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A New Synthesis of Pyrazoles through a Lewis Acid Catalyzed Union of 3-Ethoxycyclobutanones with Monosubstituted Hydrazines

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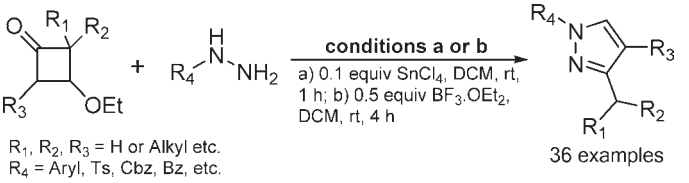
ABSTRACT



A new efficient and convenient approach toward the synthesis of pyrazoles is described. Through a Lewis acid catalyzed union of 3-ethoxycyclobutanones with monosubstituted hydrazines, a variety of pyrazole derivatives were prepared readily at ambient temperature with complete regioselectivity.

Pyrazoles and their derivatives represent an important class of compounds that find extensive use in the pharmaceutical industry.[1] Compounds containing a pyrazole motif are being developed in a wide range of therapeutic areas including metabolic, CNS, and oncological diseases.[2] To date, a number of pyrazole-containing compounds have been successfully commercialized, such as Celebrex, Viagra, and Acomplia.[3] Substituted pyrazole derivatives have also been employed as ligands for transition-metal-catalyzed cross-coupling reactions.[4]

Due to the important applications of pyrazoles, their synthesis has been extensively studied.[5,6] By far the two most prevalent strategies for constructing pyrazole rings are the classic Knorr pyrazole synthesis[7] and 1,3-dipole

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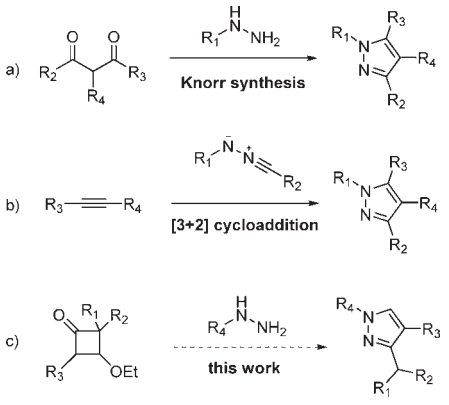
cycloaddition of diazoalkanes or nitrile imines with olefins or alkynes (Scheme 1a,b).[8] The Knorr synthesis, however, suffers from a lack of regiospecificity.[9] On the other hand, the difficulty in preparing and handling reactive 1,3-dipoles often limits their synthetic application.[10] Therefore, a general, convenient, and complementary method for pyrazole synthesis is highly desired.

Scheme 1. General Strategies for Construction of Pyrazole Rings

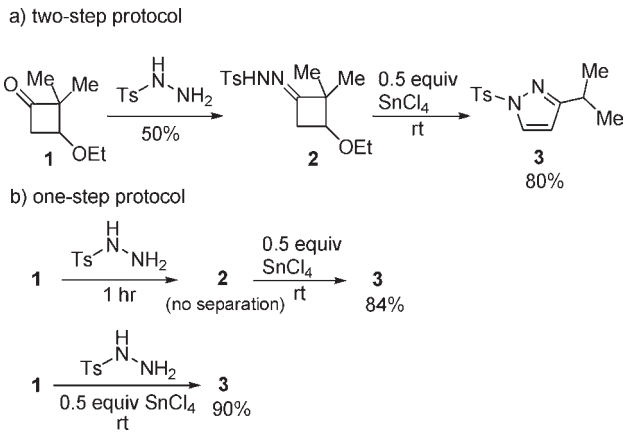


Cyclobutanones serve as important and versatile intermediates in organic synthesis.[11] Previous studies have shown that 3-ethoxycyclobutanones can be utilized to construct useful synthetic compounds such as silyloxy dienes and bicyclobutanes.[12] More recently, 3-ethoxycyclobutanones have been employed to prepare various types of six-membered cyclic compounds.[13] In those cases, it was suggested that a Lewis acid activates 3-ethoxycyclobutanones through cleavage of the more substituted C2−C3 bond of the cyclobutanone ring to form a zwitterionic intermediate,[14] which then reacts with ketones, aldehydes, silyl enol ethers, or allylsilanes to construct the corresponding cyclic compounds. In those cases, 3-ethoxycyclobutanones were used as a formal 1,4-dipole to afford a six-member ring. To the best of our knowledge, 3-ethoxycyclobutanones have never been employed as a 1,3-dicarbonyl synthon to prepare heterocyclic compounds such as pyrazoles.

Here in this paper, we report a new efficient and convenient approach to prepare pyrazole derivatives with complete regioselectivity by employing 3-ethoxycyclobutanones as 1,3-dicarbonyl synthons for reaction with monosubstituted hydrazines (Scheme 1c). We postulate that intramolecularly trapping this zwitterionic intermediate through a preformed or in situ generated NH-containing hydrazone that could be prepared from 3-ethoxycyclobutanone with hydrazine would result in the formation of the corresponding pyrazole derivatives.

Accordingly, a model study was initiated with 2,2-dimethyl 3-ethoxycyclobutanone and $TsNHNH_2$ as substrates. First, we tried a two-step protocol to test our hypothesis (Scheme 2a). As a Lewis acid catalyst, 0.5 equiv of $SnCl_4$ was added to the preformed hydrazone **2**. The reaction was very fast and went to completion in 30 min at room temperature. Delightfully the desired product was obtained in 80% yield. Two one-pot protocols were then examined (Scheme 2b) with different Lewis acid addition times. It was observed that the one-pot synthesis also went smoothly and gave the same pyrazole product **3** in excellent yields. Interestingly, even in the presence of $SnCl_4$, hydrazone **2** was formed prior to the ring openning of 2,2-dimethyl 3-ethoxycyclobutanone.

