

Tetrabutylammonium Decatungstate (Chemo)selective Photocatalyzed, Radical C–H Functionalization in Amides

Simone Angioni,^a Davide Ravelli,^a Daniele Emma,^a Daniele Dondi,^b Maurizio Fagnoni,^{a,*} and Angelo Albini^a

^a Department of Organic Chemistry, University of Pavia. Via Taramelli 10, 27100 Pavia, Italy
Fax: (+39)-0382-987-323; e-mail: fagnoni@unipv.it

^b Department of General Chemistry, University of Pavia. Via Taramelli 12, 27100 Pavia, Italy
Fax: (+39)-0382-528-544

Received: June 16, 2008; Revised: July 30, 2008; Published online: August 29, 2008

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/adsc.200800378>.

Abstract: Photoamidation of electron-poor olefins has been achieved by means of a radical-induced C–H functionalization in amides. Tetrabutylammonium decatungstate was used as photocatalyst of the reaction and allowed the smooth generation of different carbon-centered radicals depending on the amide structure.

Keywords: amides; conjugate alkylation; electron-poor olefins; photochemical reactions; radical reactions

Simple amides are the least reactive carbonyl-containing functionalities. These derivatives are virtually non basic, poor C-electrophiles and poor N–H acids, so that formation of the corresponding enolates requires strong bases. Actually, DMF or *N*-methyl-2-pyrrolidone are convenient solvents for the generation of most enolates. An increased reactivity has been obtained by a structure modification through the introduction of Weinreb amides about 20 years ago, but in this case the amide functionality is lost in the reaction. Metal-catalyzed activation of the N–H bond of primary and secondary amides for the formation of C–N bond has recently emerged, with the *N*-arylation of amides,^[1] the synthesis of enamides *via N*-vinylation,^[2] and *N*-alkynylation reactions^[3] as representative examples.

The (chemo)selective functionalization of a C–H rather than an N–H bond in amides is, however, more demanding. As summarized in Figure 1, both the C–H adjacent to the carbonyl (path *a*) and that α to the nitrogen (path *b*) could be functionalized in formamides (e.g., *N,N*-dimethylformamide, DMF), as well

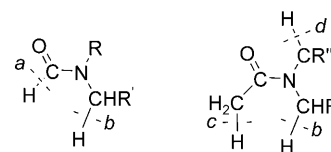


Figure 1.

as the C–H α to the carbonyl in higher homologues (e.g., acetamides, path *c*). A selective functionalization is not trivial because these C–H bonds may have a similar bond dissociation energy (BDE). As an example, in the DMF molecule the BDE of the C–H bond was calculated as 89.7 kcal mol^{−1} and 89.1 kcal mol^{−1} for the formyl and for the methyl group, respectively.^[4a] The N–H bond (BDE = 108.5 kcal mol^{−1})^[4b] and, when present, the C–H α to the carbonyl (BDE \approx 94 kcal mol^{−1})^[4c] are stronger. Moreover, in non-symmetrical amides, the selective transformation of different *N*-alkyl groups is a further issue (path *b* and *d*).

Homolytic hydrogen abstraction and electrochemical oxidation^[5] have been reported to afford the C–H functionalization of amides. In the first method, the formation of a carbon-centered radical was accomplished by using thermally generated radicals (such as *t*-BuO[•]^[6a] or ethyl radicals^[6b]) or by Fe(II) salt-mediated reactions.^[6c,d] The nucleophilic radicals thus formed have been exploited for the amidation of electron-poor olefins or of (protonated) heterocyclic bases. Unfortunately, in all of these cases the amide must be used in a large excess (as the solvent in most cases), which obviously limits the synthetic significance. Electrochemical oxidation is an interesting alternative and involves formation of the radical cations of the amides and then of carbon radicals from them by deprotonation. Under the oxidative conditions em-

ployed, however, radicals were easily transformed into the corresponding cations and thus the reaction took a different course giving alcohols or ethers by addition to water or alcohols. A way to overcome this problem was recently introduced by Yoshida and co-workers by means of the “cation pool” method.^[7] Thus, the amides (carbamates) were electrochemically oxidized and the acyliminium cations accumulated. In a later step, the last intermediates were reduced to α -amido radicals, which were trapped by electron-poor alkenes. This method requires the availability of an electrochemical equipment, establishing a low temperature (-72°C) and using a large excess both of the amide (at least 5 equiv.) and of triflic acid (50 equiv.). At any rate, the reaction was limited to the amidoalkylation of α,β -unsaturated esters or lactones. Thus, some drawbacks remained in the above methods and this fostered the interest for new C–C bond forming reactions *via* radicals from amides, and thus for the selectivity of the key hydrogen abstraction step.

