides under microwave irradiation.[13] Unfortunately, most of these methods have limited utility and applicability due to the extreme toxicity and cumbersome handling, and high costs in the availability of the reagents. Sometimes the reagents employed require tedious preparation procedures or workup, and purification of the reaction product can be problematic due to the reactivity of the isonitriles.

Taking into account our interest in the application of Ugi reaction for the synthesis of new building blocks for combinatorial chemistry, we investigated the possibility to synthesize isonitriles using a very cheap reagent, such as 2,4,6-trichloro[1,3,5]triazine (cyanuric chloride, TCT),[14] as dehydration agent of formamides.[15] The reaction was checked using a CH_2Cl_2 solution of TCT (1 equiv) and the formamide, which was charged with pyridine (2 equiv), and the mixture was refluxed on a water bath. Under these conditions the characteristic isonitrile odor was evident but the reaction occurred generally with modest yields.

Automated and focused microwave flash heating was recently proven to improve the preparative efficiency and to dramatically reduce reaction times for several different types of organic transformations.[16] Moreover, recent advances in the microwave instrumentation have made this technique more accessible and the results more reproducible. "Although the basis of these practical benefits remains speculative,[17] the preparative advantages are obvious and have motivated a large and continuing survey of nearly all classes of thermal reactions for improvement upon microwave heating.

In light of the improvements, microwave-assisted organic synthesis has bestowed upon similar thermal

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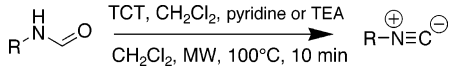
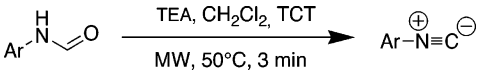
SCHEME 1. Synthesis of Aliphatic Isonitriles



SCHEME 2. Synthesis of Aromatic Isonitriles



reactions, reinvestigation of the previous conditions seemed warranted." [22] Initial efforts focused on optimizing microwave conditions for the formation of aliphatic isonitriles based on prior investigations of conventional thermal conditions.

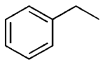
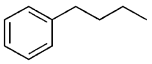
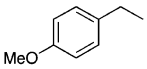
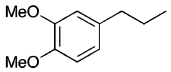
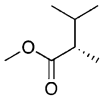
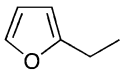
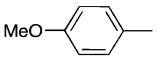
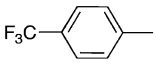
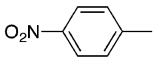
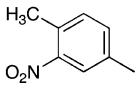
The above reaction was successfully reinvestigated (Scheme 1, entries 1 and 5) using microwave irradiation.[18] Thus the method became very reproducible and gave the desired products in excellent purities and good yields.[19] For the synthesis of aliphatic isonitriles, TCT (1 equiv), formamide (1 equiv), CH_2Cl_2, and the base (pyridine or TEA, 2 equiv) were placed sequentially under stirring in a sealed tube (CEM designed 10-mL pressure-rated reaction vial) and the reaction mixture was exposed to microwave irradiation for 10 min at 100 °C (method A, Scheme 1). The procedure could be used directly on formamides of amino acid methyl esters.

Our encouraging results in the synthesis of aliphatic isonitriles under microwave condition motivated us to assess whether the procedure may be extended to prepare aromatic isonitriles. A general method was desired, although primarily we were interested in making isonitriles from aliphatic formamides for further use as precursors for MCR reactions. Unfortunately, following the above protocol, no result was obtained with aromatic formamides.

However, after several attempts, the method was successfully applied to aromatic formamides simply by changing the base, the order of addition of the reagents, and carrying out the reaction under microwave irradiation at higher temperatures. Moreover, the best results were obtained using 3 equiv of TCT. In a typical procedure, formamide (1 equiv), TEA (3.3 equiv), CH_2Cl_2, and TCT (3 equiv) were placed sequentially under stirring and at 0 °C in a sealed tube and the reaction mixture was promptly exposed to microwave irradiation for 3 min at 50 °C (method B, Scheme 2).

The desired products were recovered in pure form and in high yields simply by washing the final reaction mixture with a saturated solution of $KHSO_4$ and concentrating the CH_2Cl_2 extracts at reduced pressure (Table 1). The triazine byproducts are easily removed by this simple aqueous workup. As can be seen from the table, this procedure provides a general, convenient method for the preparation of isonitriles; cyclic, acyclic, benzylic, and aromatic isonitriles have been prepared in very good yield. Optically active isonitriles can also be prepared (Table 1, entry 9).

