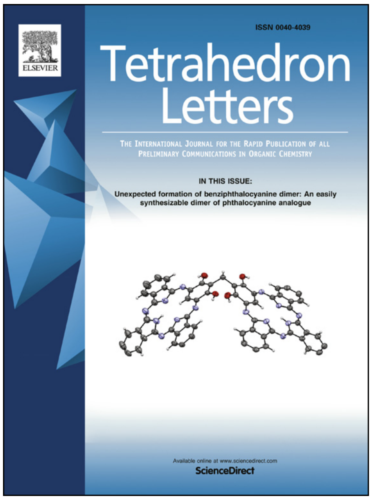

Efficient Oxidative *N*-Dealkylative Addition of Trialkylamines to Dimethyl Acetylenedicarboxylate using $BrCCl_3$ as the Terminal Oxidant

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Efficient Oxidative *N*-Dealkylative Addition of Trialkylamines to Dimethyl Acetylenedicarboxylate using $BrCCl_3$ as the Terminal Oxidant

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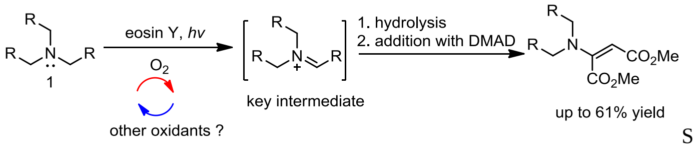
ABSTRACT

Herein we present a continuous improvement of visible-light mediated N-dealkylative addition of tertiary amines to dimethyl acetylenedicarboxylates (DMAD) using alkyl halogenides as external oxidants together with base additives. This method is highlighted by excellent tolerance with various tertiary amines and good to excellent yields in short reaction time under mild conditions.

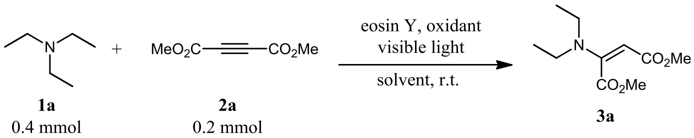
The *N*-dealkylation of tertiary amines is one of the most challenging research subjects in modern organic synthesis.[1] In general, owing to the high C-N bond dissociation energy[2] and inert reactivity, C-N cleavage reactions are usually catalyzed by transition metal catalysts.[1a, 3] Nevertheless, these methods were often encountered with some disadvantages such as harsh reaction conditions, limited substrate scope, etc. Thus, from a practical point of view, there is still a need to explore new methods enabling efficient dealkylation of tertiary amines at ambient conditions. In this regard, photoredox catalysis has recently received much attention and grown rapidly into an alternative pathway for this transformation. Rueping and co-workers reported an efficient dealkylation of various tertiary amines to secondary amines using an iridium-based photoredox catalyst.[4] We recently showed that eosin Y (EY) was a suitable organocatalyst for visible-light-driven *N*-dealkylative addition of tertiary amines to dimethyl acetylenedicarboxylates (DMAD) using O_2 as an external oxidant[5] (Scheme 1). Although our protocol was able to furnish the corresponding product, the yield and substrate scope are still unsatisfactory. In line with previous reports, we presumed that the inferior results with our title reaction might be resulted from the peroxy radical[6] during the reaction pathway, which could gave rise to some side products. On the other hand, some strategies on the improvement of photocatalytic reaction outcomes have been directed toward tuning external oxidants[7] as well as base additives.[8] As showed from our previous experimental results, we have proposed that the generation of an iminium intermediate is a key for the dealkylation of tertiary amines and subsequent interception with DMAD (Scheme 1). Taking all these considerations together, we wonder that the replacement of O_2 with other suitable oxidants that enable efficient formation of the iminium intermediate might be beneficial for this transformation in terms of yields and substrate scope. Herein, we present a continuous improvement of Eosin Y catalyzed *N*-dealkylative addition reaction by using $BrCCl_3$ as the external oxidant and Cs_2CO_3 as a base additive.



Scheme 1. Eosin Y catalyzed *N*-dealkylative addition to DMAD.

