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Regioselective 1,3-Dipolar Cycloaddition Reaction of Azides with Alkoxy Alkynyl Fischer Carbene Complexes

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Summary: Solvent-free conditions at moderate temperature promote regioselective 1,3-dipolar cycloaddition reactions between alkoxy alkynyl Fischer carbene complexes with a wide range of organic azides.

The versatility and utility of Fischer carbene complexes have been widely demonstrated during the past two decades.[1] The rich and diverse chemistry of these complexes has been utilized as key steps in the synthesis of several natural products.[2] Especially rewarding has been their participation in various cycloaddition reactions,[3] the products of which usually retain the metal carbene functionality that can be utilized in further transformations.[4]

A triple bond conjugated with a Fischer carbene complex is highly activated toward Diels−Alder and related cycloadditions.[5] The pentacarbonylmetal fragment as a powerful electron-withdrawing group makes the conjugated alkyne considerably electron-deficient and polarized.[6] The reaction of 1,3-dipolar compounds, e.g., diazomethane,[7] nitrones,[8] and nitrilimines,[9] with such Fischer carbene complexes takes place readily to afford [3+2] cycloadducts. Chalcogenide-bridged iron clusters, despite their reluctance to react with disubstituted alkynes, readily add to alkyne carbene complexes.[10] In comparison, literature reports on reaction of azides with alkynyl Fischer carbene complexes are scarce.

Sierra described[11] Cu(I)-promoted “click” cycloaddition to terminal acetylenes tethered to an alkynyl Fischer carbene complex. The “click” product was derived from a terminal alkyne in moderate yield, but it was not clear whether any reaction occurred with the alkyne conjugated to the Fischer carbene moiety. It was reported earlier[12] that the reaction of azides with an alkynyl Fischer carbene complex under thermal activation afforded a β-amino alkenyl complex instead of the expected cycloadduct.

Recently we have successfully used a [3+2] cycloaddition between an alkynyl Fischer carbene complex and an azido-terminated monolayer on glass and silicon surfaces and achieved rapid, covalent immobilization of proteins.[13] Grafting of protein was done by utilizing aminolysis of Fischer carbene complexes by pendant lysine amino groups on a protein surface. Since this reaction would not be possible with β-amino alkenyl carbene complexes, we assumed that the cycloaddition had indeed taken place. It was not possible, however, to ascertain the extent of reaction and regiochemistry of cycloaddition products on the solid

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Scheme 1. Reaction of Alkynyl Fischer Carbene Complex 1a with Benzyl Azide

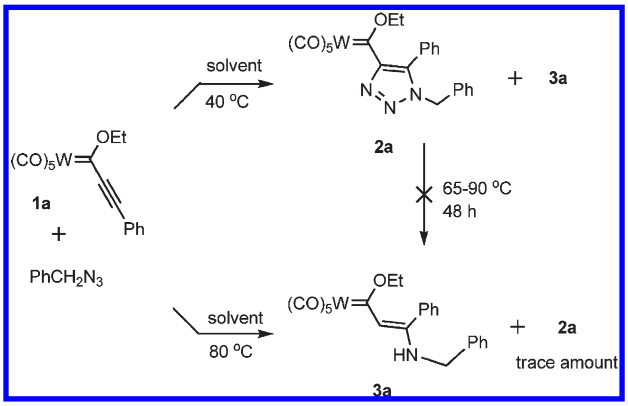


Table 1. Screening of Conditions for Azide−Alkyne Cycloaddition Reactions (depicted in Scheme 1)

entry	solvent	temp (°C)	time (h)	yield (%)[a]
1	THF	40	24	35 (42)
2	THF	40	48	30 (54)
3	dichloromethane	35	24	12 (30)
4	toluene	40	18	26 (34)
5	toluene	80	12	15 (58)
6	dioxane	40	24	28 (40)
7	dioxane	80	2	5 (60)
8	no solvent (neat)	40	3	76 (5)

[a] Isolated yield of triazole complex **2a**. Figures in parentheses are isolated yields of complex **3a**.

