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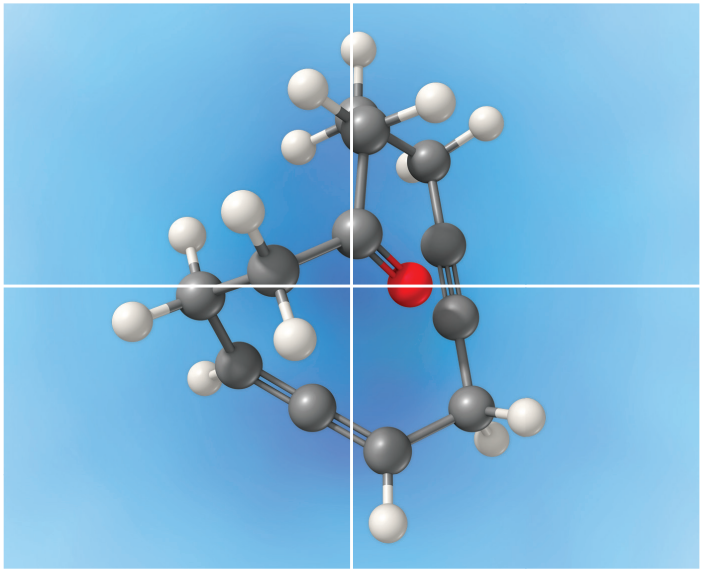

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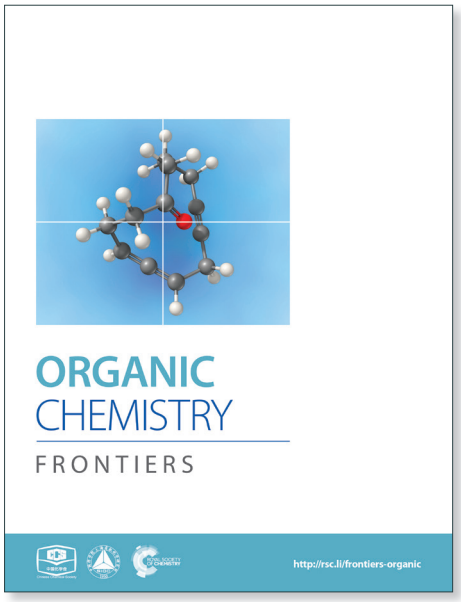

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ARTICLE

Metal free access to amide compounds *via* peroxide-mediated N=N double bond cleavage of azobenzenes

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A direct amidation of aldehydes or benzyl amines with azobenzenes through TBHP-mediated N=N double bond cleavage of azobenzenes has been developed. A series of amide compounds with a wide range of functionalities were obtained with moderate to good yields. To the best of our knowledge, it is the first example for the N=N double bond cleavage of azobenzenes used in synthesizing amide compounds.

Introduction

Recently the synthesis of amide compounds has attracted wide attention for their extensive applications in pharmaceuticals, agrochemicals and biomolecules.[1] Some pharmaceutical compounds containing amide moiety are depicted in Figure 1. One of the most traditional methods for the synthesis of amides is the condensation of activated carboxylic acids with amines. Many classical name reactions such as Beckmann,[2] Staudinger,[3] Ritter reaction[4] have been developed to form amide compounds. Furthermore, research during the past decade led to significant progress in the field of direct amidation of aldehydes,[5] yet for most of which, transition metal was a must. As a result, it is highly necessary to further develop a new method to synthesize amide compounds under mild condition from other starting materials.

Aromatic azo compounds are important materials and have been extensively applied in such fields as indicators, dyes, nonlinear optics and pharmaceuticals due to their unique properties.[6] Due to the extensive applications, substantial quantities of toxic and carcinogenic azo compounds are dumped into environment as industrial waste. Thus, it is vital to develop methods for the elimination of these compounds for environmental concerns. The cleavage of N=N double bond in azo compounds can be achieved through either electrolytic reduction[7] or chemical reduction using reducing agents such as metal iron,[8] sulfides.[9] Complementary to hydrogenations are transfer hydrogenations (CTH),[10] where typically alcohols especially isopropanol or formic acid-amine mixtures are usually used as hydrogen donors.[11]

Recently, the reaction of azobenzenes with aldehydes has been studied by the research group of Wang[12] and J. A. Ellman,[13] respectively. In Wang's work, the acylation of azobenzenes by Pd-catalyzed oxidative coupling of azobenzenes with aldehydes using *tert*-butyl hydroperoxide (TBHP) as oxidant *via* chelation-assisted *ortho* C−H bond activation was developed (Scheme 1a). While J. A. Ellman group has succeeded in synthesizing 2-aryl indazoles by Co-catalyzed reaction of azobenzenes with aldehydes (Scheme 1b). To the best of our knowledge, the N=N double bond cleavage of aromatic azo compounds under oxidative condition was rare reported.[14] To further explore this reaction as well as continue our research in aromatic azo compounds,[15] we would like to report the first example to access amide compounds *via* TBHP-mediated reaction of azobenzenes with aldehydes or benzyl amines (Scheme 1c).