With this idea in mind, we initiated our studies by examining the influence of several conventional oxidants on this reaction in the presence of 3 mol % of eosin Y as photoredox catalyst. Ceric ammonium nitrate (CAN), $K_2S_2O_8$, and $Na_2S_2O_8$ tested are less effective than O_2, giving the addition product in poor yields (12–15%) after 20 h (Table 1, entries 1–3). Gratifyingly, when *N*-Bromosuccinimide (NBS) was used as the oxidant, the reaction furnished a comparable yield with that with O_2 (Table 1, entries 4), suggesting that halogenated organic oxidant is superior to inorganic ones. Encouraged by this result, we further tested the reaction with CBr_4 and $BrCCl_3$ and were pleased to find that the yield of the reaction can be dramatically improved to 86% and 88% in much less reaction time (5 h), respectively (Table 1, entries 5–6). After $BrCCl_3$ was established to be the best oxidant, we also investigated solvent effects on the reaction outcomes. Among all the solvents tested, DCM proved to be optimal, affording the product in 88% yield (Table 1, entry 6). In line with our previous work, the addition of 1 equiv of H_2O can further increase the yield to 93% yield (Table 1, entry 12). Furthermore, only trace amount of product was observed after 20 h in the absence of the photocatalyst or visible light (Table 1, entry 13–14).

Table 1. Optimization of Reaction Conditions[a]

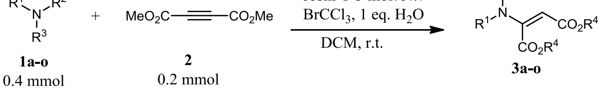


Entry	Oxidant (equiv.)	Solvent	Time (h)	Yield[b] (%)
1	CAN (3)	DCM	20	12
2	$K_2S_2O_8$ (3)	DCM	20	15
3	$Na_2S_2O_8$ (3)	DCM	20	12
4	NBS (3)	DCM	20	56
5	CBr_4 (3)	DCM	5	86
6	$BrCCl_3$ (3)	DCM	5	88
7	$BrCCl_3$ (3)	toluene	5	60
8	$BrCCl_3$ (3)	MeCN	5	59
9	$BrCCl_3$ (3)	DMF	5	58
10	$BrCCl_3$ (3)	THF	18	15
11	$BrCCl_3$ (3)	DMSO	5	45
12[d]	$BrCCl_3$ (3)	DCM	3	93 (93)[c]
13[d, f]	$BrCCl_3$ (3)	DCM	20	Trace
14[d, g]	$BrCCl_3$ (3)	DCM	20	Trace

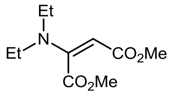
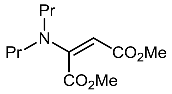
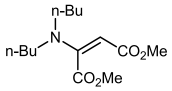
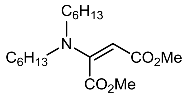
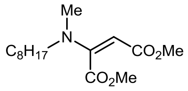
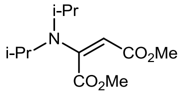
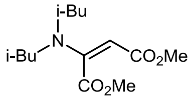
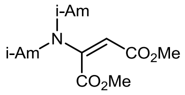
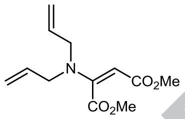
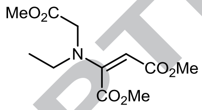
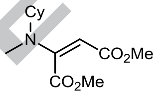
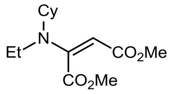
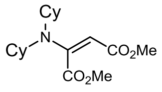
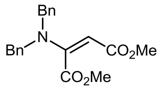
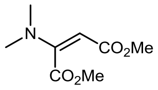
[a]Reaction conditions: DMAD (0.2 mmol), TEA (0.4 mmol), photocatalyst (3.0 mol%), solvent (2.0 mL), room temperature, using Green LEDs as the visible light source [b]Yield determined by crude ^{1}H NMR analysis. [c]Isolated yield. [d]1.0 equiv H_2O was used. [e]Under nitrogen atmosphere [f]Without catalyst [g]Performed in the dark.

