ORGANIC
LETTERS

XXXX
Vol. XX, No. XX
000–000

Efficient C−H/C−N and C−H/C−CO−N Conversion via Decatungstate-Photoinduced Alkylation of Diisopropyl Azodicarboxylate

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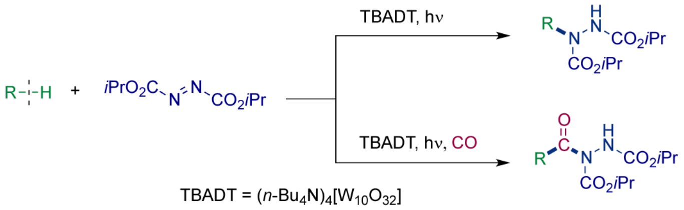
Received April 17, 2013

ABSTRACT



Tetrabutylammonium decatungstate (TBADT) accelerated the addition of C−H bonds to the N=N double bond of diisopropyl azodicarboxylate (DIAD) under irradiation conditions. The photoinduced three-component coupling between cyclic alkanes, CO, and DIAD was also achieved to give the corresponding acyl hydrazides.

The occurrence of C−N bonds in natural and non-natural biologically active molecules is extraordinarily high, and this gave impetus to the development of convenient methods for their construction. The chemistry of azodicarboxylates has generated a considerable amount of recent interest.[1] Apart from their role in the Mitsunobu reaction, the synthetic potential of dialkyl azodicarboxylates comes from their high electrophilicity[2] that was established in the pioneering work of Huisgen and coworkers.[3] Valuable C−N bonds have been obtained by pericyclic reactions such as hetero Diels−Alder and aza-ene reactions where the azo ester acted as dienophile and enophile, respectively.[1,4] The electrophilic character of azodicarboxylates has been likewise exploited in the aza-version of the Baylis−Hillman reaction and in the reactions with a wide range of nucleophiles including enolates.[1a] Recent work has also been focused on the transition-metal-catalyzed and organocatalyzed functionalization of azodicarboxylates to form substituted hydrazines.[1b]

Dialkyl azodicarboxylates, on the other hand, are commonly known to generate carbon-centered radicals via a hydrogen atom abstraction from C−H bonds, when thermally[5] or photochemically[6] activated and to function as radical traps. Recent reports have shown that the hydroacylation of azodicarboxylates by aldehydes in water[7] or in an imidazolium-based ionic liquid ([bmim]NTf_2)[8] proceeded well to give the corresponding hydroacylated derivatives. *N*-Hydroxyphthalimide (NHPI) was likewise used to catalyze the addition of α-oxy alkyl radicals[9a]

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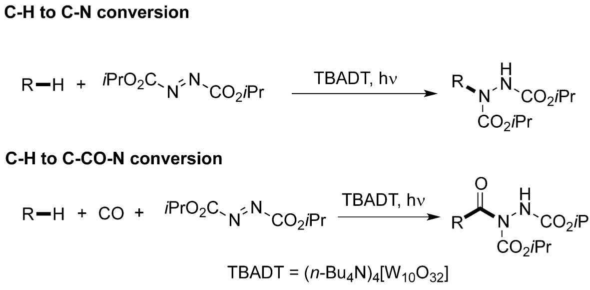
10.1021/ol401061v

and alkyl radicals[9b] onto azodicarboxylates. Moreover, azodicarboxylates can be employed for the radical-mediated oxyamination of alkenes.[10] The importance of azodicarboxylates functionalization resides in the successful conversion of the resulting products into valuable amines or carbamates via N−N bond cleavage reactions.[9b,10]

The photochemically induced addition of ethers (e.g., 1,4-dioxane)[6b] or alkenes (e.g., cycloheptene)[11] onto an azodicarboxylate gave the corresponding substituted hydrazides in variable yields. In most of these reactions, however, the radical source was employed as the reaction medium, which poses problems in terms of efficiency in synthetic planning.