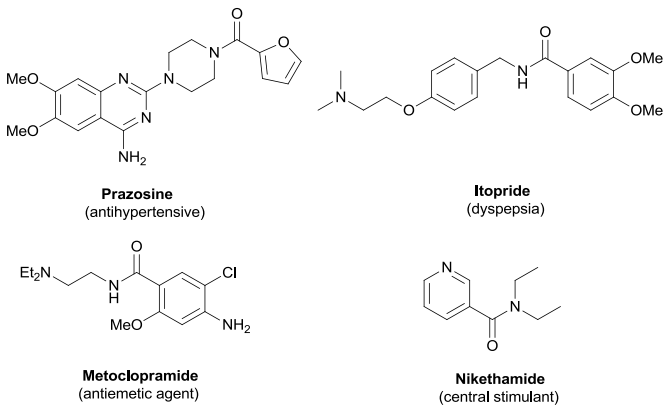
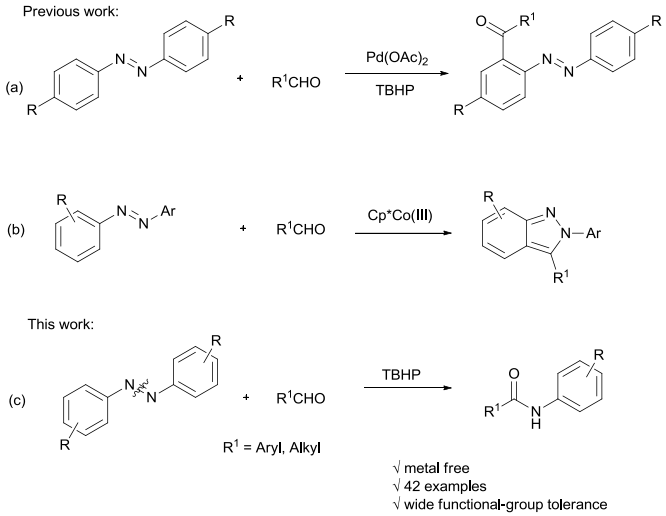


Figure 1 Structure of pharmaceutical compounds with amide bond.

Results and Discussion

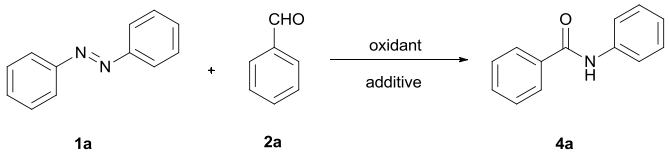
Our study started from the model reaction of azobenzene (**1a**) with benzaldehyde (**2a**) to optimize the reaction conditions. The results are summarized in Table 1. The reaction was carried out in DCE at 120 °C with *tert*-butyl hydroperoxide (TBHP) (4.0 equiv, 70% solution in water) as oxidant. Gratifyingly the product was obtained in 50% yield after 24 h (Table 1, entry 1). Inspired by this result, various oxidants including di-*tert*-butyl peroxide (DTBP), DDQ, $PhI(OAc)_2$, *tert*-butyl peroxybenzoate (TBPB) were employed with no improvement in yield (Table 1, entries 2-5). Additives were next examined (Table 1, entries 6-



Scheme 1 Reaction of azobenzenes with aldehydes studied by different groups

11). To our delight, desired product **4a** was obtained in 81% yield in the presence of TBHP and KOH. The efforts to enhance yield proved fruitless by replacing DCE with other solvents such as PhCl, Dioxane, DMF, CH_3CN, and DMSO (Table 1, entries 12-16). Additional screening revealed that the yield decreased gradually upon increasing or decreasing temperature (Table 1, entries 17-19). A decrease in the amount

Table 1 The optimization of the reaction conditions[a]

