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Alkynes as Equivalent of α -Diazo Ketones in Generating α -Oxo Metal Carbenes: A Gold-Catalyzed Expedient Synthesis of Dihydrofuran-3-ones

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Late transition metal carbenes are versatile intermediates and can undergo a wide range of highly valuable and often difficult transformations including C–H insertion/functionalization, cyclopropanation, and formation of reactive ylides.¹ It is not surprising that the generation of these species has been subjected to intensive studies. Of particular practical importance are methods that are highly reliable and do not require the assistance/participation of a tethered functional group.² The most useful method of this kind is metal-catalyzed decomposition of diazo compounds, especially relatively stable α -diazo carbonyl compounds. Consequently, there are a plethora of versatile synthetic methods developed based on these compounds using transition metals such as Rh and Cu.³ However, diazo compounds are: a) hazardous and potentially explosive; b) mostly prepared from carbonyl precursors without much enhancing molecular complexity, thus diminishing efficiency in synthetic sequences.

Recent rapid development in gold catalysis offers alternative approaches⁴ to generate α -oxo metal carbenes (gold as the metal) via intramolecular oxidation of alkynes. While several versatile synthetic methods have been developed based on this strategy, the required oxidants had to be tethered to the C–C triple bond in optimal distances (Scheme 1A).⁵ This requirement of intramolecularity imposes significant structural constraints on both substrates and products and severely limits the synthetic potential of this chemistry. So far no success has been reported with external oxidants (Scheme 1B).⁶ Significantly, the intermolecular approach makes alkynes equivalent to α -diazo ketones without their afore-mentioned drawbacks and, moreover, offers much synthetic flexibility in comparison to the intramolecular one! Herein, we report the first example of accessing α -oxo gold carbenes via intermolecular oxidation of terminal alkynes under mild reaction conditions and its application in a simple but efficient preparation of dihydrofuran-3-ones. Notably, the existing synthetic methods for this useful class of *O*-heterocycles⁷ typically require multiple steps and/or rather functionalized substrates.⁸

We began with using homopropargylic alcohol **1** as substrate, anticipating that an intramolecular O–H insertion by the gold carbene moiety in **B** would be facile and productive (Table 1). After limited success using various sulfoxides as external oxidants, we turned to pyridine *N*-oxides, hoping to limit the known 3,3-rearrangement.⁶ To our delight, dihydrofuran-3-one **2** was indeed formed using the parent pyridine *N*-oxide albeit in only 9% yield (entry 1). We suspected that basic pyridine formed during the reaction might deactivate IPrAuNTf₂.⁹ The addition of acids indeed substantially improved the reaction (entries 2–6), and the yields were around 50–56% using strong acids (entries 3–6); moreover, the stronger

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

the acid was, the faster the reaction proceeded. Consequently, the reaction could be performed conveniently at room temperature (entries 4–6) with acceptable reaction times. We chose MsOH to further optimize the reaction conditions, hoping to balance the reaction time and the acidity of the reaction system. A range of substituted pyridine *N*-oxides were examined and some were shown in entries 7–10. 3,5-Dichloropyridine *N*-oxide and 2-bromopyridine *N*-oxide turned out to work equally well. The reaction conditions were further improved by lowering the acid amount without sacrificing much of the yield (entry 11). Surprisingly, Ph₃PAuNTf₂ performed better than IPrAuNTf₂ (entries 13 and 14), which was advantageous due to its lower cost. Of note, PtCl₂ and AuCl₃ led to poor results (13 % and 15%, respectively), and no reaction was observed in the absence of a metal catalyst.

The reaction scope was then promptly studied. As shown in Table 2, this reaction proceeded well with various substrates, and the yields ranged from 55% (entry 12) to 88% (entry 18); moreover, a variety of functional groups were tolerated. Several conclusions can be drawn from these studies: a) this gold-catalyzed oxidative strategy is a reliable method for accessing α -oxo gold carbenes, and may allow predictable synthetic designs; the exceptions were terminal alkynes that can undergo facile cyclization by tethered nucleophiles (e.g., 5-*exo-dig* cyclization in the case of bishomopropargylic alcohols, which led to low efficiency); b) the reaction system was mildly acidic, and both Boc and MOM groups were tolerated (entries 5–6); although MsOH (p*K*_a, -2.6) is a strong acid, the excess pyridine *N*-oxide (p*K*_a, 0–1)¹⁰ acted as a base and tempered the reaction acidity; the mild acidity of the reaction was also evident with furan and indole substrates (entries 13 and 14); c) a general trend can be deduced based on the results of a series of aryl substrates (e.g., entries 8, 9, 12 and 13): the more nucleophilic the HO group is, the more efficient the reaction is; this is in agreement with the fact that better yields were frequently obtained with R = aliphatic or functionalized aliphatic groups (entries 2, 5, 17 and 18); d) for the furan (entry 13) and indole (entry 14) substrates, no 5-*exo-dig* or 6-*endo-dig*¹¹ cyclization to the arene ring was observed, reflecting the facile nature of the oxidation; e) finally, the efficient formation of strained 5,6-*trans*-fused **4r** suggests the synthetic potential of this chemistry and again the mild nature of the reaction as its epimerization was observed during purification using either neutral alumina or silica gel columns.

