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Synthesis of Pyrano[3,2-*c*]pyrazol-7(1*H*)-one Derivatives by Tandem Cyclization of 2-Diazo-3,5-dioxo-6-ynoates (Ynones)

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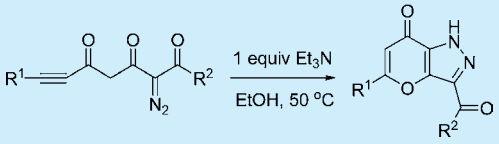
Supporting Information

ABSTRACT: The construct of the core of pyrano[3,2-*c*]pyrazol-7(1*H*)-one derivatives is realized. The key step includes a tandem cyclization, namely, a metal-free cascade 6-π electrocyclic ring closure-Michael reaction of 2-diazo-3,5-dioxo-6-ynoates (ynones). The cascade reaction cleanly generated the desired products in excellent yields under mild conditions.



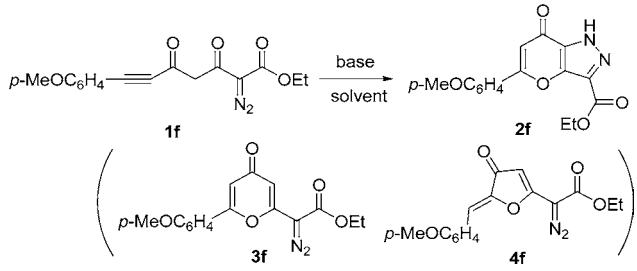
The fused-ring skeleton bearing a pyrazole ring and a γ-pyranone ring is an important structural motif that has potential among biological activities and synthetic applications based on the presence of pyrazole and γ-pyranone in natural products, bioactive compounds, pharmaceuticals, and complex ligands.[1,2] Thus, the construction of pyrazole with a γ-pyranone skeleton has always been synthetically attractive. Although numerous methods for the construction of chromeno[2,3-*c*]pyrazol-4(1*H*)-ones containing a similar core structure have been developed,[3] we are not aware of any examples of the synthesis of pyrano[3,2-*c*]pyrazol-7(1*H*)-one containing these motifs. Specially, the heterocycles with hydrogen at the position 6 of the core structure have not been documented in the literature. Accordingly, the investigation on the synthesis of the fused-ring compounds became our objective.

γ-Pyranone ring is often constructed by the intermolecular Michael addition of an enolate oxygen anion with conjugate ynones (an annulation reaction), as documented in the literature.[4] Additionally, the [3 + 2] cycloaddition of diazo compounds with carbon−carbon triple bonds has been widely applied to construct pyrazole rings;[5] however, the corresponding electrocyclizations toward these heterocycles are rarely utilized.[6] The combination of the electrocyclization toward pyrazole synthesis and the annulation for γ-pyranone synthesis is not only interesting but also challenging. In order to establish the pyrano[3,2-*c*]pyrazol-7(1*H*)-one annulation, we explored the possible cyclization of 2-diazo-3,5-dioxo-6-ynoates (ynones). To our delight, tandem cyclization reaction was observed and pyrano[3,2-*c*]pyrazol-7(1*H*)-one derivatives were obtained with high efficiency. Herein, we report the first synthesis of pyrano[3,2-*c*]pyrazol-7(1*H*)-one derivatives by using 2-diazo-3,5-dioxo-6-ynoates (ynones) as substrates and Et_3N (TEA) as base without any metal additives.

Our investigations were initiated with the reaction of ethyl 2-diazo-7-(4-methoxyphenyl)-3,5-dioxohept-6-ynoate (**1f**) (for the synthesis of **if**, see SI) under various reaction conditions, and the results are summarized in Table 1.