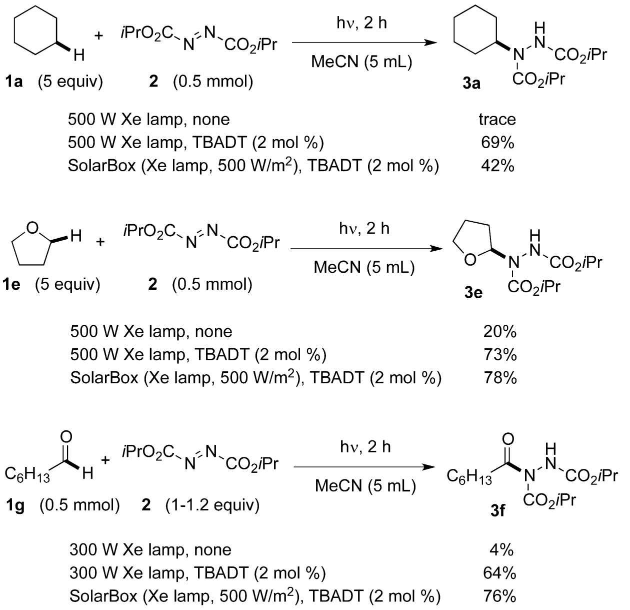
Various carbon-centered radicals such as alkyl,[12] acyl,[13] α-carbamoylalkyl,[14] and α-oxyalkyl[15] radicals are now easily accessed by a photocatalytic[16] C−H activation process that makes use of tetrabutylammonium decatungstate (TBADT, $(n\text{-Bu}_4\text{N})_4[\text{W}_{10}\text{O}_{32}]$)[17] as the photocatalyst in C−C bond forming reactions.[12−15] We were curious to assess whether this decatungstate salt could efficiently promote the smooth conversion of C−H to C−N bonds by radical addition onto azodicarboxylates, which would lead to atom-economical radical amination reactions. We report herein that a variety of C−H bonds can add to the N=N double bond of diisopropyl azodicarboxylate (DIAD) as a radical acceptor by using TBADT under irradiation conditions. We also report that the same conditions can be readily applied in the C−H to C−CO-N conversion via a three-component reaction comprising alkanes, CO, and DIAD (Scheme 1).

Scheme 1. This Work: Photoinduced C−H to C−N and C−H to C−CO−N Conversions Promoted by TBADT



At the outset, we examined the photoaddition of C−H bonds to DIAD using cyclohexane (**1a**), THF (**1e**), and heptanal (**1g**) as model substrates in order to determine how the reaction conditions affected the C−H addition to the N=N double bond (Scheme 2).

Scheme 2. Effect of Reaction Conditions on the C−H to C−N Conversion



500 W Xe lamp, none	trace
500 W Xe lamp, TBADT (2 mol %)	69%
SolarBox (Xe lamp, 500 W/m^2), TBADT (2 mol %)	42%

500 W Xe lamp, none	20%
500 W Xe lamp, TBADT (2 mol %)	73%
SolarBox (Xe lamp, 500 W/m^2), TBADT (2 mol %)	78%

300 W Xe lamp, none	4%
300 W Xe lamp, TBADT (2 mol %)	64%
SolarBox (Xe lamp, 500 W/m^2), TBADT (2 mol %)	76%

Thus, irradiation of an acetonitrile solution of **1a** and DIAD **2** for 2 h using a xenon lamp (500 W) through a Pyrex glass test tube resulted in the formation of the desired compound **3a** in only a trace amount. The reaction using an extended reaction time of 20 h gave **3a**, but still in only 20% yield. Interestingly, the addition of 2 mol % of TBADT to the reaction mixture dramatically accelerated the reaction, which gave **3a** in 69% yield after 2 h. The use of a SolarBox equipped with a 1.5 kW xenon lamp (500 W/m^2) gave **3a** in 42% yield. The photoaddition of THF (**1e**) to **2**, however, proceeded more rapidly in the absence of TBADT to give the addition product **3e** in 20% yield after 2 h, whereas the addition of 2 mol % of TBADT to the reaction mixture gave **3e** in 73% yield. The reaction carried out by using the SolarBox also worked well and gave **3e** in 78% yield. The addition of heptanal (**1g**) across DIAD **2** using a