The formation of gold carbenes was supported by the isolation of mesylate **7**¹² and the observation of pyridium **8** by crude ¹H NMR and ES⁺MS (Figure 1A). In fact, side products of these types counted for most of the remaining substrates. Although their formation could be rationalized by an S_N2' process (Figure 1B) as well, the formation of **2** would require a disfavored 5-*endo-trig* cyclization;¹³ furthermore, the efficient and easy formation of **4r** argues against this alternative kinetically. Of note, our attempts to convert **7** or **8** to **2** did not succeed even under basic conditions.

In summary, we have developed a convenient and reliable access to reactive α -oxo gold carbenes via gold-catalyzed intermolecular oxidation of terminal alkynes under mild reaction conditions. This intermolecular strategy provides much improved synthetic flexibility comparing to the intramolecular ones and offers a safe and economic alternative to those based on diazo substrates. Its synthetic potential is demonstrated by expedient preparation of dihydrofuran-3-ones containing a broad range of functional groups.

Supplementary Material

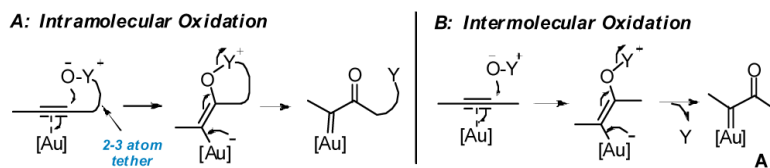
Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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**Scheme 1.**Access to α -Oxo Gold Carbenes: Intra- vs Intermolecular oxidation

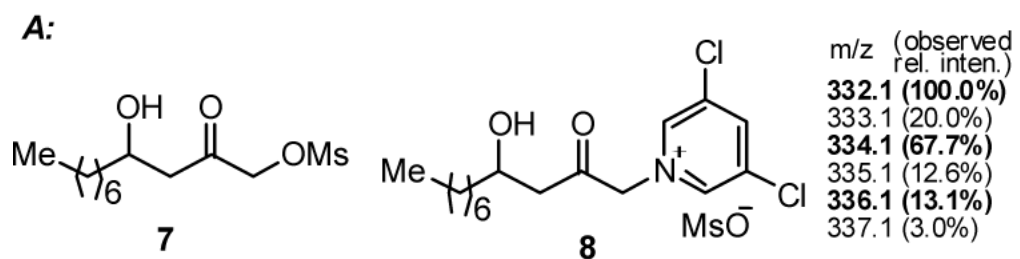


Figure 1.