First, the influence of the solvent on the reaction was examined at 50 °C in the presence of 1 equiv of TEA. When EtOAc was used as solvent, low yield (32%) of **2f** was obtained with the formation of side products **3f** and **4f**, and 30% of the raw material was recovered (Table 1, entry 1). With the utilization of 1,4-dioxane, the desired product was afforded in 47% yield, and moreover, a small amount of side product **4f** was observed (Table

Table 1. Optimization of the Tandem Cyclization[a]



entry	base	solvent	T (°C)	reaction time (min)	yield (%)[b]
1	TEA (1 equiv)	EtOAc	50	450	32
2	TEA (1 equiv)	1,4-dioxane	50	180	47
3	TEA (1 equiv)	THF	50	480	77
4	TEA (1 equiv)	acetone	50	120	81
5	TEA (1 equiv)	DCE	50	120	70
6	TEA (1 equiv)	CH_3CN	50	15	86
7	TEA (1 equiv)	EtOH	50	28	86
8	DIPEA (1 equiv)	EtOH	50	20	61
9	DABCO (1 equiv)	EtOH	50	60	61
10	DMAP (1 equiv)	EtOH	50	50	57
11	DBU (1 equiv)	EtOH	50	30	10
12	3-methylpyridine (1 equiv)	EtOH	50	990	33
13	pyridine (1 equiv)	EtOH	50	1080	24
14	TEA (1 equiv)	EtOH	reflux	25	61
15	TEA (1 equiv)	EtOH	25	300	NR
16	TEA (0.1 equiv)	EtOH	50	40	64

[a]Reaction conditions: substrate **1f** (0.2 mmol), solvent (4 mL). [b]Isolated yield.

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1, entry 2). Good yields were given when the reaction was performed in THF and acetone, albeit the formation of unknown byproduct (Table 1, entries 3 and 4). To our delight, this process cleanly gave the desired product in 70% yield when the reaction was carried out in 1,2-dichloroethane (DCE) (Table 1, entry 5). CH_3CN and EtOH were found to be the best ones among the tested solvents (Table 1, entries 6 and 7). On the basis of purely environment-friendly consideration, EtOH was employed in further exploration. However, other bases were tested, including $^iPr_2NEt$ (DIPEA), 1,4-diaza-bicyclo[2.2.2]octane (DABCO), 4-dimethylaminopyridine (DMAP), and 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU), but lower yields were obtained as a result of the formation of side product (Table 1, entries 8−11). Additionally, the utilization of 3-methylpyridine and pyridine gave low yield of desired product due to both low conversion and the generation of side product (Table 1, entries 12 and 13). Next, the effect of temperature on the reaction has been exploited in EtOH in the presence of 1 equiv of TEA. No reaction was carried out at 25 °C, owing to its insolubility under the conditions (Table 1, entry 15). In addition, the formation of side product resulted in the reduction of yield at reflux (Table 1, entry 16). In theory, only catalytic amount of TEA was needed in the transformation; however, a small amount of byproduct was observed (Table 1, entry 16).

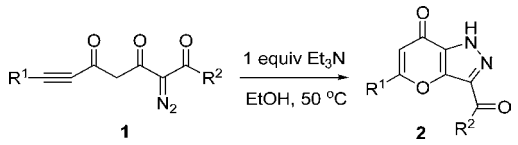
Finally, with the optimized conditions in hand (1 equiv of TEA as catalyst, EtOH as solvent, at 50 °C), the substrate scope for the annulations of 2-diazo-3,5-dioxo-6-ynoates (ynones) (**1**) was explored. These results are summarized in Table 2.

In the case of R^2 = OEt, the effect of the substituent R^1 appended to the acetylenic moiety on the reaction was exploited. The reaction of the substrate (**1a**, R^1 = Ph) proceeded to give the desired product (**2a**) in 93% yield (Table 2, entry 1). When R^1 is a substituted aryl bearing an electron-donating group, the corresponding product was cleanly formed, and but a relatively long time was needed for complete reaction (Table 2, entries 2−6). When the groups were changed to electron-deficient group, such as chloro at the 4-position of benzene ring, the reaction gave rise to the corresponding product in relatively short reaction time (Table 2, entry 7). Similarly, the reaction of **1h** and **1i** (R^1 = cyclopropyl group and aliphatic group) cleanly gave the analogues **2h** and **2i**, respectively, in high yield (Table 2, entries 8 and 9).