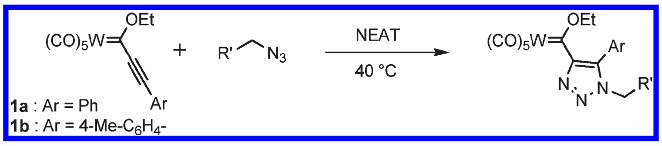
surface since usual solution spectroscopic techniques were not applicable. We, therefore, investigated this methodology in greater detail with reference to yield, modularity, and regioselectivity. We report herein a practical protocol for successful [3+2] cycloaddition reaction of azides with alkynyl Fischer carbene complexes leading to triazolyl Fischer carbene complexes regioselectively.

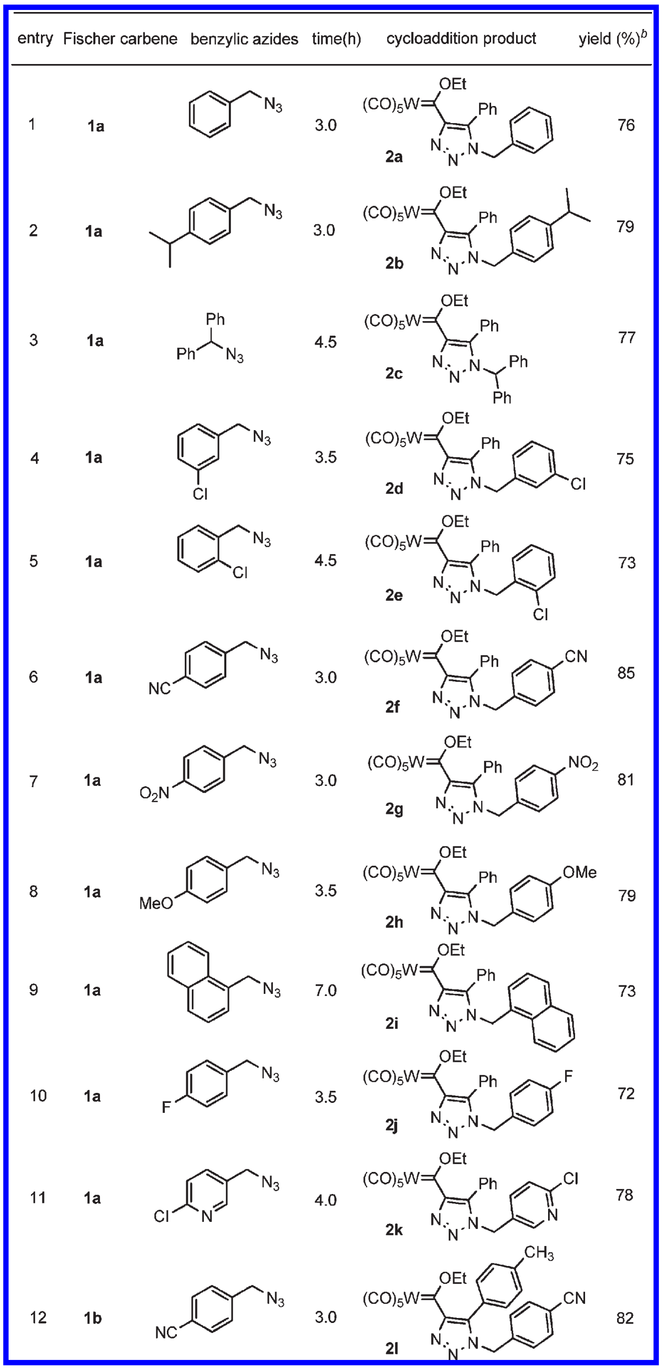
Initially, the Fischer carbene complex **1a** was treated with benzyl azide in dry THF and stirred for 24 h at 40 °C. We obtained the triazolyl carbene complex **2a** (35%) along with β-aminoalkenyl carbene complex **3a** (42%) (Scheme 1).

Screening of the reaction conditions revealed that longer reaction times and elevated temperatures decrease the yield[14] of the cycloaddition product (Table 1). Poor yield of the desired product from the cycloaddition reaction in different solvents prompted us to perform the reaction neat, i.e., without any solvent. Gratifyingly, reaction of Fischer carbene complex **1a** with benzyl azide afforded a single regioisomer of the triazole product **2a** (76%) along with a very small amount of the byproduct **3a** (5%). Hence, reactions were subsequently performed by heating the Fischer carbene complexes and azides at 40 °C for 3−8 h without any solvent under argon.

The major advantage of this protocol is fourfold: (a) no solvent is required; (b) temperature of the reaction is moderate (40 °C); (c) yield of 1,3-cycloadduct is consistently high; and (d) only one regioisomer of the product was obtained (Tables 2 and 3).