With the optimal conditions in hand, we next investigated the generalities of the *N*-dealkylative addition reaction by employing a large variety of tertiary amines **1** as the substrate (Table 2). Generally, all linear trialkyl substituted amines **1a-e** were tolerated with this protocol, giving the corresponding product in good to excellent yield (Table 2, entries 1–5). According to recent study on the reactivity of *N*-dealkylation,[4] ethyl substituted amine has relatively poor reactivity compared with methyl group, which in line with our observation that the yield of long chain substituted tertiary amines decrease progressively. In addition, when *N*-n-Octyldimethylamine **1e** was used, alongside 66% yield of **3e**, a 28% de-octyl product **3e'** was observed, which indicates that C-N cleavage prefers short alkyl chain. However, when branched alkyl-substituted tertiary amines **1f** were tested with this protocol, a considerable decrease in yields was observed, presumably due to steric hindrance of these substrates. In light that basic additives are helpful in improvement of product yield,[9] we added 2 equiv. of $CsCO_3$ into the reaction mixture. To our delight, the yields for those branched amines can be enhanced up to 95% (Table 2, entries 6–8), which are much higher than the yields with O_2. In addition, the yields for tertiary amines bearing allyl (Table 2, entry 9) or carbonyl groups (Table 2, entry 10) were also improved (54%, 40% versus 35%, 29%). When cyclohexyl substituted tertiary amines **1k-m** were employed as the substrate, the reaction affords the respective product with a yield of 83%, 70%, and 60%, which seems likely that the efficiency of *N*-deakylative addition was reversely proportional to the bulky size of the substituents at tertiary amines. Notably, the dealkylative addition of tribenzylamine to DMAD also proceeded smoothly, giving the product in 82% yield, which was in stark contrast to the reaction using O_2 as the oxidant (no reaction). Notably, when *N*, *N*-dimethylbenzylamine **1o** was used as the substrate, an excellent chemoselectivity was achieved under this protocol, giving *N*-debenzylation product **3o** as the sole product (Table 2, entry 15).

Table 2. Substrate screen of different tertiary amines[a]



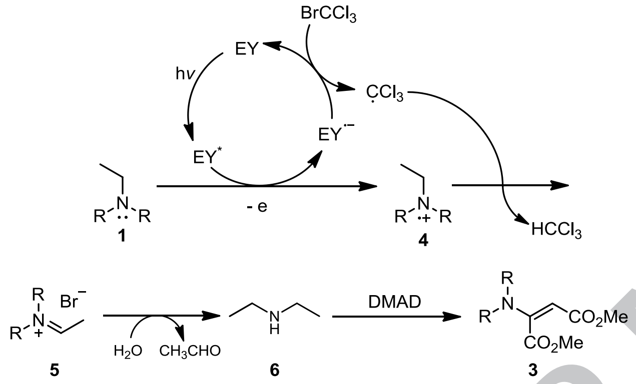
Entry	Trialkylamines	Product	Yield[b] (%)

1	NEt_3 **1a**	 **3a**	93[c]
2	NPr_3 **1b**	 **3b**	92[c]
3	NBu_3 **1c**	 **3c**	91[c]
4	$N[(CH_2)_5CH_3]_3$ **1d**	 **3d**	87[c]
5	$Me_2N(CH_2)_7CH_3$ **1e**	 **3e**	94 (2.4 : 1)[c, d]
6	DIPEA **1f**	 **3f**	62
7	$N[(CH_2)CH(CH_3)_2]$ **1g**	 **3g**	75
8	$N[(CH_2)_2CH(CH_3)_2]$ **1h**	 **3h**	95
9	$N(CH_2CH=CH_2)_3$ **1i**	 **3i**	54
10	$Et_2NCH_2CO_2Me$ **1j**	 **3j**	40
11	Me_2NCy **1k**	 **3k**	83
12	Et_2NCy **1l**	 **3l**	70
13	$MeNCy_2$ **1m**	 **3m**	60
14	NBn_3 **1n**	 **3n**	82[e]
15	Me_2NBn **1o**	 **3o**	90

[a]Reaction conditions: trialkylamine 1 (0.4 mmol), dimethyl acetylenedicarboxylate **2** (0.2 mmol), eosin Y 3 mol%, H_2O (1.0 equiv), $BrCCl_3$ (0.6 mmol), Cs_2CO_3 (0.4 mmol), DCM (2.0 mL), Green LEDs, 3 h. [b]Yield of the isolated product after column chromatography. [c]Without Cs_2CO_3. [d]Ratio of demethyl product **3e** with deoctyl product **3e'** in

parenthesis. [e]16 hours.

