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Carbodiazenylation of Olefins by Radical Iodine Transfer and Addition to Arenediazonium Salts

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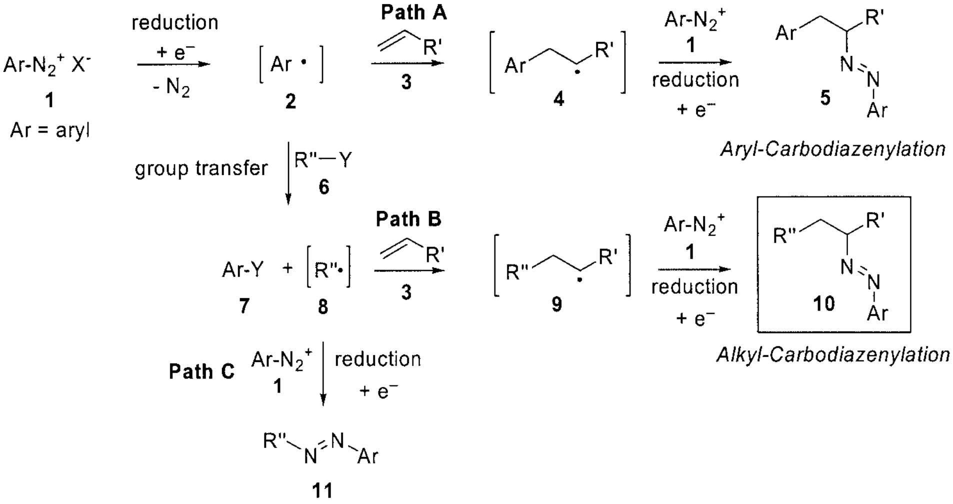
Carbodiazenylation of olefins can be achieved with arenediazonium salts under reductive conditions. The method can be extended to aliphatic substituents when iodine compounds are present in the reaction mixture. Incorporation is achieved through a radical iodine transfer.

Introduction

The ability of arenediazonium salts to act as radical scavengers was first observed by Levisalles and Rudler[1] in mechanistic studies of the Meerwein arylation about three decades ago. Some years later, Citterio[2] achieved the carbodiazenylation of suitably substituted electron-deficient olefins with arenediazonium salts under reductive conditions and applied the methodology to the synthesis of pyrazoles.[3] In addition to arenediazonium salts, only a few other nitrogen-centered radical traps are known. The carboazidation with sulfonyl azides was intensively studied by Renaud,[4] whereas reactions of diazirines and thionitrosyl compounds have been described by Barton[5] and Motherwell.[6]

Recently, we have found that the carbodiazenylation of olefins with arenediazonium salts as radical scavengers can be extended to nonactivated double bonds if the right reaction conditions are chosen.[7] A broad variety of target molecules is now accessible under simple reaction conditions and from readily available starting materials. Carboamination can be achieved with a subsequent hydrogenation step in which one aniline equivalent is recovered.



Scheme 1. Carbodiazenylation pathways.

Because the method was so far limited to the introduction of aryl substituents on the olefinic moiety, we would now like to report an extension towards aliphatic functional groups. The known carbodiazenylation reactions[1,2,7] are based on the initial formation of aryl radicals **2** from arenediazonium salts **1** under reductive conditions (Scheme 1,

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Path A). After addition of radical **2** to olefin **3**, the aliphatic radical **4** is trapped by a second arenediazonium ion **1** to give the arylcarbodiazenylation product **5** by a further reductive step.