In the case of R^2 = Ph, similar influence of R^1 on the reaction was detected. Whether R^1 is an aromatic group or aliphatic group, all examined substrates can be cleanly converted into the corresponding product under the optimized reaction conditions; however, the reactivity is obviously higher than that of R^2 = OEt (Table 2, entries 10−15). Curiously, when R^1 is *p*-FC_6H_4, DCE was found to be a more effective solvent than EtOH based on yield and selection (Table 2, entries 16 and 17). In the case of R^1 = aromatic heterocycle, desired product was also obtained in good yields (Table 2, entry 18).

The pyrano[3,2-*c*]pyrazol-7(1*H*)-one core structure was perhaps constructed through two possible pathways, namely, Pathway I in which the construct of *γ*-pyranone ring precedes that of pyrazole ring, and Pathway II in which there is an inverse sequence of cyclization. In order to elucidate the reaction mechanism, a control experiment was carried out. The treatment of **3e** with 1 equiv of TEA in EtOH at 50 °C did not afford the product **2e** (Scheme 1). Therefore, *α*-diazo *γ*-pyranone (**3**) is not an intermediate in the formation of the desired product (**2**). On the basis of the above experimental results and previous reports, a plausible reaction mechanism was proposed in Scheme 2. First,

Table 2. Scope of the Tandem Cyclization of 2-Diazo-3,5-dioxo-6-ynoates (Ynones) to Pyrano[3,2-*c*]pyrazol-7(1*H*)-one[a]

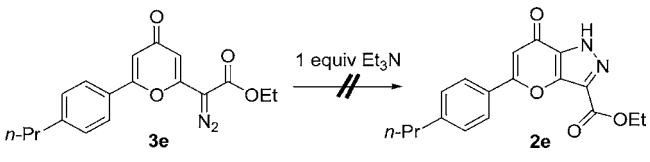


1 2

entry	R^1/R^2	2	reaction time (min)	yield (%)[b]
1	Ph/OEt (**1a**)	**a**	19	93
2	*p*-MeC_6H_4/OEt (**1b**)	**b**	22	88
3	2,4,6-$Me_3C_6H_2$/OEt (**1c**)	**c**	35	84
4	3,5-$^tBu_2C_6H_3$/OEt (**1d**)	**d**	30	74
5	*p*-$^nPrC_6H_4$/OEt (**1e**)	**e**	30	95
6	*p*-$MeOC_6H_4$/OEt (**1f**)	**f**	28	86
7	*p*-ClC_6H_4/OEt (**1g**)	**g**	15	85
8	 /OEt (**1h**)	**h**	49	88
9	^{n}Bu/OEt (**1i**)	**i**	20	85
10	Ph/Ph (**1j**)	**j**	6	83
11	*p*-MeC_6H_4/Ph (**1k**)	**k**	6	85
12	*p*-$^nPrC_6H_4$/Ph (**1l**)	**l**	6	86
13	*p*-$MeOC_6H_4$/Ph (**1m**)	**m**	5	88
14	*p*-ClC_6H_4/Ph (**1n**)	**n**	5	91
15	^{n}Bu/Ph (**1o**)	**o**	8	97
16	*p*-FC_6H_4/OEt (**1p**)	**p**	29 (65)	43 (80)[c]
17	*p*-FC_6H_4/Ph (**1q**)	**q**	5 (7)	80 (88)[c]
18	 /OEt (**1r**)	**r**	15	81

[a]Reaction conditions: substrate **1** (0.2 mmol), Et_3N (0.2 mmol) in EtOH (4 mL). [b]Isolated yield. [c]The results (given in parentheses) were obtained by use of DCE as solvent.

