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Synthesis and esterification reactions of aryl diazomethanes derived from hydrazone oxidations catalyzed by TEMPO

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ABSTRACT

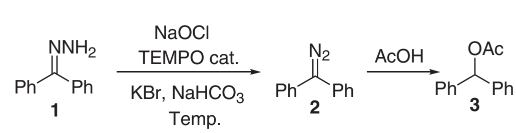
Diverse hydrazones were oxidized to the corresponding diazoalkanes using sodium hypochlorite in the presence of catalytic amounts of TEMPO (2,2,6,6-tetramethylpiperidinyloxy). A library of diverse benzhydryl esters and analogues was prepared from diazoalkanes obtained by this procedure.

Diazoalkanes are valuable and interesting synthetic materials which represent an important source of carbene/carbenoid intermediates as well as other precursors.[1] One of the well-known methods to prepare diazoalkanes involves the oxidation of diverse hydrazones.[2] However, most of the oxidation protocols for hydrazones use transition metal based oxidizers, such as HgO,[3] Ag_2O,[4] CrO_2,[5] Ni_2O_3,[6] $KMnO_4$-Al_2O_3,[7] MnO_2,[8] $Pb(AcO)_4$,[9] and triphenylbismuth carbonate.[10] Due to the inherent toxicity of transition metals, many research groups have developed environmentally friendly procedures based on the use of less toxic oxidizing agents such as OXONE™,[11] calcium hypochlorite (only for synthesis of diazoketones from hydrazono carbonyl compounds),[12] DMSO–$(COCl)_2$,[13] as well as hypervalent iodine reagents.[14–17]

In connection with a current synthetic study, we required an array of aryldiazoalkanes in which the aryl portion of the molecule was widely varied through a nonexpensive method from readily accessible reagents avoiding transition metals. Searching the available oxidation procedures, we were attracted by the oxoammonium ion mediated oxidations derived from nitroxyl radicals; an important kind of intermediates with applications as mild oxidants.[18] The most notable example of nitroxyl radical is TEMPO (2,2,6,6-tetramethylpiperidinyloxy), used mainly as catalyst in selective oxidation of primary alcohols to aldehydes.[19] Inspired by these previous reports, we initiated an investigation about the TEMPO catalyzed oxidations on hydrazones. This Letter describes the successful adaptation of this methodology to the synthesis of aryldiazomethanes and their corresponding arylmethyl esters.

In a model study, benzophenone hydrazone **1** was treated with an excess of 13% sodium hypochlorite solution in the presence of catalytic amounts TEMPO (Scheme 1). After 5 min at 0 °C, the characteristic reddish color associated with the diazo group appeared. Purification of the reaction mixture afforded a violet oil which was identified as diphenyldiazomethane **2** that shows the diazo group band C=N=N in 2050 cm^{-1} and a signal in the ^{13}C NMR spectrum in 54 ppm corresponding to the diazo group carbon. As diazoalkanes are unstable to air and ambient conditions, diphenyldiazomethane **2** was reacted with acetic acid in order to determine the reaction yield.[13] Preliminary experiments demonstrated that benzhydryl ester **3** was obtained as major product in this step.

The success of the process motivated us to optimize some reaction conditions. The experiments in Table 1 showed that temperature and reaction time play an important role in the reaction; the best yield was obtained when the reaction was carried out at −5 °C for 1 h (Table 1, entry 8). On the other hand, both calcium and sodium hypochlorite were tested as oxidizing agents in this



Scheme 1. Synthesis of benzhydryl ester **3** from diphenyldiazomethane **2** and benzophenone hydrazone **1**.

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Table 1
Effect of temperature and reaction time

Entry	Catalyst ratio (% mol)	Temperature (°C)	Reaction time (min)	Yield (%)
1	3.8	0	15	32
2	3.8	0	30	53
3	3.8	0	45	60
4	3.8	0	60	83
5	3.8	0	90	10
6	3.8	5	60	22
7	3.8	0	60	83
8	3.8	−5	60	92
9	3.8	−10	60	86

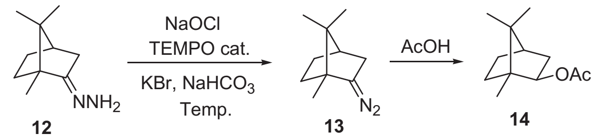
Table 2
Effect of the oxidizing agent

Entry	Catalyst ratio (% mol)	Oxidizing Agent	Oxidizing agent/ hydrazone (mmol)	Yield (%)
1	3.8	$Ca(ClO)_2$	1.0	52
2	3.8	$Ca(ClO)_2$	2.0	57
3	3.8	$Ca(ClO)_2$	3.0	65
4	3.8	$Ca(ClO)_2$	4.0	58
5	3.8	NaClO	1.0	80
6	3.8	NaClO	2.0	70
7	3.8	NaClO	3.0	92
8	3.8	NaClO	4.0	85