Due to their high reactivity, aryl radicals are suitable reactants in atom or funtional group transfer reactions, where the aryl radical takes over an atom or functional group and a new, less reactive, radical is created.[8] We reasoned that if an additional transfer reagent **6** would be present in the reaction mixture, the transfer reaction to give the iodoarene **7** and the radical **8** should be able to compete with the direct addition of the aryl radical **2** to the olefin **3** (path A). Especially iodine transfer reactions to aryl radicals appeared to be suitable, because these are known to be very specific and fast processes ($k \geq 10^9\ \text{M}^{-1}\,\text{s}^{-1}$ at 45 °C, practically diffusion-controlled).[2b] After the reaction of **8** with the olefin **3** (path B) and capture of the intermediate **9** by an arenediazonium ion **1** ($k = 10^7$–$10^8\ \text{M}^{-1}\,\text{s}^{-1}$ at 5 °C, for secondary and tertiary alkyl radicals nucleophilic radicals) the desired product **10** would be obtained. In order to avoid the formation of **11** (path C), we chose **8** from primary and electrophilic-type radicals, which add to the diazonium ions **1** more slowly ($k \leq 10^6\ \text{M}^{-1}\,\text{s}^{-1}$ at 5 °C), so that the addition of **8** to the olefin **3** would then become the preferred process.[2b]

Results and Discussion

The first reaction we investigated is represented in Scheme 2. Methyl 4-aminobenzoate (**12**) was diazotized under standard conditions. Subsequently, several substituted acetic acid derivatives **13** and allyl acetate were added, and the reaction mixture was then treated with aqueous titanium(III) chloride.

The results obtained from the variation of the transfer group in **13a** and the number of equivalents of **13a** and allyl acetate are summarized in Table 1.

It became apparent that a molar ratio of a least 2:1.5 of iodine source **13a** to the allyl acetate is necessary for acceptable results (Entries 4 and 6). Stepwise addition of the olefin led to further improvement. Both xanthate and bromide derivative failed to participate in the group transfer, despite xanthate transfer being a well-known reaction.[8] The fact that the combined yield of **5a** and **10a** is always (Entries 1–6) around 70% shows the high efficacy of the iodine transfer reaction from ethyl iodoacetate. An experiment with 2-iodopropane gave the azo compounds of type **5** and **11** in 39% and 19% yield, respectively (Scheme 1, paths A and C). This verified that the electrophilic-type radicals **8** are better suited for the formation of products **10** via path B.[2b,9]

Table 1. Optimization of reaction conditions.

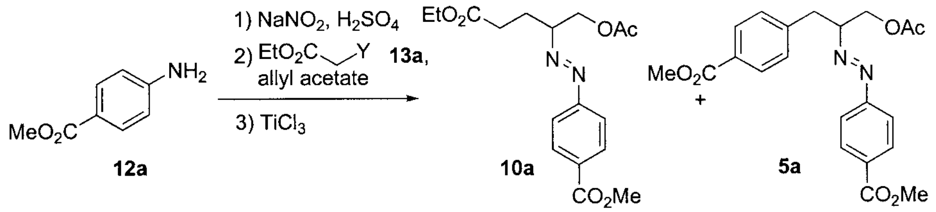
Entry	Transfer group $EtO_2C–CH_2Y$ (**13a**) Y =	Equiv.[a] **13a**	Equiv.[a] allyl acetate	Yield **10a** (%)	Yield **5a** (%)
1	I	2	10	27	40
2	I	2	5	37	29
3	I	2	2.5	44	23
4	I	2	1.5	52	17
5	I	1.5	2.5	37	27
6	I	3	1.5[b]	56	11
7	SC(S)OEt	3	1.5	trace	n.d.
8	Br	2	1.5	trace	58

[a] The reaction was carried out with 2 mmol methyl *p*-aminobenzoate (**12**) and can afford a maximum of 1 mmol product **10a**; 1 equiv. equals 1 mmol. [b] Stepwise addition of olefin (1 + 0.5 equiv.).

With optimized conditions in hand, we carried out a series of experiments to investigate the scope and limitations of the reaction. The results are summarized in Table 2.