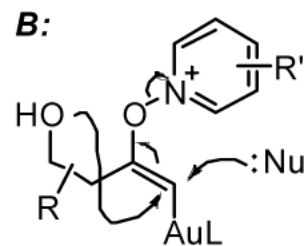


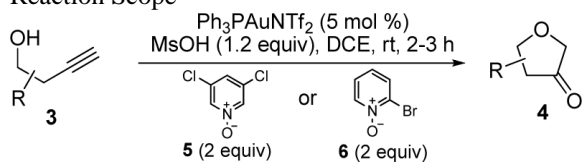
Table 1

Reaction Conditions Optimization.^a

entry	L	R ^b	acid ^b	conditions	yield ^c
1	IPr	H	-	DCE, 60 °C, 10 h	9% ^d
2	IPr	H	Cl ₃ CCO ₂ H	DCE, 60 °C, 10 h	32% ^e
3	IPr	H	F ₃ CCO ₂ H	DCE, 60 °C, 5.5 h	56%
4	IPr	H	F ₃ CCO ₂ H	DCE, rt, 8 h	53%
5	IPr	H	MsOH	DCE, rt, 4.5 h	51%
6	IPr	H	TfOH	DCE, rt, 2 h	54%
7	IPr	3-Br	MsOH	DCE, rt, 2.5 h	64%
8	IPr	3,5-Cl ₂	MsOH	DCE, rt, 2.5 h	68%
9	IPr	2-Br	MsOH	DCE, rt, 3.5 h	68%
10	IPr	4-Ac	MsOH	DCE, rt, 8 h	52%
11	IPr	2-Br	MsOH ^f	DCE, rt, 3.5 h	65%
12	Et ₃ P	2-Br	MsOH ^f	DCE, rt, 3.5 h	64%
13	Ph ₃ P	2-Br	MsOH ^f	DCE, rt, 2.5 h	78% ^g
14	Ph ₃ P	3,5-Cl ₂	MsOH ^f	DCE, rt, 2.5 h	75%

^a[I] = 0.05 M; DCE: 1, 2-dichloroethane.^b2 equivalent.^cEstimated by ¹H NMR using diethyl phthalate as internal reference.^d75% conversion.^e68% conversion.^f1.2 equivalent.^g76% isolated yield.

