Straightforward Uranium-Catalyzed Dehydration of Primary Amides to Nitriles

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During the last few years the coordination chemistry of uranium has been rediscovered and numeral exciting coordination motifs have been approached.[1] Based on the reported achievements and the intrinsic abilities of uranium, fascinating purposes have been proposed for the future, including material science and catalysis.[2] However, even if several hundred well-defined uranium complexes are accessible, the application in homogeneous catalysis has been so far scarcely reported, for example, hydroaminations, hydrosilylations, polymerization, and reductions.[3] Besides, several uranium precursors are available as industrial side products on a large scale. Hence, studies to investigate the potential of uranium and therefore convert a waste product to a valuable catalyst will be highly desired.[2a] On the other hand, from the organic chemistry point of view, compounds containing nitrile functionalities are broadly applied in organic chemistry and are fundamental building blocks in industry to access pharmaceuticals, agrochemicals, and polymers.[4] Among the diverse techniques to produce nitriles, one suitable and traditional access is the dehydration of primary amides. In particular, the dehydration of primary amides in the presence of catalytic amounts of metal precursors (e.g., Ru, Pd, Rh, W, V, Fe) can be a proficient choice.[5–14] However, established methods based on transition-metals require harsh reaction conditions, high catalyst loadings, or the addition of silanes (Si−H) to force the dehydration. In systems that contain metals and silanes, milder conditions are applicable, but difficulties can arise from either the production of hydrogen as a waste product and, in the presence of functional groups, the metal silane combination can act as reducing reagent and therefore reduce the scope of the protocol. As a consequence, highly active dehydration catalysts in combination with silanes, which have no reduction abilities, are a challenging task for current research. According to our ongoing interest in transition-metal catalysis, we herein wish to emphasize the value of a straightforward uranium catalyst for the dehydration of primary amides applying N-methyl-N-(trimethylsilyl)trifluoroacetamide (MSTFA) as dehydration reagent, which is an excellent trimethylsilyl-transfer compound.[15]

Initially, the dehydration of fluorobenzamide (1) with 3, in the presence of catalytic amounts of $UO_2(NO_3)_2 \cdot 6H_2O$ in toluene, was studied as a model reaction to evaluate suitable reaction conditions and to examine the effect of various reaction parameters (Table 1). As expected, when using

Table 1. Uranium-catalyzed dehydration of 4-fluorobenzamide (1).
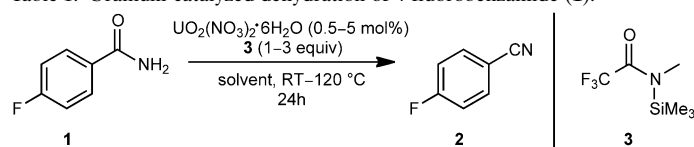
Entry[a]	Catalyst loading [mol %]	Solvent	T [°C]	t [h]	MSTFA [equiv]	Yield [%][b]
1	–	toluene	100	24	3	<1
2	5	toluene	100	24	–	<1
3	5	toluene	100	24	1	28
4	5	toluene	100	24	2	91
5	5	toluene	100	24	3	>99
6	1	toluene	100	24	3	16
7	5	toluene	120	24	3	>99
8	5	toluene	70	24	3	26
9	5	toluene	RT	24	3	<1
10	5	THP	100	24	3	76
11	5	dioxane	100	24	3	>99
12	1	dioxane	100	24	3	32
13	5	THF	70	24	3	48
14	5	DME	100	24	3	>99
15	1	DME	100	24	3	>99
16	0.5	DME	100	24	3	17

[a] Reaction conditions: 1 (0.72 mmol), $UO_2(NO_3)_2 \cdot 6H_2O$ (0.5–5 mol %), MSTFA (1.0–3.0 equiv), solvent (2.0 mL), RT–120°C, 24 h. [b] Determined by GC methods using biphenyl as an internal standard.

MSTFA in the absence of $UO_2(NO_3)_2 \cdot 6H_2O$, no formation of 4-fluorobenzonitrile (2) was observed (Table 1, entry 1). Moreover, $UO_2(NO_3)_2 \cdot 6H_2O$ without MSTFA was not capable to perform the dehydration (Table 1, entry 2).