To elucidate the mechanism, a control experiment without DMAD was performed, gratifyingly, a signal of diethyl amine was observed by means of ESI-MS spectra, suggesting that this secondary amine was possibly generated via hydrolysis of iminium under visible light irradiation (see SI). Based on our experimental results and literature reported[4], a plausible mechanism for the photocatalytic dealkylative addition is depicted in Scheme 2. Initial irradiation of EY under visible light gives rise to excited state EY* which then oxidizes tertiary amine **1** via single electron transfer (SET) to furnish the corresponding radical cation **4**. The resulting anion radical of EY reduces $BrCCl_3$ to trichloromethyl radical and bromide ion. Then, hydrogen atom transfer (HAT) from **4** to trichloromethyl radical occurs to form iminium ion **5**, which is subsequently hydrolyzed by H_2O to form secondary amine **6**. Finally, secondary amine **6** was captured by DMAD to afford the desired product.



Scheme 2. Proposed mechanism

In summary, we have developed an efficient protocol for dealkylative addition of tertiary amine with DMAD at room temperature using $BrCCl_3$ as an external oxidant and $CsCO_3$ as a base additive. The present protocol extends the scope to a large variety of tertiary alkyl amine through visible light catalysis using eosin Y, leading the corresponding products in much better yields than those with molecular oxygen as the oxidant (40-95% versus 29-61%) in a much shorter reaction time (3 h versus 20 h). Further studies will be focused on exploring the scope of this reaction to aromatic substituted tertiary amines.

Experimental Section

The 10-mL round-bottom flask was equipped with a magnetic stirrer bar. Afterwards Triamine **1** (0.4 mmol), DMAD **2** (0.2 mmol), Eosin Y (0.006 mmol), $BrCCl_3$ (0.6 mmol), Cs_2CO_3 (0.4 mmol), H_2O (0.2 mmol) and DCM (2 mL) were added. Then the reaction mixture was sealed with stopper and placed in room temperature. A 3w green LED was placed at a distance of about 5 cm from the reaction vessel. After the reaction was complete (as judged by TLC plate). The solvent was removed under reduced pressure directly. The crude product was purified by flash chromatography on silica gel to afford the desired product **3**.

Acknowledgements

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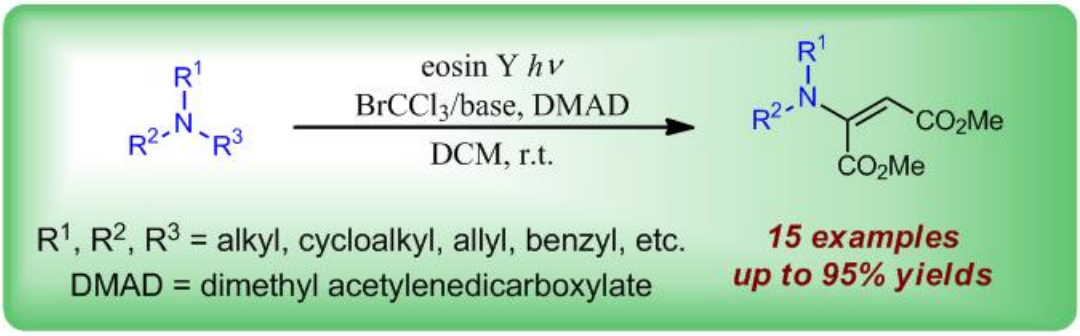
Highlights

1. An improved protocol for *N*-dealkylative addition of trialkylamines with DMAD.
2. High efficiency under mild oxygen-free conditions.
3. Good to excellent yield and better substrate tolerance.


eosin Y hν
BrCCl3/base, DMAD
DCM, r.t.
R1, R2, R3 = alkyl, cycloalkyl, allyl, benzyl, etc.
DMAD = dimethyl acetylenedicarboxylate
15 examples
up to 95% yields
CO2Me
CO2Me