

A Novel and Mild Source of Carbon-Centered Radicals by Iodosobenzene Diacetate (IBDA) and Sodium Azide from Alcohols, Ethers, Aldehydes, Amides and Alkyl Iodides.

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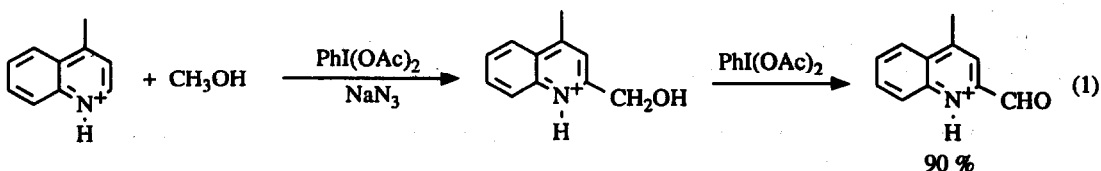
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Abstract: A radical process occurs for the thermal decomposition of IBDA in the presence of sodium azide; by this method, carbon centered radicals can be generated either by hydrogen abstraction from the solvent (an alcohol, an ether, an aldehyde or formamide) or by iodine abstraction from alkyl iodides.

Nucleophilic carbon-centered radicals are rapidly and selectively trapped by positively charged unsaturated substrates (protonated heteroaromatic bases, diazonium salts, pyrylium and iminium salts)¹; these reactions have a wide synthetic interest and they represent, at the same time, a powerful diagnostic criterion for revealing the presence of nucleophilic carbon-centered radicals in a reacting system, because the evaluated^{1,2} rate constants are in the range 10^6 - 10^8 M⁻¹s⁻¹.

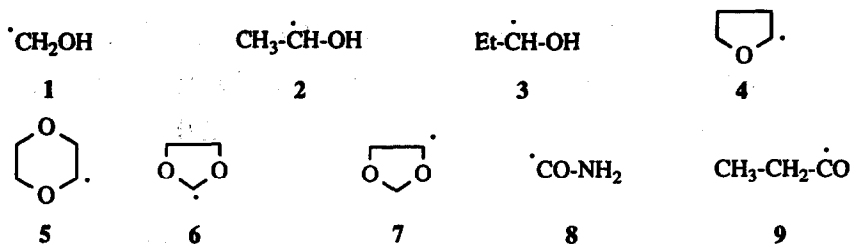
Recently, we reported how alkyl radicals can be photochemically generated from carboxylic acids ($R\text{-COOH} \longrightarrow R\cdot$)³ or alcohols⁴ through the monoester of oxalic acid ($R\text{-OH} \longrightarrow \text{ROCO-COOH} \longrightarrow R\cdot$) and IBDA. We now report a novel and mild thermal source of nucleophilic carbon-centered radicals by reaction of IBDA with sodium azide in several organic solvents. Attack on protonated lepidine has been utilized as a diagnostic criterion: nucleophilic radicals rapidly and selectively substitute at position 2 on the heterocyclic ring, thus allowing identification of the generated radical and evaluation of the efficiency of the radical source.

Accordingly, a high yield of 2-formyl-1-lepidine has been obtained by refluxing IBDA in methanol in the presence of protonated lepidine and sodium azide. A fast reaction takes place also at room temperature, leading to a mixture of the formyl and the hydroxymethyl derivatives; the latter is converted to the formyl derivative by refluxing the methanolic solution for about 2h in the presence of IBDA. The sequence depicted in eq.1 occurs, which appears synthetically interesting as a method for the direct introduction of a formyl group onto a pyridine nucleus.



Ethanol and propanol give the corresponding α -hydroxyethyl, acetyl, and respectively α -hydroxypropyl and propionyl derivatives through the same sequence. Similar results were obtained by using other solvents,

such as ethers (tetrahydrofuran, dioxane, dioxolane), formamide, aldehydes (e.g. propanal)⁵, which means that radicals 1-9 are certainly formed and trapped under these conditions.



The results are summarized in Table 1.

Table 1. Substitution on protonated lepidine in various solvents according to eq. 1^a.

SOLVENT	PRODUCTS	CONVERSION %	YIELDS ^b %
CH ₃ OH ^c	lep-CH ₂ OH lep-CHO	91	94 (69; 25)
CH ₃ CH ₂ OH	lep-CHOH-CH ₃ lep-CO-CH ₃	92	91 (84; 7)
CH ₃ CH ₂ CH ₂ OH	lep-CHOH-Et lep-CO-Et	77	96 (84;12)
iPr-OH	—	—	—
CH ₃ CH ₂ CHO	lep-CO-CH ₂ CH ₃	50	98
HCONH ₂	lep-CONH ₂	26	44
dioxane	lep-	11	96
THF	lep-	68	100
1,3-dioxolane	lep- lep-	70	80 (27; 53)

^a for experimental detail, see note 5; longer reaction times give better conversions.

^b based on the converted base; where two products are formed, yields for each are given in brackets.

^c at room temperature.

Secondary alcohols do not react with lepidine; this is not unexpected on the ground of the low redox potential of tertiary α -hydroxyalkyl radicals, which easily undergo electron-transfer oxidation⁶. When the reaction was carried out in the presence of an alkyl iodide in alcoholic or ethereal solution the alkyl radical, generated from the alkyl iodide ($R-I \rightarrow R\cdot$) was trapped by lepidine (eq.2). However, by varying the solvent, the behaviour changed considerably, as shown by the results reported in Table 2.