Table 2

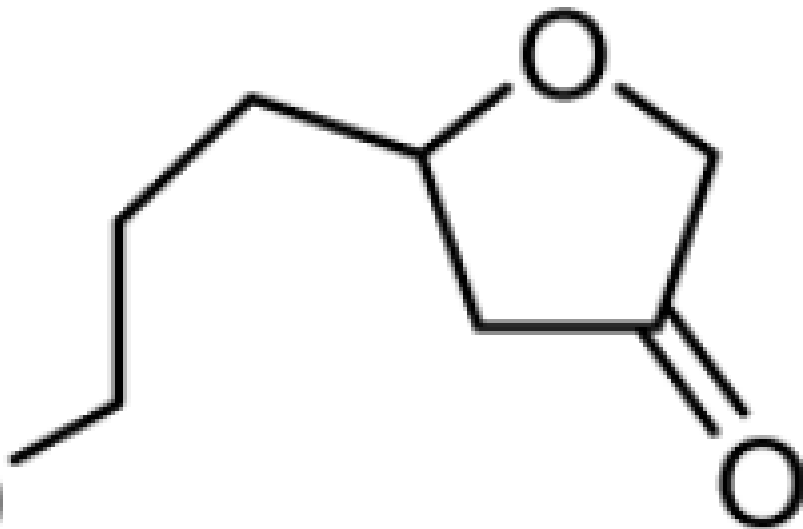
Reaction Scope^a

entry	N-oxide	product
1	5	
2	5	
3	5	
4	5	

entry	N-oxide	product	
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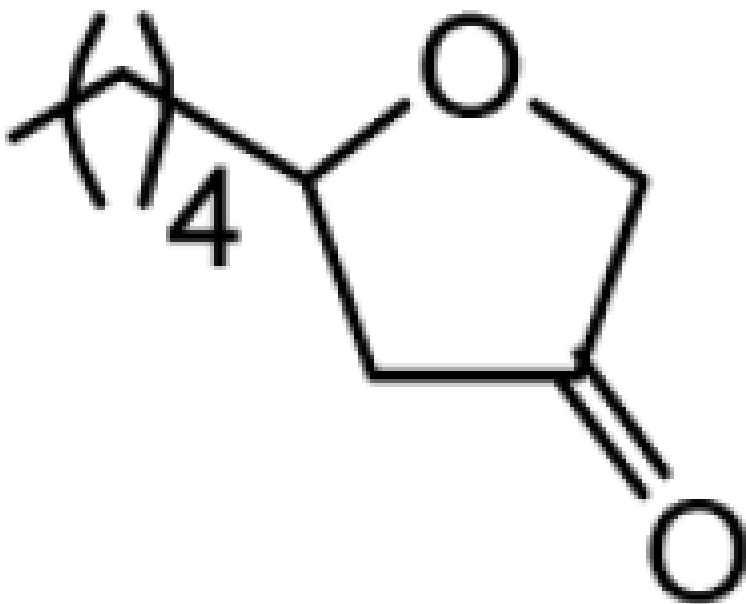
5	5		4/
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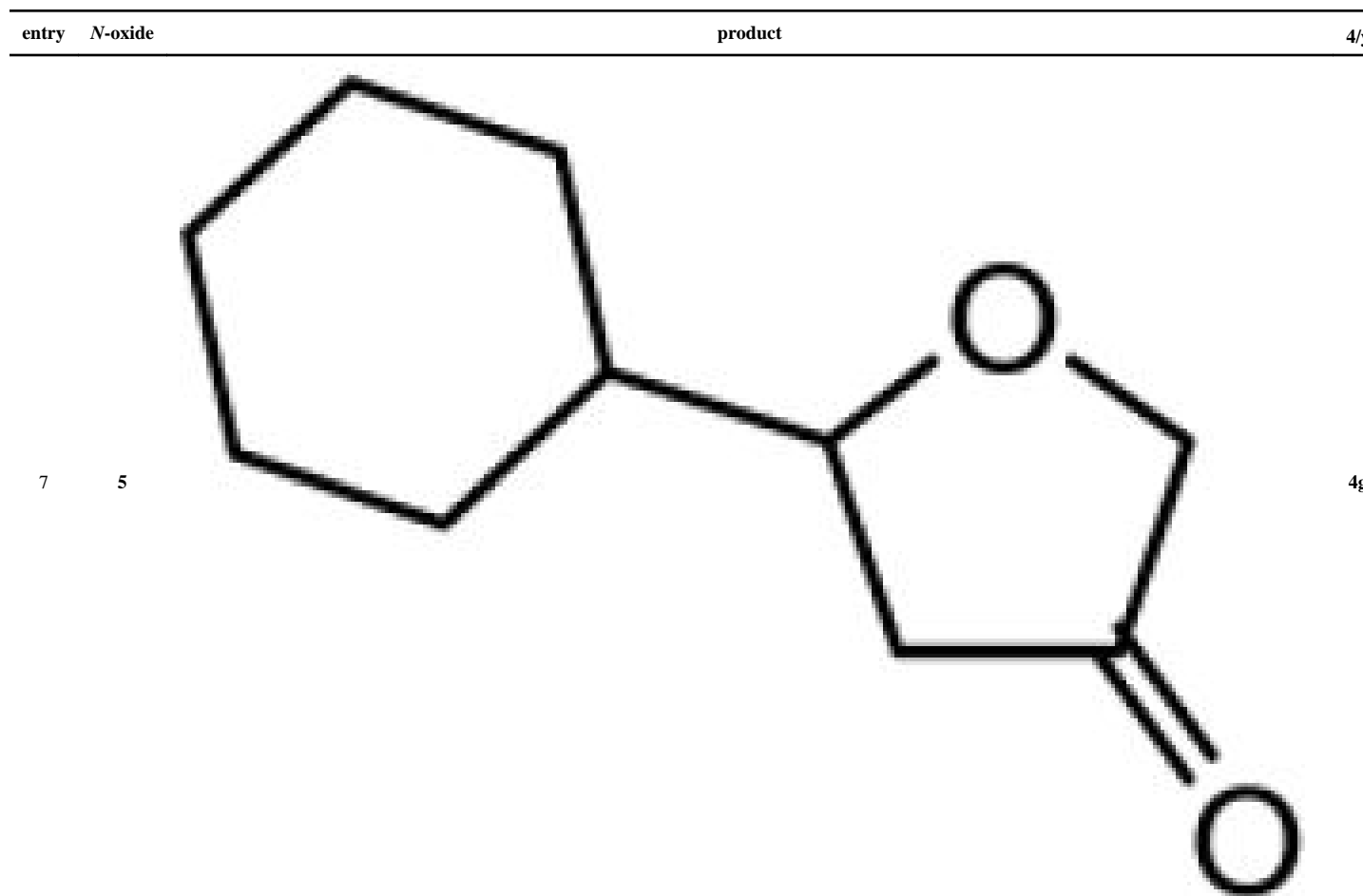
MOMO