TABLE 1. Conversion of Formamides RNHCHO to Isonitriles by TCT/Base Methods

entry	R	method	yield %
1	*n*-pentyl	A	81
2	*n*-heptyl	A	80
3	*tert*-butyl	A	85
4		A	96
5		A	98
6		A	95
7		A	90
8		A	90
9		A	80
10		A	86
11		B	90
12		B	75
13		B	90
14		B	92
15		B	90

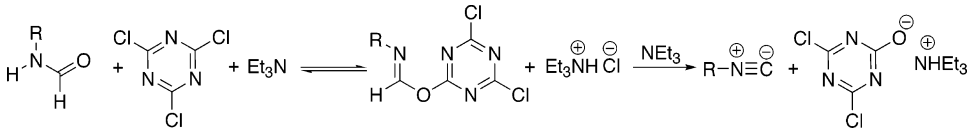
On the basis of previous hypothesis, we can postulate that even in these cases, the reaction of formamides with TCT and bases proceeds through the formation of an *O*-acylated intermediate, followed by the nucleophilic α-elimination of a proton and a TCT-derivative anion (Scheme 3).

Finally, taking into account the high reactivity of this kind of substrate and in particular for avoiding their bad

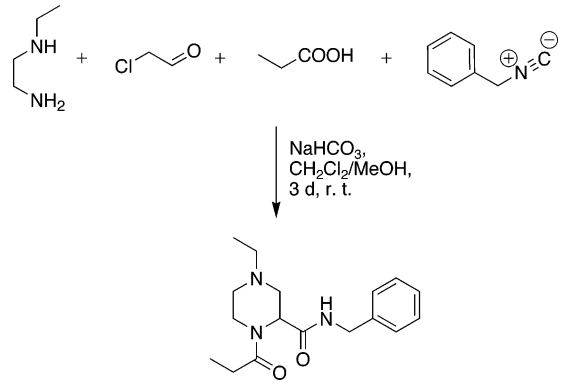
(18) All the reactions were performed with a self-tuneable microwave synthesizer. The MW experiments were performed in a self-tuning single mode CEM Discover Focused Synthesizer apparatus. The instrument continuously adjusted the applied wattage to maintain the desired temperature.

(19) For comparison, the reaction in Scheme 1 (entry 1) was also conducted using a preheated oil bath under otherwise identical conditions as for the microwave reaction, i.e., (sealed vial), RNHCHO, base, 100 °C, 10 min. As expected, lower conversion (7%) was observed with the traditional thermal conditions as compared to that with microwave irradiation (81%, Table 1).

SCHEME 3. Postulated Mechanism for the Isonitrile Synthesis



SCHEME 4. Synthesis of 2,5-Piperazines by MCR Approach



smell, we have checked the possibility that the CH_2Cl_2 solution containing isonitrile can be used directly in further reactions without any purification except the simple filtration of the salts formed.

The possibility was examined by the solution-phase synthesis of 2,5-piperazines[20] (Scheme 4). This MCR reaction is operationally very easy to perform and represents a versatile route to substituted piperazines that are important pharmacophores and attractive building blocks in the synthesis of peptide mimetics.[21]

Thus, the reaction mixture containing benzyl isocyanide, according to method A (entry 10, Table 1), was filtered on Celite and added to an equimolar mixture of *N*-1-ethylethane-1,2-diamine, chloroacetaldehyde, and propanoic acid in MeOH. The mixture was stirred for 48 h with 1 equiv of $NaHCO_3$ and the resulting *N*-benzyl-4-ethyl-1-propionylpiperazine-2-carboxamide (88% yield, 98% HPLC purity) was obtained after diluted with EtOAc, washed with 5% $NaHCO_3$ solution, dried, and concentrated in vacuo. The compound was further purified by flash chromatography: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.25 (s, 1H), 7.37−7.24 (m, 5H), 5.28 (s, 2H), 4.56−4.35 (m, 1H), 4.01−3.88 (m, 1H), 3.74−3.43 (m, 4H), 3.06 (q, 2H), 2.58 (q, 2H), 1.41 (t, 3H), 1.11 (t, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 172.7, 141.3, 127.7, 127.0, 125.1, 119.8, 66.8, 59.4, 51.5, 48.8, 47.3, 41,4, 13.4, 10.3. Anal. Calcd for $C_{17}H_{25}N_3O_2$: C, 67.30; H, 8.31; N, 13.85. Found: C, 67.39; H, 8.22; N, 13.71.

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Supporting Information Available: Physical and spectroscopic data for all unknown compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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