JOC*Note*

Oxidative Conversion of α,α-Disubstituted Acetamides to Corresponding One-Carbon-Shorter Ketones Using Hypervalent Iodine (λ^5) Reagents in Combination with Tetraethylammonium Bromide

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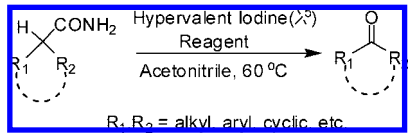
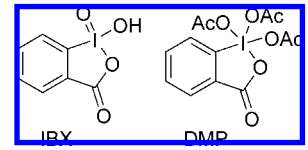


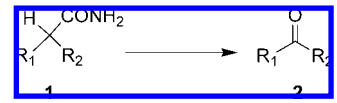
α,α-Disubstituted acetamides undergo oxidative dehomologation to give one-carbon-shorter ketones when reacted with a hypervalent iodine (λ^5) reagent in combination with tetraethylammonium bromide (TEAB) in various solvents. In further studies, one such combination of a hypervalent iodine (λ^5) reagent, *o*-iodoxybenzoic acid, and TEAB has been established as a new, mild, efficient, and general method for the transformation.

Hypervalent iodine (λ^5) reagents, mainly *o*-iodoxybenzoic acid (IBX) and Dess−Martin periodinane (DMP), have become alternative oxidizing agents for various metal oxidants. The versatility of these reagents is becoming firmly established by the various transformations they cause, like oxidative C−C coupling, oxidative cyclization, oxidative rearrangements, oxidative deoximation, oxidative ring expansion and contraction, C−N bond formation, and oxidation of alcohols,[1] etc. Because of their mildness and chemoselectivity, these are the preferred reagents in the total synthesis of various complex molecules, including natural products.[2]



The design and development of a simple method for the transformation of functional groups is one of the most attractive research themes for organic chemists. Recently, we have reported oxidative transformation of primary carboxamides to one-carbon dehomologated nitriles and N,N-disubstituted glycylamides into corresponding cyanamides.[3] In continuation of the studies of the reactions of acetamides with hypervalent iodine reagents and tetraethylammonium bromide,[3] we report, herein for the first time, a novel conversion of α,α-disubstituted acetamides, **1**, to corresponding one-carbon-shorter ketones, **2** (Scheme 1).

SCHEME 1. Oxidative Conversion of α,α-Disubstituted Acetamides to Ketones



There are no reports on the oxidative dehomologation of α,α-disubstituted (alkyl/aryl) acetamides forming ketones using hypervalent iodine reagents. However, there are some reports in which α,α-disubstituted acetamides with halide or hydroxyl groups at their α position have been converted into ketones by sodium hypohalide in low yields.[4]

There are other methods for the dehomologative conversion of carboxylic acids into ketones.[5a] These include the reaction of carboxylic acid with the iron porphyrin−iodosylbenzene system[5b] and tetrabutylammonium periodate in refluxing dioxane.[6] These methods are not convenient due to their long reaction time and lower yields. The oxidative decarboxylation of carboxylic acid derivatives via dianion formation, using lithium diisopropylamide (LDA) and followed by oxygenation, gives ketone in poor yields and also is an inconvenient method.[7]

In our preliminary experiments, 1.0 equiv of α,α-diphenylacetamide was treated with 2.5 equiv of IBX in combination with 2.5 equiv of TEAB in acetonitrile at 60 °C. As expected, benzophenone, **2a**, was obtained in excellent yields in 15 min, whereas the reaction carried out at room temperature required a longer reaction time. Studies on optimization of the reaction were carried out, and the results are summarized in Table 1. The best yield was obtained with 2.0 equiv of IBX in

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(6) Santaniello, E.; Ponti, F.; Manzocchi, A. *Tetrahedron Lett.* **1980**, *21*, 2655.

(7) (a) Wasserman, H. H.; Lipshutz, B. H. *Tetrahedron Lett.* **1975**, *16*, 4611. (b) Nokami, J.; Kawada, M.; Okawara, R.; Torii, S.; Tanaka, H. *Tetrahedron Lett.* **1979**, *20*, 1045. (c) Trost, B. M.; Tamaru, Y. *J. Am. Chem. Soc.* **1977**, *99*, 3101.

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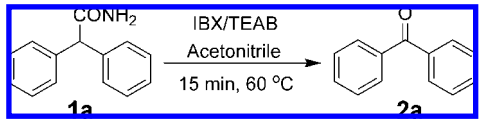
TABLE 1. Studies on the Mole Ratio of Substrate IBX:TEAB[a]



entry	IBX (equiv)	TEAB (equiv)	yield[b] (%)	recovered starting material (%)
1	2.5	2.5	98	0
2	2.0	2.0	98	0
3	1.5	1.5	74[c]	13
4	1.0	1.0	60[c]	33
5	2.0	0.1	10[c]	85
6	2.0	1.0	98	0
7	2.0	1.5	98	0

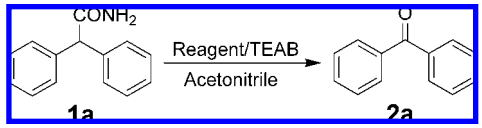
[a] Reactions were conducted on a 5 mmol scale. [b] Yield was by gas chromatography. [c] No further conversion occurred, even with increased reaction time.