6	5		4/
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BoCHN

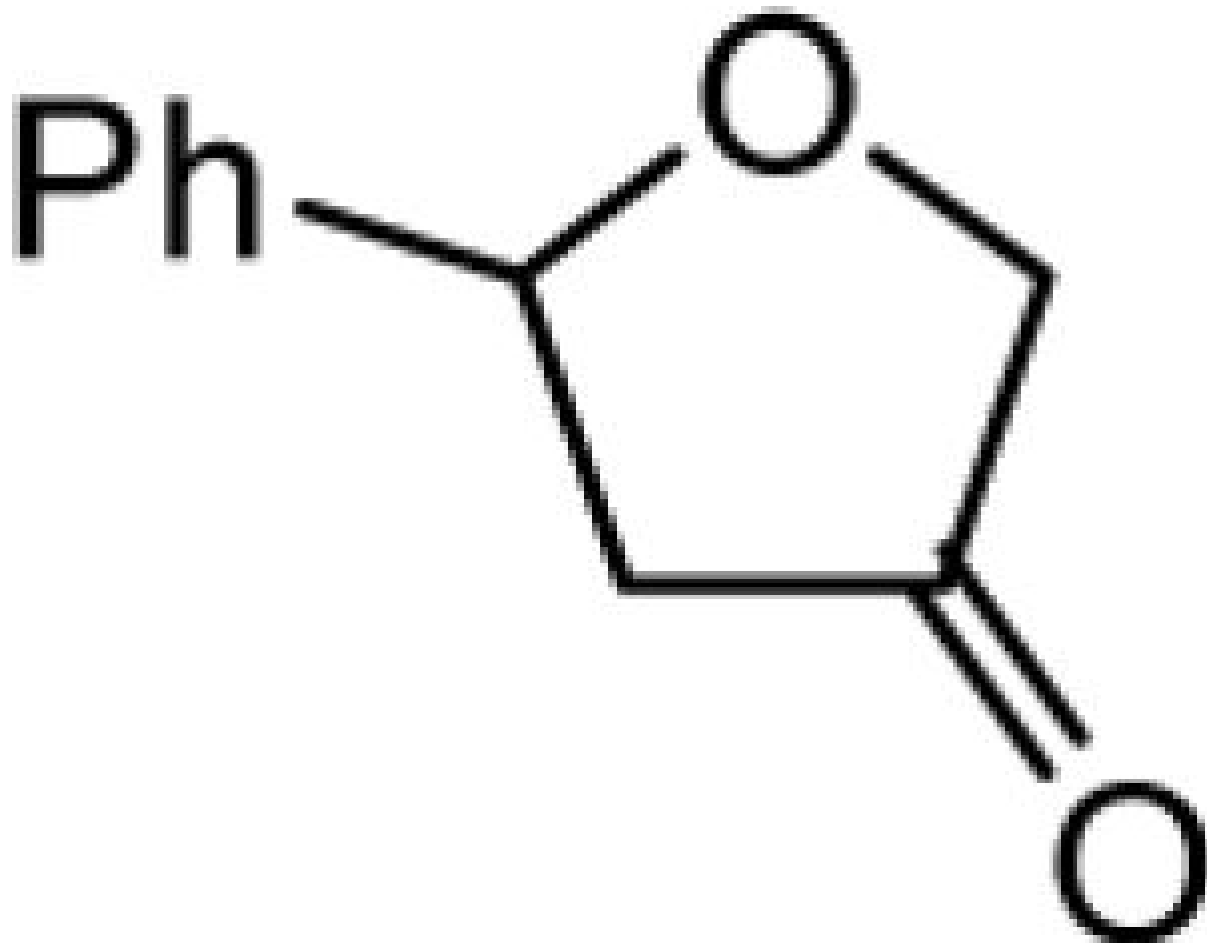




entry *N*-oxide