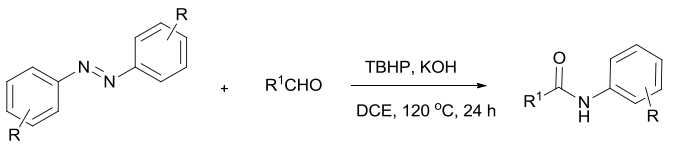


1a **2a** **4a**

Entry	Oxidant	Additive (equiv)	Solvent	T (°C)	Yield (%)[b]
1	TBHP	/	DCE	120	50
2	DTBP	/	DCE	120	N.P.
3	DDQ	/	DCE	120	N.P.
4	$PhI(OAc)_2$	/	DCE	120	N.P.
5	TBPB	/	DCE	120	46
6	TBHP	TBAB (1.0)	DCE	120	75
7	TBHP	I_2 (0.2)	DCE	120	8
8	TBHP	KI (0.2)	DCE	120	N.P.
9	TBHP	$FeCl_2$ (0.1)	DCE	120	trace
10	TBHP	KOH (1.0)	DCE	120	81
11	TBHP	PivOH (2.0)	DCE	120	54
12	TBHP	KOH (1.0)	PhCl	120	61
13	TBHP	KOH (1.0)	CH_3CN	120	43
14	TBHP	KOH (1.0)	Dioxane	120	63
15	TBHP	KOH (1.0)	DMF	120	trace
16	TBHP	KOH (1.0)	DMSO	120	33
17	TBHP	KOH (1.0)	DCE	110	56
18	TBHP	KOH (1.0)	DCE	rt	N.P.
19	TBHP	KOH (1.0)	DCE	140	77
20[c]	TBHP	KOH (1.0)	DCE	120	60
21[d]	TBHP	KOH (1.0)	DCE	120	62

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.25 mmol), oxidant (4.0 equiv), additive, solvent (1.0 mL), 24 h, air. [b] Isolated yield. [c] TBHP (3.0 equiv) was used. [d] Under argon

Table 2 The direct amidation of aldehydes with azobenzenes[a]



1 **2** **4**

Entry	**1**, R =	**2**, R^1 =	Product **4**	Yield (%)[b]
1	H	Ph	**4a**	81
2	2-Me	Ph	**4b**	47
3	3-Me	Ph	**4c**	70
4	4-Me	Ph	**4d**	72
5	4-OMe	Ph	**4e**	41
6	4-F	Ph	**4f**	64
7	4-Cl	Ph	**4g**	75
8	4-Br	Ph	**4h**	91
9	3-Cl	Ph	**4i**	57
10	3-Br	Ph	**4j**	58
11	4-COOEt	Ph	**4k**	82
12	4-OCF_3	Ph	**4l**	70
13	2,4-Me, Me	Ph	**4m**	29
14	H	2-MeC_6H_4	**4n**	57
15	H	3-MeC_6H_4	**4o**	72
16	H	4-MeC_6H_4	**4p**	68
17	H	2- $OMeC_6H_4$	**4q**	46
18	H	3-$OMeC_6H_4$	**4r**	64
19	H	4-$OMeC_6H_4$	**4s**	66
20	H	4-dimethylamino C_6H_4	**4t**	43
21	H	4-FC_6H_4	**4u**	41
22	H	4-ClC_6H_4	**4v**	53
23	H	4-BrC_6H_4	**4w**	39
24	H	3-FC_6H_4	**4x**	79
25	H	4-$NO_2C_6H_4$	**4y**	40
26	H	4-$CF_3C_6H_4$	**4z**	43
27	H	4-CNC_6H_4	**4aa**	38
28	H	2-$CF_3C_6H_4$	**4ab**	43
29	H	cyclohexyl	**4ac**	34
30	H	furan-2-yl	**4ad**	38
31	H	*n*-propyl	**4ae**	47

[a] Reaction conditions: azobenzenes **1** (0.25 mmol), aldehydes **2** (0.25 mmol), TBHP (4.0 equiv), KOH (1.0 equiv), DCE (1.0 mL), 120 °C, 24 h, air. [b] Isolated yield.