Clearly, radical species are involved, which can abstract hydrogen or iodine from C-H or C-I bonds, respectively. In all cases, no radical trapping occurs in the absence of sodium azide under the same conditions.

The overall mechanism of the reaction is under investigation; the role of sodium azide can be related to the study, developed many years ago in this laboratory, about the oxidation of the azide ion (N_3^-) to the

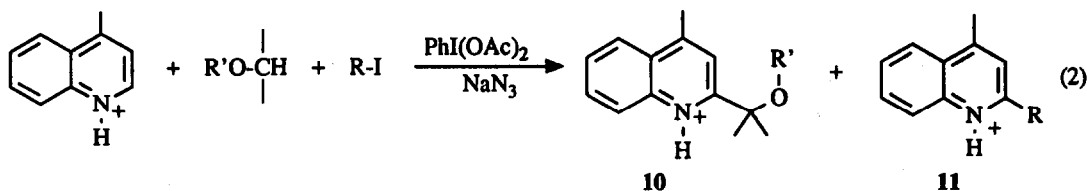
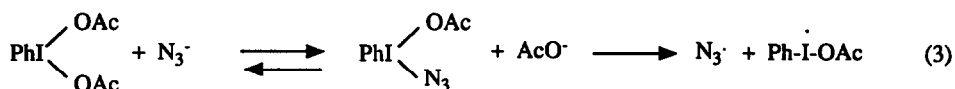


Table 2. Hydroxyalkylation (10) and alkylation (11) on lepidine by IBDA and sodium azide (eq. 2).

ALCOHOL	R	10 (%)	11 (%)
CH ₃ OH	i-Pr	82	18
CH ₃ -CH ₂ OH	"	39	61
iPrOH	"	---	100
CH ₃ OH	cyclohexyl	86	14
CH ₃ -CH ₂ OH	"	36	64
iPrOH	"	---	100

corresponding radical ($\text{N}_3\cdot$) by a variety of oxidants (H_2O_2 , $\text{S}_2\text{O}_8^{2-}$, MnO_4^- , $\text{Ce}(\text{IV})$, R_2NCl) and its trapping by alkenes, which has been proved to be a useful, general method for the synthesis of alkyl azides⁷. On the basis of that investigation, we suggest that the initial radicals might be formed by a ligand exchange between AcO^- and N_3^- in the molecule of IBDA, followed by a fast thermal homolysis of the weak I-N bond formed (eq.3).



Recently, Tiecco and coworkers successfully used alkenes to trap azido radicals, formed by oxidation of azido ions by IBDA; these Authors did not specify the mechanism of this oxidation, but their result would support the mechanism of eq.3, which can be considered an inner-sphere electron-transfer oxidation, since IBDA generally does not act as an outer-sphere electron-transfer oxidant.

The hydrogen abstracting radical has not yet been characterized. The presence of sodium azide is absolutely necessary for the generation of radicals, but this reagent has a somewhat catalytic behaviour (three moles of CH_2OH radical are generated per mole of N_3^- in methanolic solution).

This observation could be explained by a chain character of the reaction, involving the azido radical as the abstracting species (eq.4), which would react according to eq.3 in a chain process:



This hypothesis would be supported by the fact that hydrogen abstraction takes place only from relatively weak C-H bonds, characterized by high electron availability, given the electrophilic character of the azido radical⁷. Thus, no carbon-centered radicals are formed by using acetonitrile or cyclohexane as solvents. In any case, the kinetic chain is quite short. Iodine abstraction from alkyl iodides could be performed by α -hydroxyalkyl radicals.

References and Notes

1. Minisci, F.; *Substituent Effects in Radical Chemistry*; Viehe, H.G. Ed.; D.Reidel Publ.Co.: Dordrecht, 1986; pp. 391-430.
2. Recent reviews: Minisci, F.; Vismara, E.; Fontana, F. *Heterocycles* 1989, 28, 489-519; *J.Heterocyclic Chem.* 1990, 27, 79-96.
3. Minisci, F.; Vismara, E.; Fontana, F.; Nogueira Barbosa, M.C. *Tetrahedron Lett.* 1989, 30, 4569-4572.
4. Coppa, F.; Fontana, F.; Lazzarini, E.; Minisci, F.; Pianese, G.; Zhao, L. *Chem.Lett.* 1992, 1295-1298.
5. A typical example: a solution of 1 mmol lepidine, 1 mmol CF₃COOH, 2 mmol NaN₃, 4 mmol IBDA in 20 mL methanol was refluxed for 2h. The solution was then diluted, made basic and extracted with AcOEt. After distillation of the solvent, the residue was analyzed by g.l.c. and identified as 2-formyl lepidine (0.92 mmol). In a different example, only 0.2 mmol NaN₃ were used at room temperature; 67% conversion of lepidine was obtained with formation of 0.58 mmol 2-hydroxymethyl lepidine and 0.07 mmol 2-formyl lepidine. All the reaction products of Tables 1 and 2 were identified by comparison with authentic samples previously obtained by different procedures².
6. Minisci, F.; Citterio, A.; Vismara, E.; Giordano, C. *Tetrahedron* 1985, 41, 4157-4170.
7. Minisci, F. *Acc.Chem. Res.* 1975, 8, 165-171; *La Chimica e l'Industria* 1967, 49, 706-713; *Tetrahedron Lett.* 1962, 533-538; 1963, 357-360.
8. Tingoli, M.; Tiecco, M.; Chianelli, D.; Balducci, R.; Temperini, A. *J.Org.Chem.* 1991, 56, 6399-6401.

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