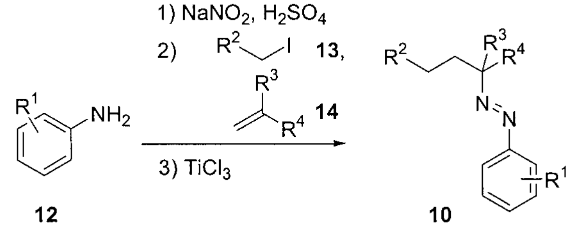
Most of the reactions proceeded in the expected way with acceptable yields for a three-component one-pot reaction. In three cases (Entries 7, 8 and 10), the expected product of type **10** appeared as a by-product and larger amounts of the iodinated compounds **15** were isolated. In these reactions, the arenediazonium salt is no longer acting as radical scavenger for the intermediate radical **16**. The radical cascade reaction is terminated by a final iodine transfer (Scheme 3) and the aryl radical now plays the role of an initiator of a chain reaction. With yields based on the amount of olefin used, remarkable results of 57% (**15a**) and 81% (**15c**) were obtained.

Iodoacetonitrile (**13c**) therefore appears to be a more efficient source for iodine radicals than the acetic acid derivatives **13a** and **13b**. From the three related experiments (Table 2, Entries 6, 7 and 10) the three reagents can be placed in the following order according to the observed radical iodine donor capability: **13c** > **13b** > **13a**, which is in agreement with similar experiments by Curran and Newcomb.[10] It is interesting to note that this effect is completely suppressed when the intermediate radical **16** is located at a tertiary carbon atom (Table 2, Entries 9 and 11). At the same time the increased nucleophilicity favors the addition to the diazonium salt.[2b]



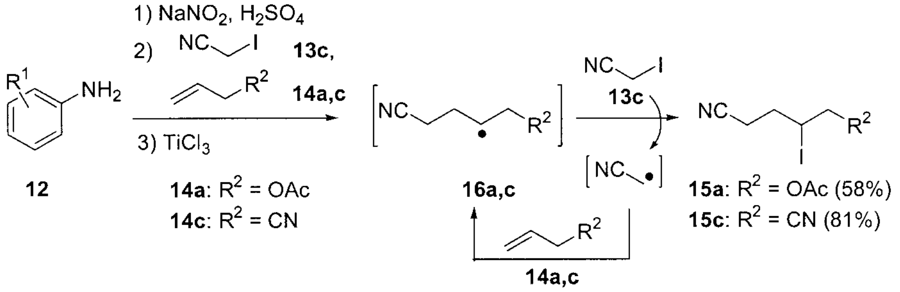
Scheme 2. Alkyl- vs. aryl-carbodiazenylation.

Table 2. Alkylcarbodiazenylation of olefins.