Photocatalysis^[8] is a mild alternative for the functionalization of C–H bonds that has proven to be ef-

fective even for unreactive substrates, such as alkanes, for the introduction of oxygen functionalities^[9] as well as for C-alkylation reactions.^[8,10] Tetrabutylammonium decatungstate (TBADT) has been recently introduced and has been found to promote the photocatalyzed alkylation of enones, unsaturated esters and nitriles starting directly from alkanes.^[11] A selective transformation was obtained through the same method in the alkylation by aliphatic alcohols and ethers^[12] and in the acylation by aliphatic aldehydes.^[13]


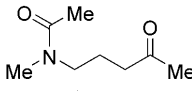
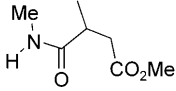
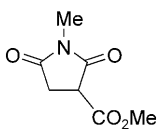

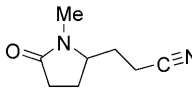
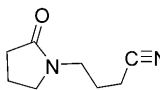
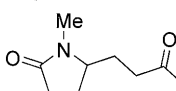
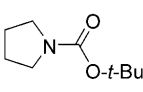
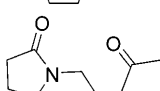
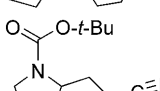
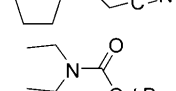
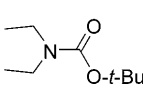
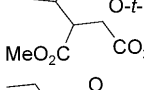
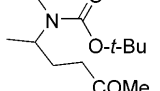
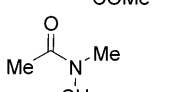
We surmised that TBADT might be conveniently applied for the (chemo)selective photocatalyzed functionalization of amides. We thus explored the reaction of a variety of amides and carbamates in the presence of electrophilic alkenes under TBADT photocatalysis.

The results obtained are gathered in Table 1. Thus, formamide (**1a**, 4 equiv.) was irradiated (24 h, $\lambda_{\text{irr}} = 310\text{ nm}$) in an acetonitrile solution of cyclohexenone (**2a**, 1 equiv.) and TBADT (2% mol) and gave 3-oxocyclohexanecarboxamide (**3**) as the only detected product. This compound was isolated in a 51% yield

Table 1. Photocatalyzed amidation of electron-poor olefins.

Amide		Olefin		Product		Yield [%] ^[a,b]
HCONH ₂	1a		2a		3	51
	1a		2b		4	76
	1b		2c		5	86
	1b		2d		6	71
	1b		2e		7	61
	1b		2f		8	47
	1c		2f		9	47

Table 1. (Continued)

Amide	Olefin	Product	Yield [%] ^[a,b]
	1c	2e 	10 60
	1d	2b 	11 46
	1d	2c 	12 60 ^[c]
	1e	2d 	13 56 ^[d]
			13'
	1e	2e 	14 50 ^[e]
	1f^[f]		14'
		2d 	15 59
	1g^[f]	2c 	16 51 ^[g]
	1g^[f]	2e 	17 26
		2d 	18 44
	1h^[h]		18' 28

^[a] Conditions: Amide (0.4 M), electron-poor olefin (0.1 M), TBADT (2×10^{-3} M), irradiated in acetonitrile.

^[b] Isolated yields.

^[c] See text.

^[d] **13/13'** ca. 13:1 ratio.

^[e] **14/14'** ca. 13:1 ratio.

^[f] About 70–75% of the carbamate recovered based on consumed **1f–g**.

^[g] Two diastereoisomers formed in ca. 1:1 ratio.

^[h] About 73% of the silyl amide recovered based on consumed **1h**.

by a two-step procedure involving elimination of excess **1a** under vacuum followed by chromatographic separation. No reaction took place in the absence of TBADT. Using a lower amount of the amide led to a

sluggish reaction and a marked decrease of the product yield. Likewise, the succinamic ester derivative **4** was obtained under the same conditions in 76% yield from the reaction of **1a** and methyl crotonate (**2b**).