Scheme 1. Control Experiment



the carbanion (**5**) was formed by using TEA as base. The reaction might be triggered by 6-*π* electrocyclic ring closure[6] of the intermediate (**5**) (path A) (constructing pyrazole ring in the first cyclization) to give the intermediate (**6**). Subsequent intramolecular Michael addition of the enolate oxygen anion (**6**) to

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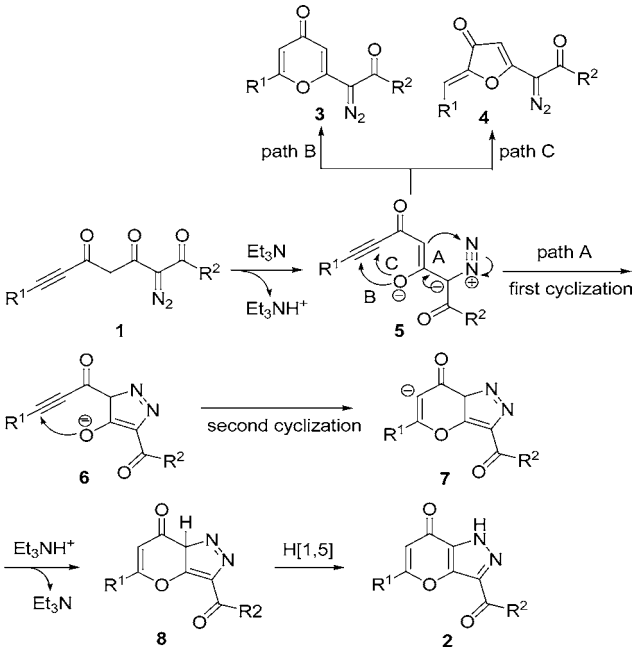
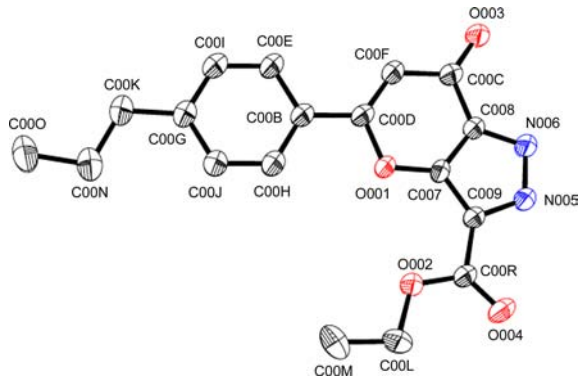
Scheme 2. Possible Mechanism



carbon−carbon triple bond generated the carbanion (**7**) (constructing γ-pyranone ring in the second cyclization), followed by protonation-[1,5]-hydrogen migration to afford the product (**2**). The generation of side products (**3**) and (**4**) could be rationalized by path B and path C, respectively. The structure of pyrano[3,2-*c*]pyrazol-7(2*H*)-one (**2**) was finally established by single-crystal X-ray diffraction analysis of product **2e** (Scheme 3).

Scheme 3. X-ray Crystal Structure of Product 2e



In conclusion, the tandem cyclization of 2-diazo-3,5-dioxo-6-ynoates (ynones) was developed for the synthesis of pyrano[3,2-*c*]pyrazol-7(1*H*)-one derivatives. These cyclization reactions proceed smoothly under mild conditions to cleanly generate the desired products in excellent yields. This protocol has advantages of 100% atom-economic, metal-free additives, and simple manipulation. In addition, a reasonable reaction mechanism has been proposed. Six-π electrocyclic ring closure of diazo compounds has been disclosed for the first time. Similar reactions may be possible for other types of diazo compounds. Investigations along this line are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02369.

Experimental details, NMR spectra of all new products (PDF)

CIF info of product **2e** (CIF)

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Notes

The authors declare no competing financial interest.

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