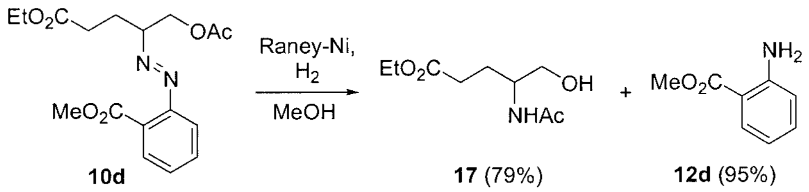


Entry	Aniline derivative **12** R^1	Transfer reagent **13** R^2	Olefin **14** R^3	R^4	Product[a]	Yields [%][b]
1	*p*-CO_2Me (**12a**)	CO_2Et (**13a**)	CH_2OAc	H (**14a**)	**10a**	56 + 11[c]
2	*p*-F (**12b**)	CO_2Et (**13a**)	CH_2OAc	H (**14a**)	**10b**	30 + 8[c]
3	*p*-COMe (**12c**)	CO_2Et (**13a**)	CH_2OAc	H (**14a**)	**10c**	33 + 22[c]
4	*o*-CO_2Me (**12d**)	CO_2Et (**13a**)	CH_2OAc	H (**14a**)	**10d**	53 + trace[c]
5	*o*-CO_2Me (**12d**)	CO_2Et (**13a**)	CH_2OH	Me (**14b**)	**10e**	40 + 19[c]
6	*o*-CO_2Me (**12d**)	CO_2Et (**13a**)	CH_2CN	H (**14c**)	**10f**	44 + 16[c]
7	*o*-CO_2Me (**12d**)	CO_2H (**13b**)	CH_2CN	H (**14c**)	**10g**	36[e] + *43*[d–f]
8	*o*-CO_2Me (**12d**)	CN (**13c**)	CH_2OAc	H (**14a**)	**10h**	15 + *43*[d,f]
9	*o*-CO_2Me (**12d**)	CN (**13c**)	CH_2OH	Me (**14b**)	**10i**	68 + trace[c]
10	*o*-CO_2Me (**12d**)	CN (**13c**)	CH_2CN	H (**14c**)	**10j**	9 + *61*[d,f]
11	*o*-CO_2Me (**12d**)	CN (**13c**)	CH_2OAc	Me (**14d**)	**10k**	46 + trace[c]

[a] For a general procedure, see below. [b] Yields based on aniline **12** (2.00 mmol) after purification by column chromatography, unless otherwise noted. [c] Yield of compound type **5**. [d] Iodinated compound **15** as major product (yields printed in *italics*); see Scheme 3. [e] Inseparable product mixture, yields determined by NMR. [f] For comparison, yields based on **12d** (2.00 mmol).



Scheme 3. Formation of iodinated products **15**.



Scheme 4. Hydrogenation of azo compound **10d**.

We finally investigated the reductive cleavage of the azo products to obtain the γ-amino acid derivatives. When **10d** was hydrogenated in methanol with Raney nickel as catalyst, the amide **17**[11] was isolated in 79% yield along with 95% of methyl anthranilate (**12d**) (Scheme 4). The transfer of the acetate group probably takes place after the first reductive step to the hydrazine. The slightly lower yield of **17** compared to **12d** might be due to an incomplete transfer of the acetate group.

Conclusions

In summary, we have found that the known carbodiazenylation of olefins can be extended to suitably substituted aliphatic substituents by a three-component one-pot reaction. Iodoacetonitrile as well as ethyl iodoacetate participate well in the iodine transfer step and 1,1-disubstituted olefins have shown to be the preferred substrates. γ-Iodonitriles were obtained by double iodine transfer from iodoacetonitrile and mono-substituted olefins in good yields. Therefore, arenediazonium salts can serve as effective initiators for iodine transfer reactions. All reactions are one-pot procedures that can be carried out under simple conditions with no need for dry solvents nor for protecting gas atmosphere. Neither a high excess of iodine transfer reagent nor of olefin is necessary. The carboamination products, which are γ-amino acid derivatives in the case shown here, are accessible through hydrogenation.

Experimental Section

General Procedure (see Table 1, Entry 6): A pre-cooled solution of sodium nitrite (145 mg, 2.10 mmol) in water (0.5 mL) was added dropwise to an ice-cooled solution of the aniline **12** (2.00 mmol) in 10% sulfuric acid (5 mL). Olefin **14** (1.00 mmol), iodine transfer reagent **13** (3.00 mmol) and methanol (1 mL) were added subsequently. A solution of titanium(III) chloride (3.00 mmol) was added dropwise to the reaction mixture. After the addition of 1/3 of the titanium chloride solution, additional olefin **14** (0.50 mmol) was added and the addition of titanium(III) chloride was continued. The reaction mixture was then stirred for a further 15 min at 0 °C. After dilution with water (50 mL), the reaction mixture was extracted with ethyl acetate (2 × 50 mL). The combined organic phases were washed with brine and dried with sodium sulfate. Purification by column chromatography gave the azo compounds as yellow oils.

Supporting Information (see footnote on the first page of this article): Experimental and spectroscopic details.

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