



A practical system to synthesize the multiple-substituted 2,5-dihydrofuran by the intermolecular dipolar cycloaddition reactions involving acceptor/acceptor-substituted diazo reagents

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ABSTRACT

A practical system for synthesizing the multiple-substituted 2,5-dihydrofuran through intermolecular dipolar cycloaddition reactions of acceptor/acceptor diazo reagents, aldehydes, and acetylenedicarboxylate was developed. The reactions proceeded effectively under ambient temperature with low reactant ratios. The control reactions revealed that there are two competitive paths: one forms 1,3-dioxolane and the other forms 2,5-dihydrofuran. These two paths could be controlled by modifying the steric hindrance of the diazo reagents.

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1. Introduction

Dipolar cycloadditions (DC) are powerful reactions to rapidly build structurally complex heterocycles. The typical multicomponent nature of DC reactions has been used frequently in drug discovery chemistry.¹ Metal-catalyzed DC reactions involving carbonyl ylides can generate stereochemically complex molecules from three simple starting materials.² The scope of such DC reactions is broad when carbonyl ylides are formed by intramolecular processes.^{1c} In contrast, analogous three component intermolecular reactions involving aldehydes, diazo compounds, and dipolarophiles had been relatively limited in terms of selectivity and substrate ratios. Because of competing dioxolane formation, excess dipolarophiles are often needed to diminish the side reaction.^{3,4} However, this reaction is still highly desirable in terms of green chemistry (the dinitrogen molecule N₂ is the only by-product) and atom economic considerations when the carbonyl ylides are formed from the aldehydes and diazo compounds.

Recently, Fox and co-workers have reported an unusually three-component DC reaction of the carbonyl ylides from α -alkyl diazo compounds. With dirhodium tetrapivalate (Rh₂Piv₄) as the catalyst, the reactions can proceed at –78 °C with the substrates ratio close to equimolar (aldehyde/diazo compound/dipolarophile=1.0:1.1:1.1).⁵

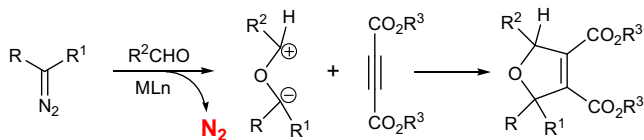
We are very interested in the reactions involving the acceptor/acceptor-substituted diazo compounds, such as diazomalonalate, diazoacetoacetate, nitro diazoacetate, and cyano diazoacetate; because these diazo compounds still remain undeveloped comparing to acceptor-substituted and donor/acceptor-substituted diazo compounds in the field of metal catalyzed selective carbene transfer reactions due to their inherent low reactivities.⁶

2,5-Dihydrofurans are a class of commonly observed structural units in natural products and unnatural products with biological potential.⁷ Although many new methods have been developed for the efficient synthesis of 2,5-dihydrofurans.⁸ However, it is still challenging to selectively synthesize multi-substituted 2,5-dihydrofuran. It is obvious that transitional metal catalyzed three component DC reactions involving aldehydes, diazo compounds, and acetylenedicarboxylate is one of the most efficient and straightforward methods to construct the multi-substituted 2,5-dihydrofurans structure (Scheme 1). In this paper, we want to report a practical system to synthesize the multiple-substituted 2,5-dihydrofuran by the intermolecular DC reactions involving different acceptor/acceptor-substituted diazo reagents.

2. Results

Initially, the DC reaction of different acceptor/acceptor-substituted diazo compound with benzaldehyde and dimethyl acetylenedicarboxylate (dipolarophiles) catalyzed by Rh₂(OAc)₄

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Scheme 1. The DC reactions of aldehydes, diazo compounds, and acetylenedicarboxylate.

was chosen as the model reaction. For practical purpose, the reactions were set at room temperature with aldehydes as limiting reagent; the substrates molar ratio of aldehyde/diazo/dipolarophile is 1.0:1.2:1.2, such low reaction temperature and substrates molar ratio for the acceptor/acceptor-substituted diazo compounds was never reported before. From the results listed in Table 1, diazo compounds **1a–4a** showed quite different activity in the DC reactions. For dimethyl diazomalonate **1a**, the desired dihydrofuran products **7a** could be formed in 41% isolated yield (Table 1, entry 1). Ethyl diazoacetoacetate **1b**, however, only trace amount of product **8a** was given (<5% by ¹H NMR) (entry 2). When nitro diazoacetate **1c** was used as the substrate, no any detectable amount of desired dihydrofuran product **9a** was observed, which could be attributed to the strong electron-withdrawing property of the –NO₂ group (entry 3). Unexpectedly, the cyano diazoacetate **1d** could furnish the desired product **10a** in 57% isolated yield, with cis/trans ratio being 67:33 (entry 4). When the reaction time was prolonged to 24 h, the yield of **10a** could be improved to 85% with the diastereoselectivity remaining unchanged (entry 5). It seems the reactivity order of these diazo compounds is **4a**>**1a**>**2a**>**3a**.