A tertiary amide, DMF (**1b**), was next tested and found likewise to react under TBADT photocatalysis. A fully chemoselective transformation of the *N*-methyl C–H bond resulted, with no competition by the formyl group. Accordingly, ω -functionalized *N*-methyl-*N*-propylformamides **5–8** were obtained in yields ranging from 47–86% by using α,β -unsaturated ketones, esters and nitriles (**2c–f**) as the olefins. A 4 to 1 excess amide was likewise used and was distilled off after the reaction (toluene azeotrope). Changing the proportion of the reagents gave no satisfactory results, for example, using excess of the alkene lowered the yield, as shown in the formation of **5** in the reduced 46% yield in the reaction between **1b** (1 equiv.) and **2c** (4 equiv.). This is due to the formation of by-products that, as far as can be judged from the mass spectrum, resulted from the addition of two or more olefin units.

In the case of *N,N*-dimethylacetamide (**1c**), functionalization of the *N*-methyl group was likewise exclusive and ω -functionalized *N*-methyl-*N*-propylacetamides **9** and **10** were formed in a satisfactory yield (ca. 50–60%) from methyl vinyl ketone and ethyl acrylate respectively.

A complete change in the chemoselectivity was observed when passing to a secondary amide, *N*-methylformamide (**1d**). In this case, the photocatalytic transformation involved only the formyl group. Accordingly, the succinamic ester derivative **11** and succinimide **12** were obtained from methyl crotonate and dimethyl maleate, respectively. In the latter case, the isolated product contained an imide function formed by intramolecular condensation upon heating during the distillation under vacuum of the excess **1d**.

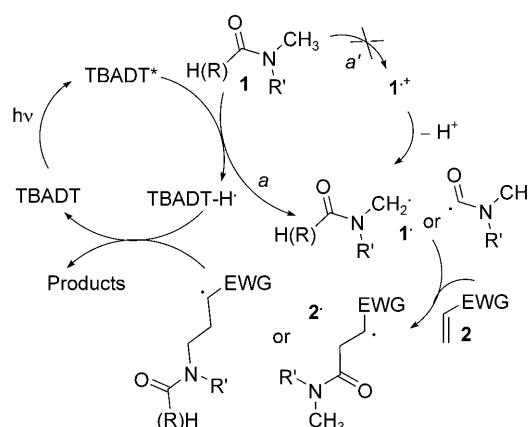
The non-symmetrical lactam **1e** (*N*-methyl-2-pyrrolidone) was chosen as a test for assessing the potential of the method since three different C–H bonds were potentially susceptible to functionalization under photocatalytic conditions. In the experiment, homolytic abstraction from the *N*-methylene group greatly predominated with respect to that of the *N*-methyl group (ca. 13:1), while the methylene α to the amide function had no role. Thus, the alkylated pyrrolidones **13** and **14** predominated over isomeric **13'** and **14'** in the amidation of **2d** and **2e** (see Table 1).

Carbamates were next considered as a logical extension of the work on amides. Positive results were obtained in the reaction of *tert*-butyl pyrrolidinyl carbamate **1f** in the presence of acrylonitrile, where nitrile **15** was synthesized in 59% isolated yield. The reaction was successful despite the competitive absorption of **1f** that caused a lengthening of the reaction time (ca. 40 h). The product was isolated by column chromatography, which further allowed recovering excess **1f** (about 70–75%). The diethylamino carbamate **1g** likewise gave an alkylation product with dimethyl maleate in a medium yield as a ca. 1 to 1 dia-

stereoisomeric mixture (**16**). The alkylation of methyl vinyl ketone, on the other hand, gave only a modest yield of carbamate **17**.

A final reaction was carried out with the *N*-trimethylsilylmethyl acetamide **1h**, in order to ascertain whether the silyl group may be cleaved competitively with a hydrogen atom. In the experiment, the photocatalyzed reaction of **1h** with **2d** gave two silicon-containing products (**18** and **18'**), resulting from the functionalization of the *N*-methylene and methyl groups, respectively. The same reaction, when carried out in acetonitrile–water 7:1 (water 7M), was slightly slower than that in neat MeCN but led to the same products distribution.