product

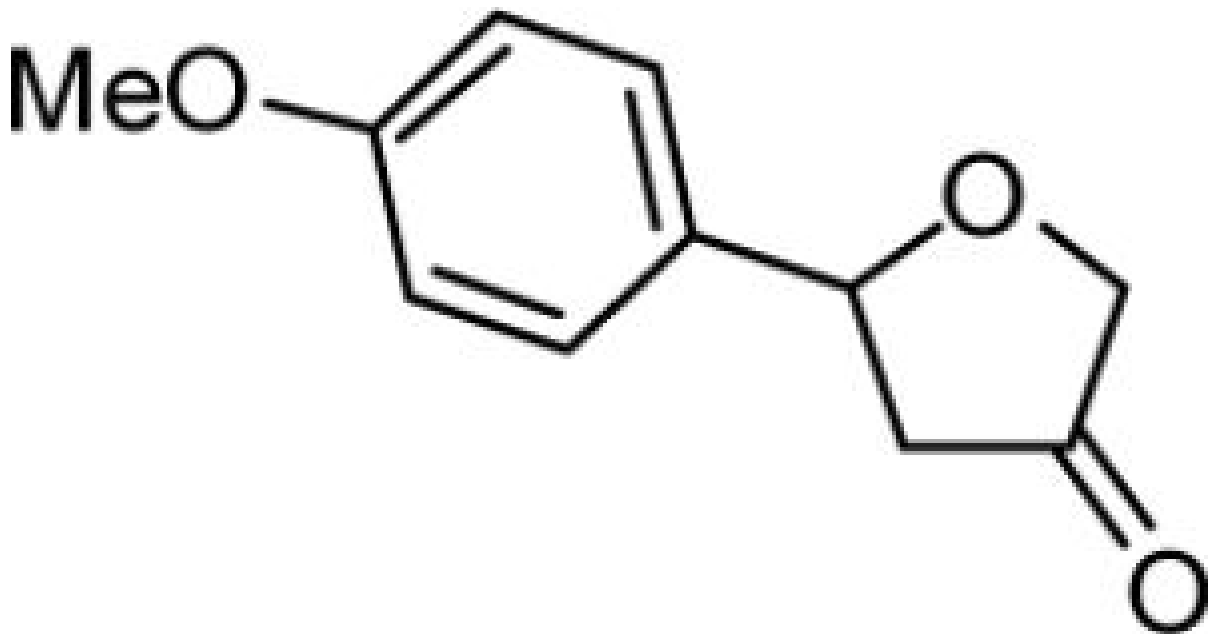
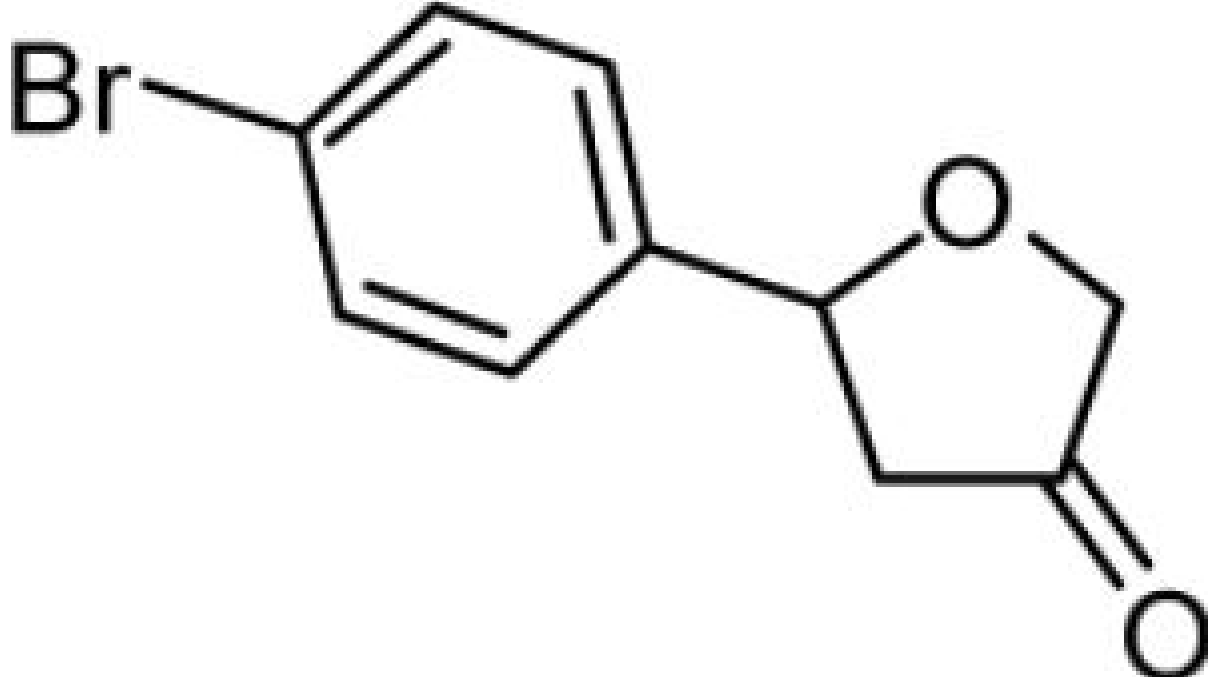
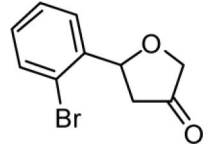
4/