Table 2. Cycloaddition Reactions of Alkoxy Alkynyl Fischer Carbene Complexes with Arylmethyl Azides[a]





entry	Fischer carbene	benzylic azides	time(h)	cycloaddition product	yield (%)[b]
1	1a		3.0	2a	76
2	1a		3.0	2b	79
3	1a		4.5	2c	77
4	1a		3.5	2d	75
5	1a		4.5	2e	73
6	1a		3.0	2f	85
7	1a		3.0	2g	81
8	1a		3.5	2h	79
9	1a		7.0	2i	73
10	1a		3.5	2j	72
11	1a		4.0	2k	78
12	1b		3.0	2l	82

[a] Fischer carbene complex (1.0 equiv) and azide (1.5 equiv) heated at 40 °C under argon. [b] Yields of isolated products.

The entries of Table 2 comprise arylmethyl azides of a wide structural variety, whereas Table 3 lists azides ranging from alkyl to ketoaryl, aryl, and allyl. There was no significant difference in yield when substituents in benzylic azides were changed. Steric factors appear to influence the yield of this cycloaddition reaction to some extent. For example, diphenyl azidomethane, 2-chlorobenzyl azide, and 1-napthylmethyl

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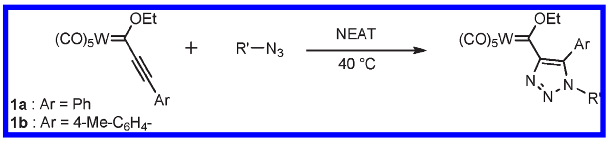
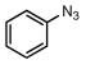
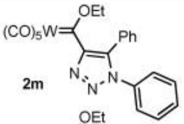
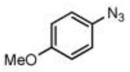
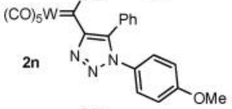
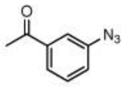
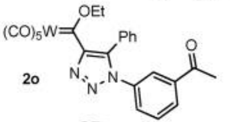
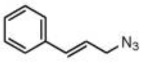
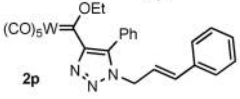
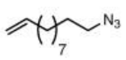
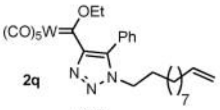
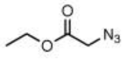
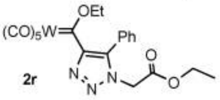
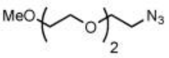
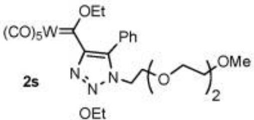
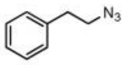
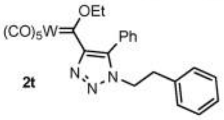
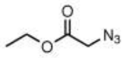
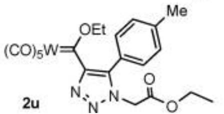
[14] We established that carrying out the reaction at higher temperature (65−90 °C) resulted in decomposition of the azide and formation of product **3a** predominantly. Although heating product **2a** at elevated temperature (~90 °C) led to gradual decomposition, compound **3a** was not one of the decomposition products, as clearly seen by TLC.

Table 3. Reactions of Alkoxy Alkynyl Fischer Carbene Complexes with Alkyl, Aryl, and Cinnamyl Azides[a]



entry	Fischer carbene	azides	time (h)	cycloaddition product	yield (%)[b]
1	**1a**		6.0	 **2m**	69[c]
2	**1a**		5.0	 **2n**	75[c]
3	**1a**		8.0	 **2o**	67[c]
4	**1a**		4.5	 **2p**	77
5	**1a**		4.0	 **2q**	72
6	**1a**		3.5	 **2r**	79
7	**1a**		4.0	 **2s**	71
8	**1a**		3.5	 **2t**	75
9	**1b**		4.0	 **2u**	74

[a] Fischer carbene complex (1.0 equiv) and azide (1.5 equiv) heated at 40 °C under argon. [b] Yield of isolated products. [c] β-Aminoalkenylcarbene isolated: 14%, 11%, and 17% for entries 1, 2, and 3, respectively.

azide required more time for completion (Table 2, entries 3, 5, and 9). A heterocyclic azide such as 5-azidomethyl-2-chloropyridine afforded an excellent yield of cycloaddition product (Table 2, entry 11).