Table 1
The reactions of acceptor/acceptor diazo **1a–4a** with benzaldehyde **5a** and dimethyl acetylenedicarboxylate **6a**^a

Entry	Diazo compounds	Product	Yield ^b	dr ^c
1		1a 7a	41%	—
2		2a 8a	Trace ^d	—
3		3a 9a	ND ^d	—
4		4a 10a	57%	67:33
5 ^d		4a 10a	85%	67:33

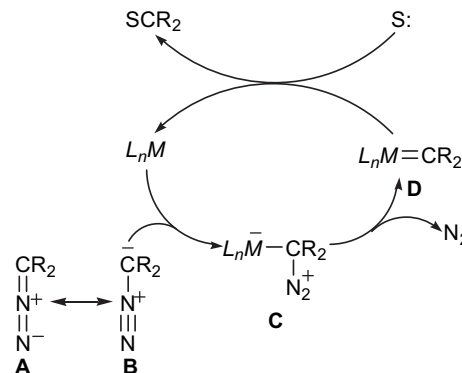
^a [5a]=0.25 M, 5a:(1a–4a):6a=1.0:1.2:1.2.

^b Isolated yield.

^c dr (cis/trans) was determined by ¹H NMR.

^d The reaction time was 24 h.

To obtain a better understanding of the reactivity of diazo **1a–4a**, we turned our attentions to the theory calculation. As supposed from the reaction mechanism: the step **B**→**C** (the catalyst metal center was nucleophilically attacked by diazo carbon) and the step **C**→**D** (breaking the C–N₂ bond to release N₂ gas) were often believed to be the key steps for the reaction (Scheme 2).



Scheme 2. The proposed mechanism.

Natural bond orbital analysis provides an efficient method for investigating charge distribution in molecular systems.⁹ The charge density of carbon atom and the C–N bond distance of the diazo moiety (C=N₂) could directly reflect the activities of the diazo compounds to some extent. The natural bonding orbital (NBO) population analysis of diazo carbon and the C–N bond distance (C=N₂) could be obtained by computer calculation using Gaussian software. The theoretical calculations were performed using the Gaussian 03 software package. The results are listed in Table 2.

The calculation results are well consistent with the trends found in Table 1. The NBO charge order is **4a**=**1a**<**2a**<<**3a**, which indicate the more negative of the diazo carbon, the more active of the diazo compound. The order of C–N bond distance is **4a**>**1a**>**2a**>**3a**, the longer C–N bond distance implies the easier happening the process of **C**→**D** (it also means that the nitrogen gas is more volatile in the intermediate **C**). Although C–N (**2a**) is a little bit larger than that of C–N (**3a**) by 0.0010 Å, however, the higher positive value of NBO charge (**3a**) dominates the reactivity expression in the catalytic process. Both the experimental results and calculation data supported that diazo **4a** is the most reactive diazo reagent. Therefore, cyano diazoacetates **4** were chosen as the diazo reagent for the model reaction to optimize the reaction conditions (Table 3).

As summarized in Table 3, the reaction is very sensitive to the solvents. DCM is the superior solvent for the reaction (Table 3, entry 1). Interestingly, **10a** was obtained only in 38% isolated yield without changing the diastereoselectivity when similar halogen solvent DCE was used (entry 2). Toluene and CH₃CN could be used as the solvents as well, although in relatively lower yields (entries 3, 4). With toluene being the solvent, the cis/trans ratio dropped to 52:48; with CH₃CN being the solvent, the cis/trans ratio increased to 77:23. When THF was used as the solvent, however, no desired product was detected; presumably the strong coordination capability of the oxygen atom in THF ring poisons the catalyst, which prohibited the reaction. In order to improve the diastereoselectivity of product, more bulky *tert*-butyl cyano diazoacetate (**4b**) was used for the reaction. It gave product **10a'** in similar yield with the diastereoselectivity remaining unchanged (entry 6).

With the optimized reaction conditions in hand, the scope of the starting material was then investigated (Table 4). As summarized in the top part of Table 4, the yields of the products derived from aromatic aldehydes substituted by electron-withdrawing groups (**10c**, **10d**, and **10e**) are generally higher than electron-rich aromatic aldehydes (**10b**). The diastereoselectivities are generally moderate,

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