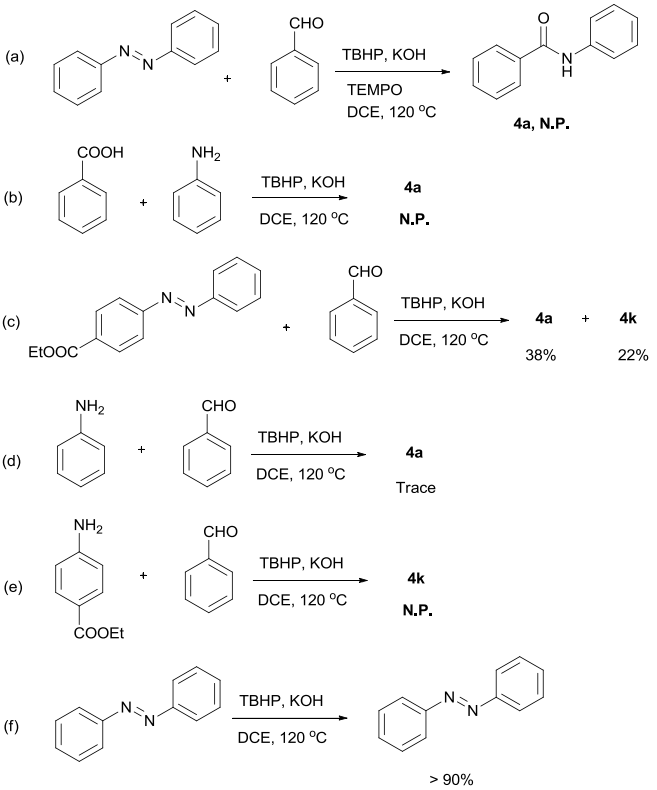
of TBHP led to the decrease of the yield of the product (Table 1, entry 20). There was a slight decrease in yield when the reaction was conducted under Argon (Table 1, entry 21).

With the optimized conditions in hand, we explored the scope of this novel TBHP-mediated reaction of aldehydes with azobenzenes, and the results are summarized in Table 2. Generally, electron-poor azobenzenes were more reactive than electron-rich aromatic azo compounds. Azobenzenes with electron-withdrawing group (such as 4-F, 4-Cl, 4-Br, 3-Cl, 3-Br, 4-COOEt, 4-OCF_3) on the aromatic ring worked well with benzaldehyde giving the corresponding products in good to excellent yields (Table 2, entries 6-12), while electron-donating groups (such as 4-OMe, 2-Me, 3-Me, 4-Me) on the aromatic ring had a slight negative effect on the yield of the reaction (Table 2, entries 2-5). The fact that the *ortho*-substituted and 2,4-disubstituted azobenzenes afforded a relative lower yield than *para*- or *meta*-substituted azobenzenes showed that steric hindrance largely affected the efficiency of this reaction (Table 2, entries 2 and 13). Next, the scope of aldehydes was explored. Contrary to the electronic effect observed in substituted

azobenzenes, the aromatic aldehydes with electron-donating groups at *ortho*, *meta* and *para* position of the aromatic ring afforded corresponding products in yields of 43-72% (Table 2, entries 14-20), while electron-withdrawing groups (such as 4-F, 4-Cl, 4-Br, 3-F, 4-NO_2, 4-CN, 4-CF_3, 2-CF_3) on the aromatic ring gave a slight lower yields (Table 2, entries 21-28). Notably, *meta*-F benzaldehyde worked well with azobenzene affording the corresponding product **4x** in 79% yield (Table 2, entry 24). To our delight, aliphatic aldehydes such as cyclohexanecarbaldehyde, butyraldehyde could also be transformed into corresponding amide compounds (Table 2, entries 29 and 31). When azobenzene was treated with furaldehyde, product **4ad** was isolated in 38% yield (Table 2, entry 30).

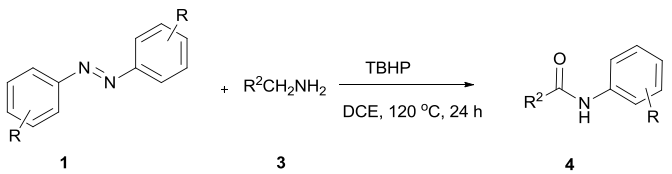
Proceeding further toward the substrate exploration of this protocol, a broad range of readily available benzyl amines were also screened for this reaction protocol, which are summarized in Table 3. The optimized reaction parameters were: azobenzene (0.25 mmol), benzyl amines (0.5 mmol), TBHP (4.0 equiv), DCE as solvent, at 120 °C for 24 h (See ESI for optimization table). It was found that no obvious decrease in yield was observed when aldehydes were replaced with corresponding benzyl amines, and the electronic effect of benzyl amine observed was similar with substituted aldehydes. The reaction of azobenzene with benzyl amines with substituents such as Me, OMe, F, Cl, Br on different position of phenyl ring delivered the corresponding products in 47-80% yields (Table 3, entries 2-10). Furthermore, when benzylamine hydrochloride was employed, the corresponding product was also formed as long as KOH was added as additive (Table 3, entry 11).