TABLE 2. Solvent Study for the Conversion of α,α-Diphenylacetamide 1a to Benzophenone 2a[a]

sr. no.	solvent	yield[b] (%)
1	toluene	90
2	dioxane	71
3	tetrahydrofuran	65
4	acetonitrile	98
5	chloroform	92

[a] Reactions were conducted on a 5 mmol scale at 60 °C with IBX (2.0 equiv) and TEAB (1.0 equiv). [b] Yield was by gas chromatography.

TABLE 3. Reactions with Other Hypervalent Iodine (λ^5) Reagents[a]



entry	reagent	temperature	time	yield[b] (%)
1	IBX	rt	8 h	92
		60 °C	15 min	98
2	DMP	rt	22 h	90
		60 °C	50 min	90
3	HIO_3	rt	24 h	NR[c]
		60 °C	24 h	NR[c]

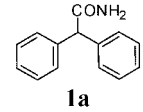
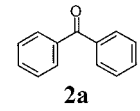
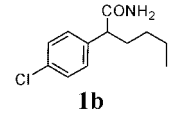
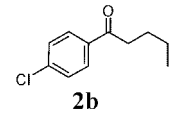
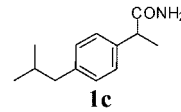
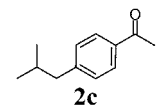
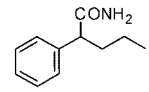
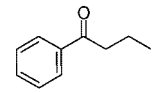
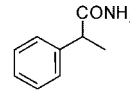
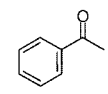
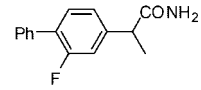
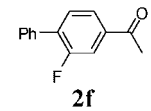
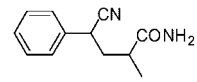
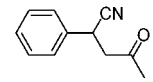
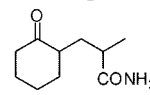
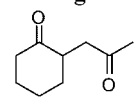
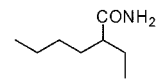
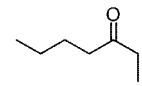
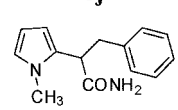
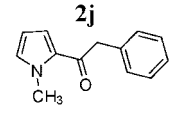
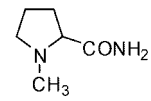
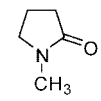
[a] Reactions were conducted on a 5 mmol scale. [b] Yield was by gas chromatography. [c] No reaction.

combination with 1.0 equiv of TEAB (entry 6). When a catalytic amount of TEAB was used, the reaction did not proceed to completion (entry 5).

Reactions were carried out in different solvents, and many solvents were found to be viable. The best results were obtained with acetonitrile (Table 2). Also, both DMP and HIO_3 were screened for the reaction. DMP gave a 90% yield in 50 min, whereas no reaction occurred with HIO_3 (Table 3).

To explore the generality of the reaction, a variety of substrates was reacted with optimized reaction conditions, i.e., 2.0 equiv of IBX in combination with 1.0 equiv of TEAB at 60 °C in acetonitrile. The results are summarized in Table 4. The results indicate that acetamides having at least one aromatic substituent at the α position reacted comparatively faster and gave relatively higher yields in comparison to the reaction speed and yields of the dialkyl and cycloalkyl acetamides (entries 7−10). Acetamides containing a heterocyclic substituent also underwent smooth transformation (entries 11 and 12).

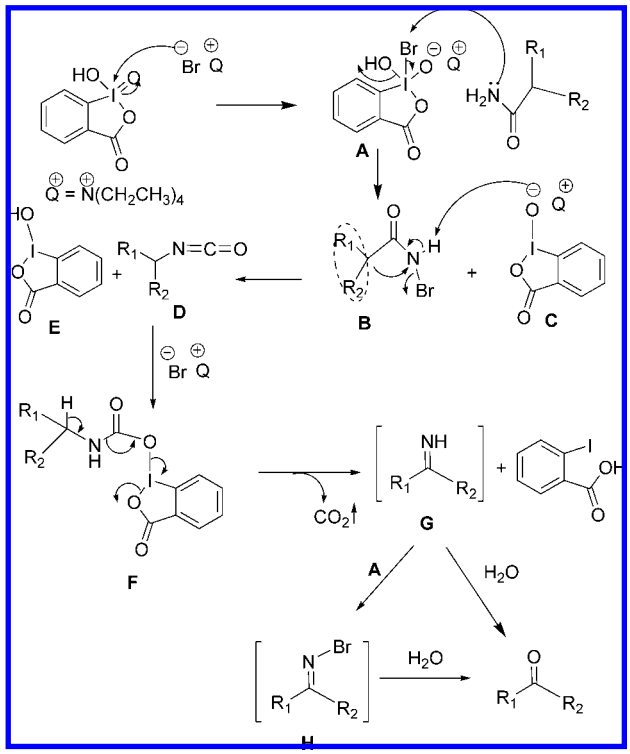
TABLE 4. Oxidative Conversion of α,α-Disubstituted Acetamide to Ketone[a,b]