Aryl azides are less stable. As a result, the yields of the cycloaddition products obtained from aryl azides were inferior to those obtained from benzylic azides. The presence of an electron-withdrawing group in aryl azide slowed the reaction and decreased the yield of cycloaddition product, whereas an electron-donating group in aryl azide (e.g., 4-methoxyphenyl azide) improved the yield of the reaction and shortened the reaction time (Table 3, entries 1, 2, and 3).

Alkyl azides proved to be good substrates for cycloaddition reaction with Fischer carbene complexes. Long-chain alkyl azides responded well under similar reaction conditions (Table 3, entries 5 and 7). Ethyl 2-azidoacetate reacted with Fischer carbenes **1a** and **1b** to give high yield of triazole complexes **2r** and **2u**, respectively (Table 3, entries 6 and 9). (2-Azidoethyl)benzene rapidly furnished the cycloadduct in 75% yield (Table 3, entry 8). Cinnamyl azide also afforded the desired cycloadduct in good yield (Table 3, entry 4).

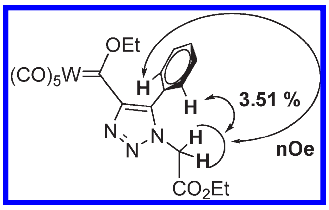


Figure 1. NOE analysis of compound **2r**.

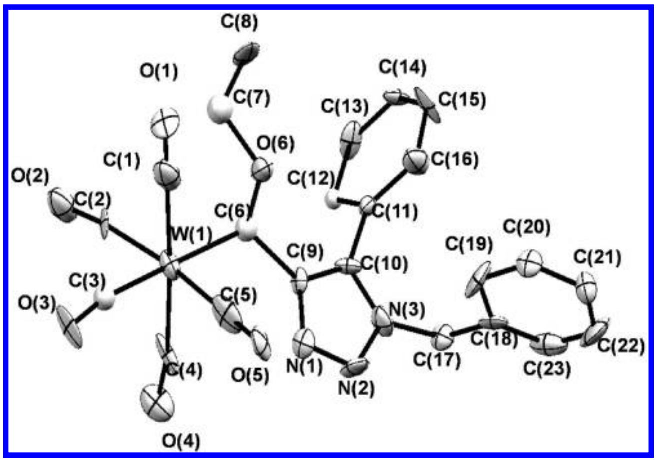
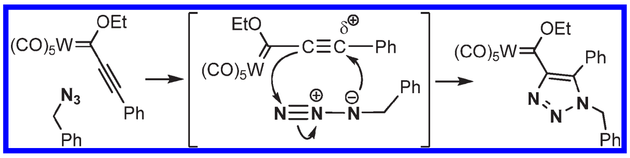


Figure 2. ORTEP diagram of **2a** with thermal ellipsoids drawn at the 50% probability level.

Scheme 2. Plausible Mechanism for Cycloaddition Reaction



The assignment of regiochemistry of a representative 1,2,3-triazolyl carbene complex (**2r**) was based on analysis of its NMR spectral data (NOESY and NOE). Significant NOE enhancement was observed among the marked protons (Figure 1).

A single crystal of a representative triazolyl Fischer carbene complex **2a** was grown, and the crystal structure of the complex was solved (see Supporting Information). The molecular structure shown in Figure 2 corroborated the structural assignment.

The regioselectivity of the triazole complex can be explained by considering the polarity of the triple bond conjugated with the carbene moiety (partial positive charge is localized on β-carbon) and the dipole of the azide[15] as depicted in Scheme 2.

In summary, we have reported a facile, regioselective [3+2] cycloaddition reaction of alkynyl Fischer carbene complexes with different organic azides under mild conditions. The present procedure is superior to earlier methods for cycloaddition in that it does not require any organic solvent. The strongly polarized triple bond of the carbene complex is responsible for

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promoting this reaction without an additive, although the rate may not be competitive with a Cu-promoted "click" reaction.[11] The method appears to be general and of a wide scope.

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Supporting Information Available: Experimental details, including copies of ^{1}H and ^{13}C NMR spectra of complexes **2a**−**u**, and X-ray crystal data of compound **2a**. This material is available free of charge via the Internet at http://pubs.acs.org.