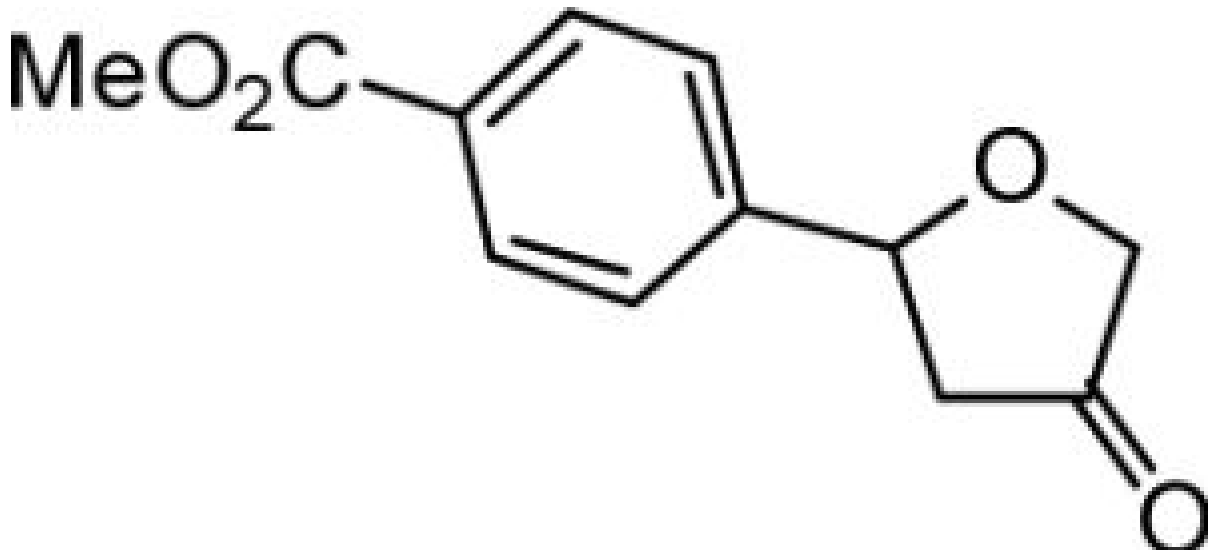
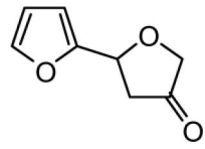
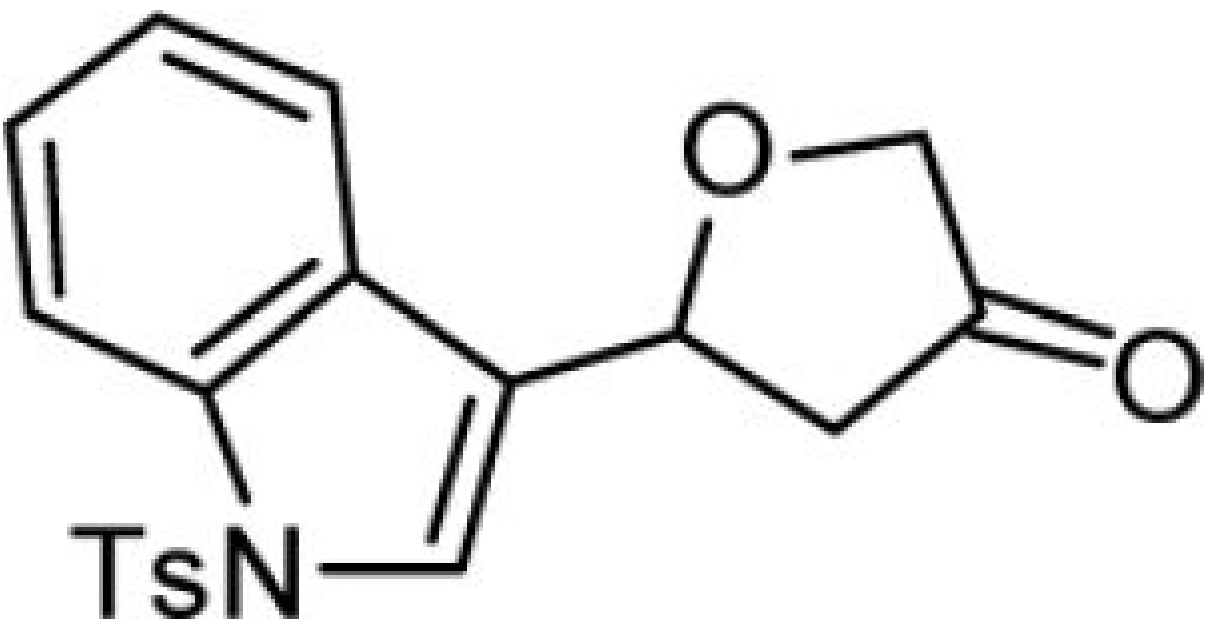


