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Reductive Carbodiazenylation of Nonactivated Olefins via Aryl Diazonium Salts

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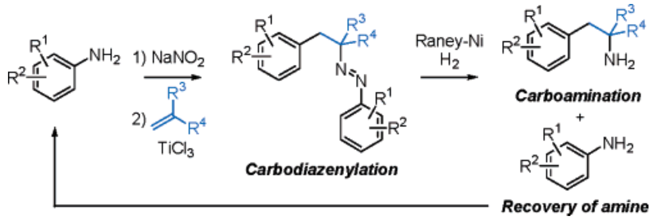
ABSTRACT



The reduction of aryl diazonium salts in the presence of nonactivated olefins provides rapid entry to carbodiazenylation products. The regioselective functionalization of double bonds is achieved in a one-pot process starting from aniline derivatives. Carboamination of olefins is possible via a two-step carbodiazenylation–hydrogenation sequence in which one aniline equivalent is recovered.

Several attempts have been made to achieve carboamination of nonactivated olefins and acetylenes recently. Among the organometallic methods, substituted pent-4-enylamines have been cyclized to give pyrrolidines via palladium catalysis.[1] 2-Alkynyl-substituted anilines[2] as well as isocyanates[3] have served as precursors for indoles in the presence of transition metals, and imines have been reacted with alkynes using zirconium[4] and titanium[5] catalysts.

Among the radical methods, the carboazidation of olefins, where sulfonyl azides are employed as nitrogen equivalents, has found broader applications.[6] In addition to sulfonyl azides, diazirines,[7] and thionitrosyl compounds,[8] aryl diazonium salts can serve as nitrogen-centered radical scavengers. This ability of diazonium salts has so far rarely been used for the functionalization of olefins.[9]

The principle of a carbodiazenylation, which can be described as a combination of Meerwein arylation[10] and radical addition to diazonium salts, is depicted in Scheme 1. A large number of arylamines **1** can be converted to aryl diazonium salts **2** via diazotization. When the diazonium salts **2** are treated with reductants in the presence of an olefin **3**,

Scheme 1. Carbodiazenylation of Olefins

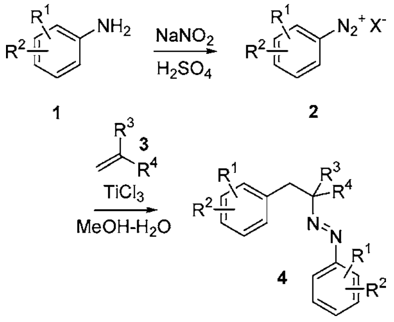


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Table 1. Carbodiazenylation of Olefins

	aniline	R^1	R^2	olefin	R^3	R^4	product	yield^a (%)
1	**1a**	H	H	**3a**	CH_2OAc	H	**4a**	47^b
2	**1b**	*o*-Cl	H	**3a**	CH_2OAc	H	**4b**	67 (61)^b
3	**1c**	*m*-Cl	*p*-CO_2H	**3a**	CH_2OAc	H	**4c**	55^b
4	**1d**	*p*-CO_2Me	H	**3a**	CH_2OAc	H	**4d**	80
5	**1e**	*o*-CO_2Me	H	**3a**	CH_2OAc	H	**4e**	59 (64)^c
6	**1f**	*p*-CF_3	H	**3a**	CH_2OAc	H	**4f**	68
7	**1d**	*p*-CO_2Me	H	**3b**	CH_2CN	H	**4g**	70
8	**1d**	*p*-CO_2Me	H	**3c**	$(CH_2)_2COMe$	H	**4h**	60
9	**1d**	*p*-CO_2Me	H	**3d**	CH_2OAc	Me	**4i**	58^d
10	**1d**	*p*-CO_2Me	H	**3e**	CH_2OH	Me	**4j**	73^d

[a] Yield according to method A (2.1 equiv of $TiCl_3$) and column chromatography. [b] Yield according to method B (1.1 equiv of $TiCl_3$ and 4.0 equiv of $FeSO_4$). [c] Reaction on a larger scale (5×). [d] Byproduct: 10−20% hydrazine.

azo compounds **4** are obtained. Both an aryl and an aryl diazenyl substituent are added regioselectively to the double bond during the course of the reaction.

This reaction so far seemed to be limited to suitably substituted electron-deficient[9a,b] double bonds, which is not surprising, since these olefins have also been reported to be the most effective substrates in the Meerwein arylation.[10] In the case of electron-rich olefins, the process is disturbed by electron-transfer which may overcome trapping.[9c]

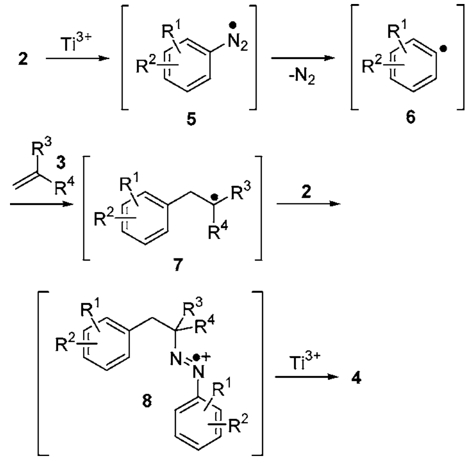
Our goal now was to find conditions that would allow the effective functionalization of nonactivated olefins. Such a procedure could decisively enlarge the scope of the carbodiazenylation reaction. In fact, the carbodiazenylation of nonactivated olefins was first observed by Levisalles and Rudler.[11] In mechanistic studies of the Meerwein arylation, low yields around 10% (with one maximum yield of 28%) were obtained with unsaturated alcohols and acetates under copper(I) catalysis. For better evaluation and comparison of our results, we chose similar olefins for the optimization.