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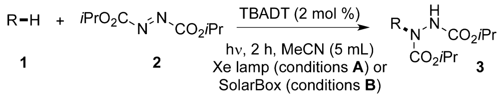
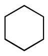
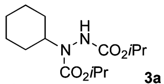
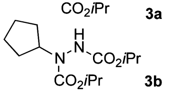
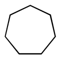
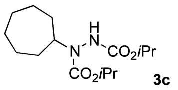
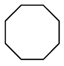
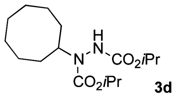
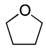
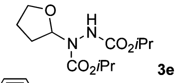
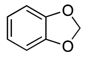
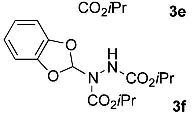
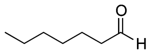
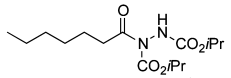
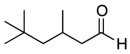
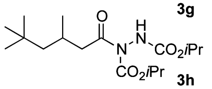
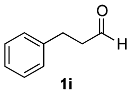
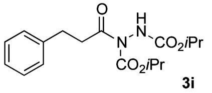
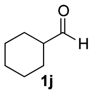
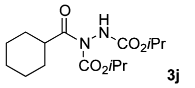
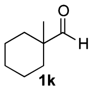
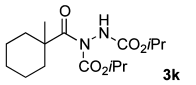
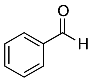
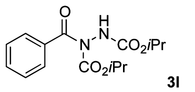
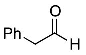
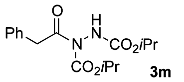
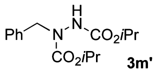
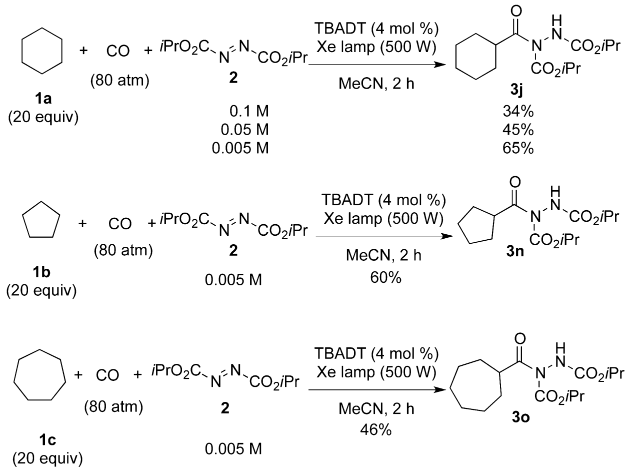
Table 1. TBADT-Photoinduced Addition of C−H Bonds to DIAD **2**[a]



entry	substrate	conditions[a]	product	yield (%)[b]
1	 **1a**	A	 **3a**	69
2		B		42
3	 **1b**	A	 **3b**	64
4	 **1c**	A	 **3c**	63
5	 **1d**	A	 **3d**	61
6	 **1e**	A	 **3e**	73
7		B		78
8	 **1f**	B	 **3f**	92
9[c]	 **1g**	A	 **3g**	69
10		B		76
11[c]	 **1h**	A	 **3h**	63
12	 **1i**	A	 **3i**	63
13[c]	 **1j**	A	 **3j**	76
14		B		98
15[c]	 **1k**	A	 **3k**	60
16[c,d]	 **1l**	A	 **3l**	62
17	 **1m**	B	 **3m**	21
			 **3m′**	45

[a] **1** (2.5 mmol) and DIAD **2** (0.5 mmol) for entries 1−7; **1** (0.5 mmol) and **2** (0.6 mmol) for entries 8, 10, 14, and 17; **1** (0.5 mmol) and **2** (0.5 mmol) for entries 9, 11−13, 15, and 16. Conditions A: Xe lamp (500 W, Pyrex filtered) for entries 1, 3−6; Xe lamp (300 W, Pyrex filtered) for entries 9, 11−13, 15, and 16. Conditions B: SolarBox equipped with a 1.5 kW Xe lamp (500 W/m^2). [b] Isolated yield by SiO$_2$ chromatography. [c] 20 h irradiation. [d] TBADT (4 mol %).

Scheme 3. C−H Carbonylation and Addition to DIAD Leading to Acyl Hydrazides **3j**,**n**,**o**



xenon lamp was sluggish, and even after 20 h the desired adduct **3f** was formed in 16% yield (only 4% after 2 h).[18] Again, a dramatic acceleration was observed when the reaction was carried out in the presence of 2 mol % of TBADT, which gave the corresponding amide **3g** in 64% yield after 2 h and 69% yield after 20 h. We also carried out a similar reaction using the SolarBox (1.2 equiv of DIAD), which gave **3g** in 76% yield.

Having confirmed this significant acceleration by TBADT when using different C−H bonds, we then embarked on a study to examine the generality of the C−H to C−N conversion, for which xenon lamp irradiation (conditions **A**) and/or SolarBox irradiation (conditions **B**) were used, and the results are summarized in Table 1.