The above results fit with the mechanism in Scheme 1.^[14] The radicals from amides add to electrophilic alkenes and the catalytic cycle is terminated by



Scheme 1. Photocatalyzed functionalization of C–H bonds in amides.

back H transfer to adduct radical **2•**. Functionalization of amides by the excited photocatalyst involves either hydrogen transfer (path *a*) or electron transfer (ET) followed by deprotonation of the radical cation (**1•+**, path *a'*). In fact, although amides are not easily oxidized (e.g., $E_{1/2}^{ox} = 2.29$ V vs. SCE for DMF),^[17] the highly positive reduction potential of excited TBADT [$E_{red}(TBADT^*) = E_{red}(TBADT) + E_{exc} = 2.26$ to 2.61 V vs. SCE]^[16,18a] makes the ET process conceivable next to the thermoneutral one.^[18b] There is evidence in the literature for the operation of a photochemical ET path when using a strong photochemical oxidant such as 1,2,4,5-tetracyanobenzene (TCB)^[22a] or the dicyanoanthracene/biphenyl system.^[22b] Thus we decided to explore this issue by using the silylated amide **1h**, since the loss of the good electrofugal group $SiMe_3^+$ from radical cation **1h•+** is largely favored^[22b] and thus desilylation would reveal the ET mechanism. However, the products obtained with TBADT conserved the silyl group even in the presence of water (a protic/nucleophilic cosolvent) that should favor the

desilylation step^[22b,c] supporting that path *a*, not *a'*, was operative. In contrast, we found that the photochemistry of **1d** in the presence of TCB, a *bona-fide* ET sensitizer, gave *N*-(2,4,5-tricyanobenzyl)formamide as the exclusive product (see Supporting Information). It should further be noticed that a different reaction course involving a transformation of the methyl rather than the formyl group was previously observed in the electrochemical reaction of **1d**.^[23]

From the synthetic point of view, the key characteristic is the chemoselective functionalization of C–H bonds by electrophilic TBADT*. With tertiary amides, only a hydrogen α to the amide nitrogen is abstracted, not a formyl C–H from formamides or the electrophilic H α to the carboxamide group.^[24] On the other hand, the presence of an N–H group prevents H abstraction from the *N*-alkyl group in secondary amides, apparently due to the different interaction with TBADT*, which makes abstraction from a formyl group (when present) preferable. Also stereoelectronic factors have a role, as apparent in the case of pyrrolidones, with the selective H abstraction from the methylene group due to a favorable alignment of the C–H bond with the nitrogen lone pair. The course of the present amidation can thus be rationalized (and predicted). The convenient absorption characteristics of TBADT (300–320 nm, where aliphatic amides do not absorb) and high reactivity of the excited state makes this photocatalyst superior to alternatives, such as acetone, benzophenone^[25] or TiO₂^[26] where, as in thermal methods,^[6] amides must be used in a much larger excess with a lower selectivity in the hydrogen abstraction step. Also, the reaction has now been extended to carbamates, so that it can be envisaged as a way for introducing an alkylaminomethyl group in the *N*-protected form. Noteworthy, substituents at the olefin β -position (see **2a** and **2b**) do not hinder the reaction, a fact that offers a useful entry to γ -amino acid derivatives (e.g., **5**, **8–9**, **16**).

In conclusion, the present amidation has been applied to different classes of electron-poor olefins and is a convenient alternative to the electrochemical transformation of amides *via* the cation pool,^[7] while it is different from the electrochemical oxidation, where a carbocation^[5] rather than a radical is the intermediate.

Experimental Section

Typical Procedure for the Photoamidation of Olefins

A solution (30 mL) of an amide (**1a–h**, 0.4 M), and an olefin (**2a–f**, 0.1 M) in the presence of 200 mg of TBADT^[11b] (2×10^{-3} M) in MeCN was poured in two quartz tubes and purged for 10 min with argon, serum capped and irradiated with six 15-W phosphor-coated lamps (emission centered at 310 nm). The solvent was removed under vacuum from the

photolyzed solution and the products isolated by elimination of the excess amide by (azeotropic) distillation and purification of the residue by column chromatography (cyclohexane/ethyl acetate as eluants) or distillation. In the case of carbamates **1f**, **g** and amide **1h**, column chromatographic separation of the raw photolysate allowed the separation of the alkylated olefins and a partial recovery of the starting reagent.

Supporting Information

Experimental details and ¹H and ¹³C NMR spectra of compounds **3–18** are available as Supporting Information.

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