When optimizing the reaction conditions, we found that the use of 2.1 equiv of titanium(III) chloride often gave better results than mixtures of titanium(III) and iron (II) (1.1 and 4.0 equiv). Iron(II) as the only reductant (5 equiv) leads to a very slow conversion and numerous side products.

Since the main solvent of the reaction is water, solubility of the organic reactants is a key issue. We thus varied the amount of methanol added to the reaction mixture. As a result, it became clear that small quantities of methanol are favorable. In this way, the solubility of the olefin is enhanced, but the azo compounds formed still remain mostly insoluble.[12]

The low solubility of the products was intended, as it helps to protect the azo compounds from isomerization to hydrazones under acidic conditions and from further reduction to hydrazines by the excess of reductant present in the reaction mixture. An overview of reactants and substrates is presented in Table 1. The described method allows the facile synthesis of azo compounds **4** on a gram scale (entry 5). Only in some rare cases were small amounts of the corresponding hydrazines, resulting from an excess of titanium(III) in the reaction mixture, observed (entries 9 and 10). To explain the product formation, the mechanism shown in Scheme 2 is plausible.[9,11]

Scheme 2. Mechanism of the Carbodiazenylation



The diazonium salt **2** is first reduced to an aryl diazenyl radical **5**, which readily acts as a source of aryl radicals **6** with loss of nitrogen.[13] After addition of radical **6** to olefin **3**, the radical intermediate **7** is trapped by another aryl

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diazonium ion **2**. The final azo compound **4** is formed from the radical cation **8** via a further reductive step.[9,14]

As yet, we cannot exclude the possibility that the presence of titanium has an activating effect on the double bonds of the olefinic reactants so that the attack of the nucleophilic aryl radical is facilitated. This could counterbalance the low solubility and the lower reactivity of nonactivated olefins. Despite the low solubility of allyl acetate, the yield of the reaction with methyl 4-aminobenzoate (**1d**) (Table 1, entry 4) decreases only to 58% when the excess of olefin is lowered to 2.0 equiv.

The carbodiazenylation products **4** can serve as reactants for numerous further transformations. Some examples are shown in Figure 1. Hydrazine **9** is available from **4e** via hydrogenation with palladium on charcoal. When **4e** is treated with zinc powder in acetic acid at 80 °C the dihydroisoquinolone **10** is obtained. Heating azo compound **4h** in hydrochloric acid in methanol leads to the formation of pyrrole **11**, and simple stirring of **4e** with potassium carbonate in methanol gave hydrazone **12**.

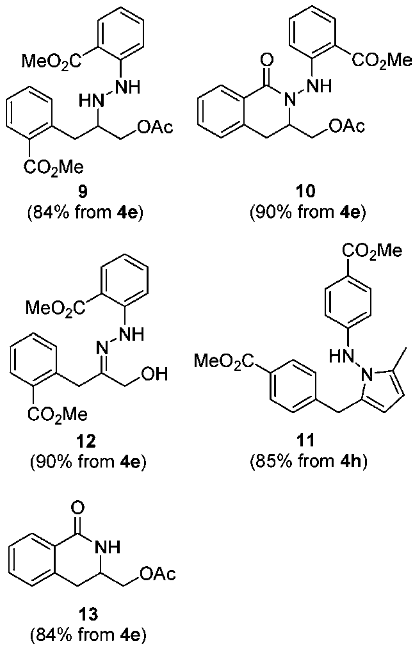

Figure 1. Synthesis of consecutive products from **4e** and **4h**.

Since all azo compounds **4** are obtained in good purity from the carbodiazenylation process, the transformations described above can be carried out without intermediate purification.

Last, but not least, we found that the hydrogenation of unsymmetric azo compounds to give the two amine components proceeds cleanly with Raney nickel in methanol. By this method, lactam **13** was obtained in 84% yield from **4e**, and 95% of the starting material methyl anthranilate (**1e**) was recovered.[15] Known literature methods for the reduction of azo compounds using zinc and formic acid or palladium on charcoal gave unsatisfactory results.[16]

In summary, we have found a simple and practical procedure for the carbodiazenylation of nonactivated olefins. Most aromatic amines are readily available, many of them from commercial sources. Moreover, there is no need for dry solvents or protecting gas atmospheres. The aryl diazonium salts which occur as intermediates, do not have to be isolated. The reaction can, therefore, be carried out on larger scales without safety concerns, which is a certain advantage over other nitrogen-centered radical traps. We have also shown that the azo compounds obtained are valuable precursors for many polyfunctionalized target molecules, which are now accessible in good yields. The carboamination products of the olefins are obtained via hydrogenation, and 1 equiv of the aniline, which was used as starting material, is recovered.

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Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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