In contrast, in the presence of $UO_2(NO_3)_2 \cdot 6H_2O$ (5.0 mol %) and MSTFA (3 equiv), an excellent yield of >99 % and a chemoselectivity of >99 % were attained under non-inert conditions after a reaction time of 24 h (Table 1, entry 5), whereas with lower amounts of MSTFA (1–2 equiv), a diminished yield was observed (Table 1, entries 3 and 4). A decrease in reaction temperature to 70°C resulted in a decreased yield of 2, whereas at room tempera-

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ture the reaction is hampered (Table 1, entries 8 and 9). In addition, tetrahydropyrane (THP), 1,4-dioxane, THF, and dimethoxyethane (DME) were applied (Table 1, entries 10–15) and excellent performance was found for THP, dioxane, and DME. The loading of $UO_2(NO_3)_2 \cdot 6H_2O$ could be decreased to 1.0 mol%, resulting in an excellent yield of >99% of **2** with DME as solvent (Table 1, entry 15). This outstanding catalyst activity at low loading and mild conditions is so far unreported for other transition-metal/silane systems.[8,14] To explore the scope and limitations of the presented uranium catalyst, the dehydration of a range of primary amides was carried out (Table 2). The reaction conditions are in agreement with Table 1, which means the corresponding amides were transformed in the presence of $UO_2(NO_3)_2 \cdot 6H_2O$ (2.5 mol%) and MSTFA (3.0 equiv) in DME at 100 °C for 24 h. Remarkably, the uranium-based catalyst proved to be extraordinarily active for the dehydration of 17
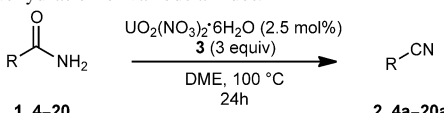
different substrates to give the products in quantitative yields. To investigate the reaction in more detail, the influence of substitution in the aromatic unit of the benzamide was first investigated (Table 2, entries 1–10). Notably, in all cases, excellent yields and selectivities were achieved. The catalyst was active for electron-withdrawing as well as electron-donating groups. Moreover, nitrogen-, and sulfur-based heteroaromatics, which are challenging substrates, were dehydrated with excellent yields (Table 2, entries 13–15). Besides, alkyl amides were converted to the corresponding nitrile in excellent yields (Table 2, entries 17 and 18). Significantly, the system $UO_2(NO_3)_2 \cdot 6H_2O$/MSTFA demonstrated excellent selectivity in presence of sensitive functional groups (for example, nitro and C—C double bonds), whereas for other transition-metal/R_3Si—H-based systems, side reactions can occur.[16]

With respect to the reaction mechanism, we assume a similar pathway as proposed by Nagashima et al. for ruthenium catalysts and Beller et al. for iron catalysts (Scheme 1).[8a,14] Initially, the uranium catalyst activates the primary amide through coordination of the carbonyl oxygen and allows the interaction of the NH_2 functionality with MSTFA to form the monosilylated species **23**, which undergoes a second silylation step to obtain the bis-silylated intermediate **24**.

The *N,N*-bis(trimethylsilyl)amide intermediate **24** rearranges to the *N,O*-bis(trimethylsilyl)imidate **25**. The presence of the uranium catalyst permits the elimination of the desired nitrile and siloxane **26** as a side product. Finally, the recovered catalyst can perform the process again (Scheme 1). Notably, the monosilylated species **23** can be also seen as a potential source for nitriles, which means the rearrangement to an *O*-trimethylsilylimidate and elimination of Me_3SiOH yields the corresponding nitrile. Indeed, various experiments have been performed, which elucidate the underlying "bis-silylation" mechanism. To illuminate the role of the pre-catalyst, MSTFA and **1** were reacted in [D_8]THF in the absence of UO_2-$(NO_3)_2 \cdot 6H_2O$. However, no product formation, as well as

Table 2. Uranium-catalyzed dehydration of various amides.

Entry[a]	Substrate		Yield [%][b]	Entry	Substrate		Yield [%][b]
1	(4-methylbenzamide)	4	**4a**: >99 (94)	10	(4-bromobenzamide)	12	**12a**: >99 (92)
2	(3-methylbenzamide)	5	**5a**: >99 (95)	11	(2-naphthamide)	13	**13a**: >99 (98)
3	(2-methylbenzamide)	6	**6a**: >99 (92)	12	(1-naphthamide)	14	**14a**: >99 (93)
4	(4-tert-butylbenzamide)	7	**7a**: >99 (95)	13	(nicotinamide)	15	**15a**: >99 (93)
5	(4-methoxybenzamide)	8	**8a**: >99 (92)	14	(picolinamide)	16	**16a**: >99 (87)
6	(4-trifluoromethylbenzamide)	9	**9a**: >99 (89)	15	(thiophene-2-carboxamide)	17	**17a**: >99 (84)
7	(4-nitrobenzamide)	10	**10a**: >99 (97)	16	(cinnamamide)	18	**18a**: 94 (86)
8	(4-fluorobenzamide)	1	**2**: >99 (96)	17	(2-phenylacetamide)	19	**19a**: >99 (91)
9	(4-chlorobenzamide)	11	**11a**: >99 (91)	18	(adamantane-1-carboxamide)	20	**20a**: >99 (92)