To probe the reaction mechanism of this reaction, several control experiments were performed (Scheme 2). When a typical radical scavenger tetramethylpiperidine *N*-oxide (TEMPO) was added to the reaction of azobenzene (**1a**) with benzaldehyde (**2a**) under the optimized conditions, no corresponding product was detected, which indicates a radical process may be involved in this reaction (Scheme 2a). Subsequently, benzoic acid was employed to react with aniline under standard condition, no product was observed either, which excludes the possibility that formal disproportionation reaction between azobenzene and benzaldehyde was involved (Scheme 2b). As for the unsymmetrically substituted azobenzene, two amidation products, **4a** and **4k**, were isolated in 38% and 22% yields, respectively (Scheme 2c). On the other hand, there was only trace of corresponding product detected when aniline reacted with benzaldehyde (Scheme 2d) and no corresponding product was furnished for ethyl 4-aminobenzoate under standard conditions (Scheme 2e). Moreover, more than 90% of azobenzene survived in the absence of aldehyde (Scheme 2f). These results indicate that amines may not be the intermediates in the transformation, and the amidation reaction may start from the attack of aldehydes to N=N double bond of azobenzenes and acyl radical can attack the different position of the N=N double bond when unsymmetrically substituted azobenzene is used.



Scheme 2 Control experiments for investigation of the mechanism.

Table 3 The direct amidation of benzyl amines with azobenzenes[a]



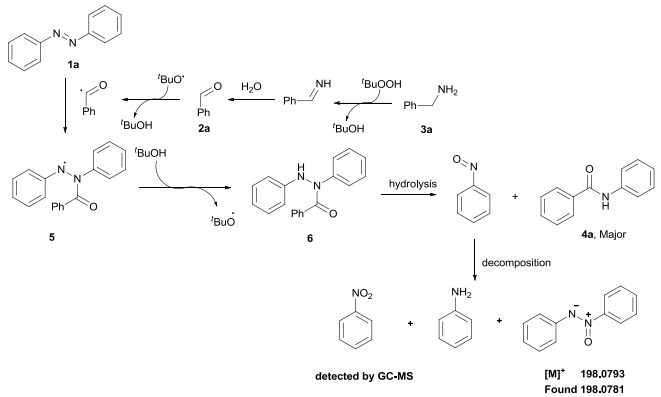
1 3 4

Entry	**1**, R =	**3**, R^2 =	Product **4**	Yield (%)[b]
1	H	Ph	**4a'**	72
2	H	2-MeC_6H_4	**4n'**	54
3	H	3-MeC_6H_4	**4o'**	74
4	H	4-MeC_6H_4	**4p'**	66
5	H	4-$OMeC_6H_4$	**4s'**	61
6	H	4-FC_6H_4	**4u'**	53
7	H	4-ClC_6H_4	**4v'**	56
8	H	4-BrC_6H_4	**4w'**	47
9	H	3-FC_6H_4	**4x'**	80
10	H	2-FC_6H_4	**4af**	57
11	H	4-$NO_2C_6H_4$	**4y'**	37[c]

[a] Reaction conditions: azobenzene **1a** (0.25 mmol), benzyl amines **3** (0.5 mmol), TBHP (4.0 equiv), DCE (1.0 mL), 120 °C, 24 h, air. [b] Isolated yield. [c] *p*-nitrobenzylamine hydrochloride was used; KOH (1.0 equiv) was added.

On the basis of the previous reports[12, 16, 17, 18, 19] and the above results, a tentative mechanism for TBHP-mediated reaction of aldehydes or benzyl amines with aromatic azo compounds was depicted in Scheme 3. Benzylamine (**3a**) first underwent oxidation, hydrolysis and the second radical oxidation by a solution of TBHP in water to form the acyl radical.[12, 17] Then, the N=N double bond of azobenzene (**1a**) was attacked by this acyl radical to form the intermediate **5**.[14, 16] This intermediate **5** may then abstract one H from ^{t}BuOH to provide **6**.[19] Finally, intermediate **6** could afford the product **4a** and nitrosobenzene *via* hydrolysis process. [18] At the same time, the decomposition of the unstable nitrosobenzene led to the formation of trace of aniline and azoxybenzene (detected by HRMS, see ESI for Figure S1) and nitrobenzene (determined by GC-MS, see ESI for Figure S2 and S3).

Conclusions



Scheme 3 Tentative mechanism for the amidation of aldehydes or benzyl amines.

In conclusion, we have developed a novel method for the synthesis of amide compounds by reaction of aldehydes or benzyl amines with aromatic azo compounds using TBHP as oxidant. Appreciable aldehydes including aliphatic aldehydes can be used in this reaction allowing a direct preparation of the corresponding amide compounds in 29-91% yields. Based on the extensive experimental data, we propose a plausible mechanism. Further studies to refine the mechanism and to extend the application of azobenzenes as synthon are currently underway in our laboratory.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures, optimization of reaction conditions, analytical data and NMR spectra for products. See DOI: 10.1039/b000000x/

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