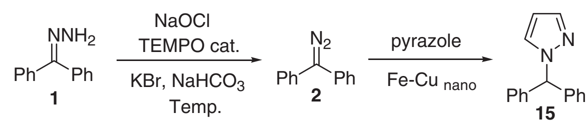
Table 3
Effect of catalyst, co-oxidizing agent, base, and KBr

Entry	Catalyst ratio (% mol)	NaOCl/ hydrazone (mmol)	$NaHCO_3$/ hydrazone (mmol)	KBr/ hydrazone (mmol)	Yield (%)
1	3.8	3.0	0.3	0.2	62
2	3.8	3.0	0.6	0.2	73
3	3.8	3.0	1.0	0.2	60
4	3.8	3.0	0.6	0.1	43
5	3.8	3.0	0.6	0.2	80
6	3.8	3.0	0.6	0.4	72
7	1	3.0	0.6	0.2	52
8	2	3.0	0.6	0.2	91
9	4	3.0	0.6	0.2	48
10	2	1	0.6	0.2	75
11	2	2	0.6	0.2	70
12	2	3.5	0.6	0.2	95

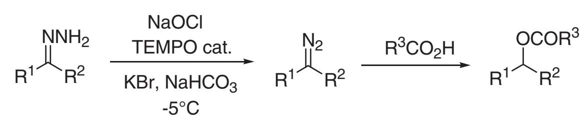
process. Although calcium hypochlorite is relatively more stable, the best results were observed using sodium hypochlorite (Table 2).



Scheme 2. Synthesis of bornyl acetate **14** from diazoalkane **13** and camphor hydrazone **12**.



Scheme 3. Synthesis of pyrazole **15** from diphenyldiazomethane **2** and benzophenone hydrazone **1**.



Scheme 4. Synthesis of benzhydryl esters.

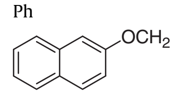
In addition, other additives (TEMPO, $NaHCO_3$, KBr) were evaluated. Thus, the yield of ester **3** was improved to 95% (Table 3). Using these optimized conditions, a series of benzhydryl esters were prepared from diazoalkanes which in turn were synthesized from diverse hydrazones (Scheme 4 and Table 4). All the compounds were fully characterized by the conventional spectroscopic techniques.[20] Not only was this process readily applicable to the synthesis of benzhydryl esters from aryl diazomethanes. For example, isopropyl ester derived from diazopropane was successfully prepared by this procedure (Table 4, compound **9**). Moreover, sterically hindered esters such as bornyl acetate **14** were prepared from diazolakane **13** which in turn was obtained from (±)-camphor hydrazone **12** (Scheme 2).[33]

This synthesis of functionalized benzhydryl esters has one important limitation. Substrates with sensitive groups such as free alcohols, amines, and aldehydes did not give the desired esters, affording probably other oxidation side products.

On the other hand, we noted azine formation in most of cases, similar to those found by Myers and Furrow,[17] and probably through a diazoalkane oxidation–dimerization mechanism, as previously described by Sharma[34] and Shechter and co-workers.[35]

Other kind of reactions that involves diazoalkanes is the carbenoid insertion to heterocyclic rings. In this regard, our group

Table 4
Benzhydryl esters prepared via Scheme 4

Compound	R^1	R^2	R^3	m.p. (°C)	m.p. lit. (°C)$^{ref.}$	Yield (%)
3	Ph	Ph	CH_3	40	39–41[21]	95
4	Ph	Ph	Ph	89	88–89[22]	81
5	Ph	Ph	4-$NO_2C_6H_4$	132	131–132[23]	73
6	Ph	Ph	3-$NO_2C_6H_4$	95	ND[24]	55
7	Ph	Ph	3-$CH_3C_6H_4$	79	ND[24]	79
8	Ph	CH_3	CH_3	Oil	Oil[25]	74
9	CH_3	CH_3	Ph	Oil	Oil[26]	62
10	Ph	Ph		88	89–90[27]	63
11	Ph	Ph	2-Naphthyl	105	ND[28]	50
12	Ph	Ph	4-$CH_3C_6H_4$	109	110[29]	75
13	Ph	Ph	4-ClC_6H_4	87	86.5–88[30]	70
14	Ph	Ph	3-ClC_6H_4	115	115–117[31]	55
15	4-ClC_6H_4	H	CH_3	Oil	Oil[32]	30
16	4-ClC_6H_4	H	Ph	Oil	Oil[27]	38