[a] Reaction conditions: Amide (0.72 mmol), $UO_2(NO_3)_2 \cdot 6H_2O$ (2.5 mol%), MSTFA (3.0 equiv), DME (2.0 mL), 100 °C, 24 h. [b] Determined by GC methods and ^1H NMR spectroscopy. The yield of the isolated product is stated in brackets.
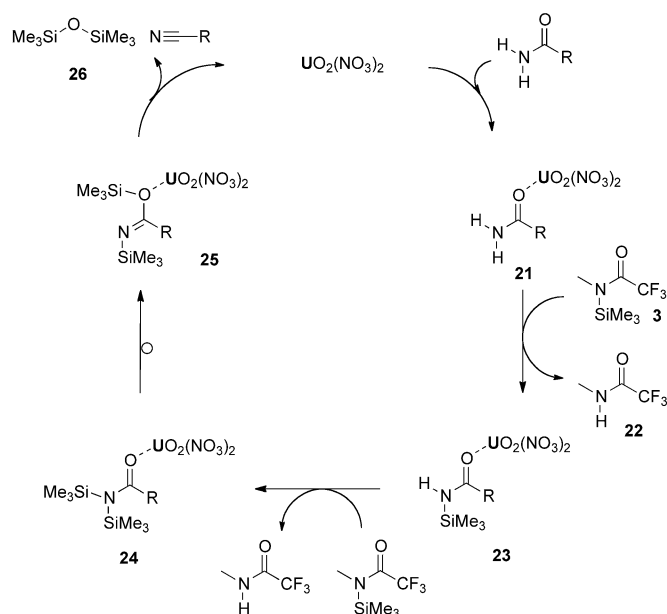
Scheme 1. Proposed reaction mechanism for the uranium-catalyzed dehydration of primary amides.

Experimental Section

General procedure for the dehydration of amides: A pressure tube was charged with $UO_2(NO_3)_2 \cdot 6H_2O$ (0.018 mmol, 2.5 mol%), the corresponding amide (0.72 mmol) and MSTFA (3.0 equiv, 2.2 mmol). After the addition of DME (2.0 mL) the reaction mixture was stirred in a preheated oil bath at 100 °C for 24 h. The mixture was cooled on an ice bath and biphenyl (internal standard) was added. The solution was diluted with dichloromethane and an aliquot was taken for GC-analysis (30 m Rxi-5 ms column, 40–300 °C). The solvent was carefully removed and the residue was purified by column chromatography (*n*-hexane/ethyl acetate 5:1). The analytical properties of the corresponding nitriles are in agreement with those reported in the literature.

no mono- or bis-silylation of **1** were detected by ^{19}F NMR spectroscopy after heating for 24 h at 70 °C, which evidently demonstrates the need for uranium as the silylation catalyst. Clearly, for the dehydration of amides, all three reagents are essential. After addition of MSTFA to this mixture, three new peaks appeared that could be attributed to MSTFA and the hydrolyzed product **23**. After heating for 24 h, the product was analyzed by using ^{19}F NMR spectroscopy, which illustrated the formation of *para*-fluorobenzonitrile (**2**, $\delta = -104.9$ ppm, sept, $J = 4.56$ Hz). Nevertheless, no mono- or bis-silylated intermediates of amide **1** were detected on the NMR timescale. To distinguish between mono- and bis-silylation the monosilylated and the bis-silylated compounds of **1** were synthesized.[8a] The reaction of both compounds with catalytic amounts of $UO_2(NO_3)_2 \cdot 6H_2O$ confirmed that the bis-silylated species was a source for the nitriles, whereas the monosilylated species was inactive. In addition, the ^{29}Si NMR spectrum revealed the formation of $Me_3SiOSiMe_3$ (**27**, $\delta = 7.1$ ppm), whereas the signals for MSTFA (**2**, $\delta = 25.6$ ppm) disappeared.

In summary, we have established for the first time an excellent method for the dehydration of primary amides to the corresponding nitriles in the presence of a straightforward uranium catalyst and MSTFA as dehydration reagent under mild reaction conditions. The outstanding performance of the system was exhibited in the dehydration of several substrates with exceptional yields, selectivities, and a broad functional group tolerance. Mechanistic investigations point to a dual function of uranium; on the one hand it functions as a silylation catalyst and on the other hand, as a catalyst for the elimination step. However, future work will be dedicated to the investigation of the precise reaction mechanism.

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