Cyclic alkanes with five- to eight-membered rings, **1a**−**d**, were successfully converted to the corresponding substituted hydrazides **3a**−**d** in good yields (entries 1−5). When using an ether (THF, **1e**, see above and entries 6−7) or an acetal (1,3-benzodioxole, **1f**, entry 8) as hydrogen donors, compounds **3e** and **3f** were isolated in 78% and 92% yield, respectively. Aldehydes **1g**−**k**, irrespective of whether they were primary, secondary, or tertiary, were cleanly converted to amides **3g**−**k** in good yields (entries 9−15). The reaction of benzaldehyde (**1l**) with **2** also worked well to give **3l** in 62% yield (entry 16). The reaction of phenylacetaldehyde (**1m**) gave the corresponding imide **3m** in 21% yield along with 45% of decarbonylated product **3m′** (entry 17).[19,20]

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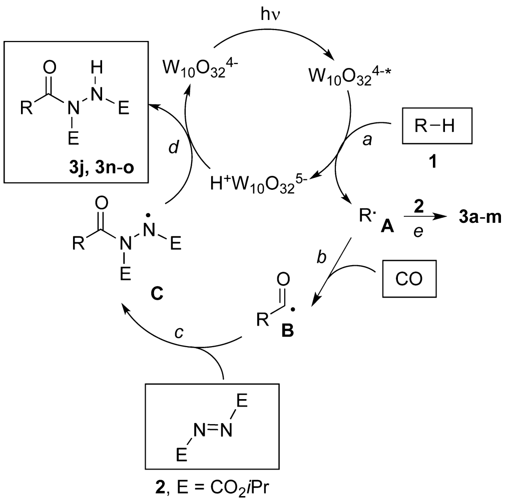
Scheme 4. Possible Mechanism for TBADT-Photoinduced Synthesis of **3**



C−H carbonylation constitutes a challenge in both radical[21] and transition-metal catalysis.[22] We recently reported that a TBADT-catalyzed C−H carbonylation reaction can be successfully applied to a three-component coupling reaction leading to unsymmetrical ketones.[23,24]

If a similar C−H carbonylation took place in the presence of **2**, the acyl radicals would be trapped by DIAD to give acyl hydrazides as the carbonylated products. Thus, we examined a three-component reaction comprising cyclohexane (**1a**), CO, and DIAD in the presence of catalytic amounts (4 mol %) of TBADT, and the results are summarized in Scheme 3. At a 0.1 M concentration of DIAD and 80 atm of CO, the desired carbonylation product **3j** was formed in 34% yield along with comparable amounts (28% yield) of the alkylated product **3a**, which suggests that the addition of a cyclohexyl radical to DIAD is very fast.[25] To encourage radical carbonylation over the premature addition of a cyclohexyl radical to DIAD, we examined the reaction by lowering the concentration of **2**, which indeed proved to be effective. Thus, when using 5×10^{-2} M of **2**, a **3j**/**3a** = 69/31 mixture was formed, whereas adopting 5×10^{-3} M of **2** afforded a **3j**/**3a** = 96/4 ratio. In the last case, product **3j** was actually isolated in 65% yield after purification by silica gel chromatography. Similarly, by using the same DIAD concentration (5×10^{-3} M), cyclic imides **3n** and **3o** were obtained in 60 and 46% yield, respectively.

Scheme 4 illustrates the possible reaction mechanism for the catalytic C−H to C−CO−N (or C−N) conversion. Thus, excited polyoxodecatungstate anion abstracts a hydrogen from the C−H bond of **1** to form radical **A** (path *a*), which undergoes consecutive addition to CO and DIAD **2**, to form acyl radical **B** (path *b*) and aminyl radical **C** from it (path *c*). Back-hydrogen atom transfer from the reduced form of the decatungstate anion to **C** furnishes acyl hydrazides **3j**, **n**−**o** restoring the starting TBADT (path *d*). However, in the absence of CO a smooth formation of hydrazides **3a**−**m** took place (path *e*). The great capability of **2** as radical trap completely (for **1a**−**l**) or in part (for **1m**) prevented the decarbonylation of the acyl radicals formed from aldehydes.

In summary, we have demonstrated that TBADT effectively accelerated the photoinduced addition of different types of C−H bonds to diisopropyl azodicarboxylate (DIAD) to form C−N bonds. Under pressurized conditions of CO, the 100% atom-economical three-component coupling reaction of cyclic alkanes, CO, and DIAD proceeded smoothly to give acyl hydrazides, a class of potential antioxidants.[26] Moreover, in selected cases the greeness of the reaction is witnessed by the feasibility of the process under solar light irradiation. Additional work is underway to gain more insights into the potentiality of the reaction.

Acknowledgment. I.R. acknowledges financial support by a Grant-in-Aid for Scientific Research from the MEXT and the JSPS. We thank Miss V. Cassinelli (University of Pavia) for preliminary experiments.

Supporting Information Available. Experimental procedure and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.