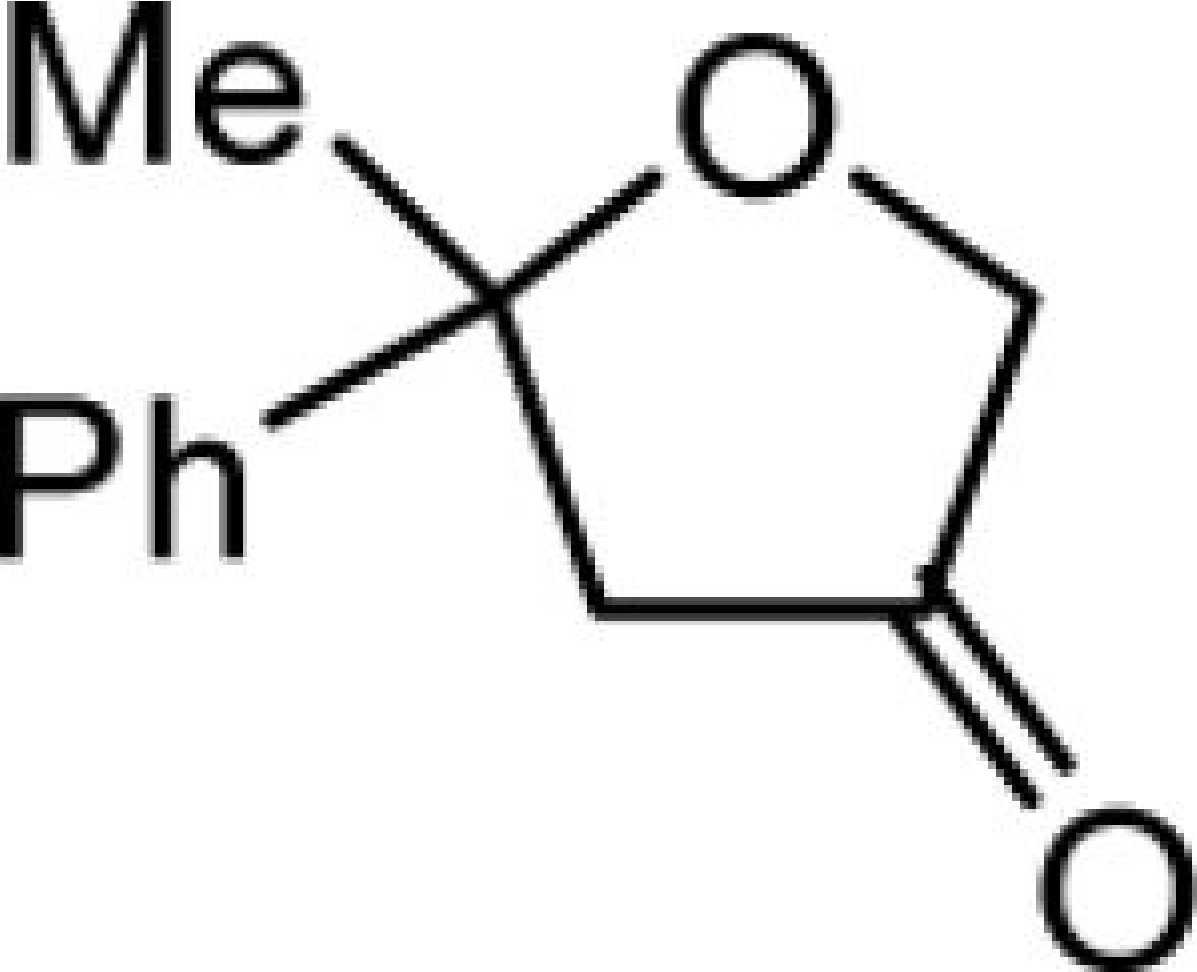
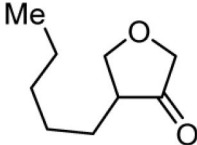
8

6

4/

entry	<i>N</i> -oxide	product	
9	6		4
10	6		4
11	6		4

entry	<i>N</i> -oxide	product	
12	6		4/
13	6		4n
14	6		4n

entry	<i>N</i> -oxide	product	4/
15 ^c	5		4/
16	5		4/

entry	<i>N</i> -oxide	product	
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17 ^d	5		4/
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18 ^e	5		4r
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^a[3] = 0.05 M.

^bisolated yields.

^cTime: 6h.

^dTime: 4 h.

^eTemperature: 0 °C; time: 5 h.

^fAbout 4% of **4q** was formed upon silica gel column purification.