Entry	Substrate	Product	Time, min	Yield[c] (%)
1	 **1a**	 **2a**	15 (480)[d]	96 (90)[d]
2	 **1b**	 **2b**	20	96
3	 **1c**	 **2c**	20 (720)[d]	92 (85)[d]
4	 **1d**	 **2d**	20	90
5	 **1e**	 **2e**	20	90
6	 **1f**	 **2f**	20	90
7	 **1g**	 **2g**	30	85
8	 **1h**	 **2h**	40	83
9	 **1i**	 **2i**	50 (780)[d]	87 (85)[d]
10	 **1j**	 **2j**	60	80
11	 **1k**	 **2k**	40	75
12	 **1l**	 **2l**	45	78

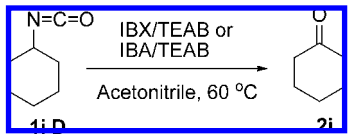
[a] Reactions were conducted on 5 mmol scale in acetonitrile at 60 °C with IBX (2.0 equiv) and TEAB (1.0 equiv). [b] For preparation of α,α-disubstituted acetamides, see Supporting Information. [c] Yield after column chromatography, and the compounds were characterized by IR, ^{1}H NMR, and physical constants. [d] Numbers in parentheses indicate the reaction time and the yield for the reaction at rt, respectively.

Some investigations were carried out to study the transformation. During the reaction, in all cases, the formation of a nonpolar intermediate (as seen with TLC) was observed, which disappears during the workup to form ketone. In the

SCHEME 2. Plausible Mechanism for the Oxidative Conversion of α,α-Disubstituted Acetamides to Ketones

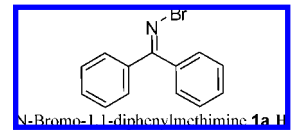


SCHEME 3. Reaction of Cyclohexyl Isocyanate with IBX/TEAB



case of α,α-diphenylacetamide, this intermediate, **H** (Scheme 2), was isolated and characterized by NMR, IR, and MS, and it was found to be N-bromo-1,1-diphenylmethanimine, **1a H**.

It is reported that N-bromoimines are less stable and slowly hydrolyze to give ketones.[8] Because of this observation and on the basis of our previous investigations,[3a] a tentative mechanism is proposed for the transformation (Scheme 2). The formation of the N-bromoimine intermediate, **H**, which results into removal of bromide ions from reaction medium, explains why the use of a catalytic amount of TEAB is not feasible.



N-Bromo-1,1-diphenylmethimine **1a H**

In order to justify the isocynate inclusion as a possible intermediate in the mechanism, cyclohexyl isocynate, **1i D**, was reacted with IBX/TEAB and with *o*-iodosylbenzoic acid (IBA)/TEAB. Both were found to be very fast reactions, giving cyclohexanone, **2i**, in 85−90% yield (Scheme 3).

In summary, an efficient and mild method for the conversion of α,α-disubstituted acetamides to the corresponding one-carbon-shorter ketones with hypervalent iodine (λ^5) reagents was developed, particularly when using IBX in combination with TEAB.

Experimental Section

General Experimental Procedure for the Preparation of Ketones. To a stirred suspension of 10 mmol of hypervalent iodine (λ^5) reagent and 30 mL of CH_3CN was added 5 mmol of TEAB, and the mixture was stirred for 5 min. A yellow suspension was observed to which was added α,α-disubstituted acetamides, **1** (5 mmol), in one portion at rt. The temperature of the reaction mixture was raised to 60 °C, and the mixture was stirred until complete consumption of the starting material, as observed with TLC. Acetonitrile was removed under reduced pressure, and the resultant residue was suspended in 30 mL of chloroform and filtered. The organic layer was washed with 30 mL of 10% sodium bisulfite solution, 30 mL of saturated sodium bicarbonate, and 30 mL of brine. The organic layer was dried over anhydrous sodium sulfate and concentrated to give crude ketone. Pure ketones, **2**, were isolated after silica gel column chromatography (EtOAc:hexane = 5:95). Benzophenone, **2a**. White solid, mp 47−48 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80−7.78 (d, J = 7.8 Hz, 4H), 7.59−7.54 (t, J = 7.35 Hz, 2H), 7.49−7.44 (t, J = 7.5 Hz, 4H). IR (KBr) ν_{max}: 3060, 3030, and 1659 cm^{-1}.

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Supporting Information Available: General methods and spectral data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO801580G

(8) Praly, J. P.; Senni, D.; Faure, R.; Descotes, G. *Tetrahedron* **1995**, *51*, 1697.