Scheme 2. Preliminary Investigation with 2,2-Dimethyl 3-Ethoxycyclobutanone



After gaining these preliminary results, we started to optimize this reaction by screening different conditions

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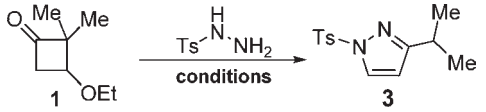
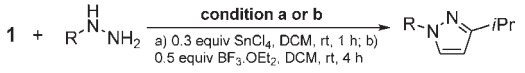
Table 1. Optimization of the Reaction Conditions



Entry	Catalyst	Condition	Yield[a]
1	$BF_3 \cdot OEt_2$	0.1 equiv, DCM, rt, 0.5 h	88%
2	$TiCl_4$	0.1 equiv, DCM, rt, 0.5 h	82%
3	$SnCl_4$	0.1 equiv, DCM, rt, 0.5 h	90%
4	TMSOTf	0.1 equiv, DCM, rt, 0.5 h	53%
5	TfOH	0.1 equiv, DCM, rt, 0.5 h	72%
6	$SnCl_4$	0.3 equiv, DCM, rt, 0.5 h	88%
7	$SnCl_4$	0.5 equiv, DCM, rt, 0.5 h	86%
8	$SnCl_4$	1.0 equiv, DCM, rt, 0.5 h	74%
9	$SnCl_4$	0.1 equiv, DCE, rt, 0.5 h	88%
10	$SnCl_4$	0.5 equiv, CH_3CN, rt, 0.5 h	79%
11	$SnCl_4$	0.5 equiv, THF, rt, 0.5 h	71%
12	$SnCl_4$	0.1 equiv, DCM, 0 °C, 1 h	85%

[a] Isolated yield.

Table 2. Reaction Scope with Respect to Monosubstituted Hydrazines

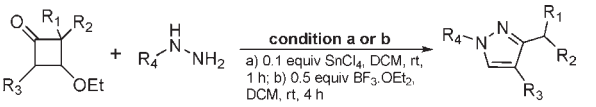


Product	Condition	Yield[a]	Product	Condition	Yield[a]
Cbz-N(N)-iPr	**4 a**	83%	p-O2NPh-N(N)-iPr	**7 b**	63%
Bz-N(N)-iPr	**5 b**	74%	p-ClPh-N(N)-iPr	**8 b**	66%
			p-MeOPh-N(N)-iPr	**9 b**	71%
Ph-N(N)-iPr	**6 b**	80%	Cl,Cl-Ph-N(N)-iPr	**10 b**	89%

[a] Isolated yield.

(Table 1). In the case of $TsNHNH_2$, we found that in addition to $SnCl_4$, other Lewis acids, such as $BF_3 \cdot OEt_2$ and $TiCl_4$, can catalyze pyrazole formation with almost equally high levels of efficiency. In general, a small catalyst amount, such as 0.10 or 0.30 equiv of $SnCl_4$, can promote the reaction as effectively as higher catalyst loadings. It was observed that the reaction also proceeded smoothly in various solvents, such as DCM, DCE, CH_3CN, and THF, and gave pyrazole **3** in good to excellent yields. Lower temperatures only have a slight effect on the yield and reaction time. Typically the reaction will proceed to completion within 1 h in a fast and clean manner. Entry 3 in Table 1 shows the best conditions for $TsNHNH_2$. Attempts

Table 3. Reaction Scope with Respect to 3-Ethoxycyclobutanones and Monosubstituted Hydrazines



Product	Condition	Yield[a]	Product	Condition	Yield[a]
Ts-N(N)-Me	**11 a**	77%	Cbz-N(N)-Bn	**25 b**	85%
Ts-N(N)-Et	**12 a**	76%	Ph-N(N)-Et	**26 b**	61%
Ts-N(N)-Pr	**13 a**	91%	Ph-N(N)-Bn	**27 b**	73%
Ts-N(N)-Bn	**14 a**	86 %	Ph-N(N)-cyclopentyl	**28 b**	82%
Ts-N(N)-Bn	**15 a**	85%	Ph-N(Et)-Et	**29 b**	72%
Ts-N(N)-cyclopentyl	**16 a**	87%	Ph-N(iPr)-Me	**30 b**	80%
Ts-N(N)-cyclohexyl	**17 a**	89%	p-O2NPh-N(N)-Me	**31 b**	84%
Ts-N(Et)-Et	**18 a**	93%	p-O2NPh-N(iPr)-Et	**32 b**	69%
Ts-N(Et)-Me	**19 a**	88%	p-MeOPh-N(N)-Pr	**33 b**	79%
Ts-N(iPr)-Me	**20 a**	82%	p-MeOPh-N(N)-Bn	**34 b**	87%
Ts-N(iPr)-Et	**21 a**	85%	p-MeOPh-N(N)-cyclopentyl	**35 b**	74%
Cbz-N(N)-Et	**22 b**	80%	Cl,Cl-Ph-N(N)-cyclopentyl	**36 b**	76%
Cbz-N(N)-Pr	**23 b**	82%	Cl,Cl-Ph-N(N)-Pr	**37 b**	79%
Cbz-N(N)-cyclohexyl	**24 b**	84%	Cl,Cl-Ph-N(N)-Bn	**38 b**	77%

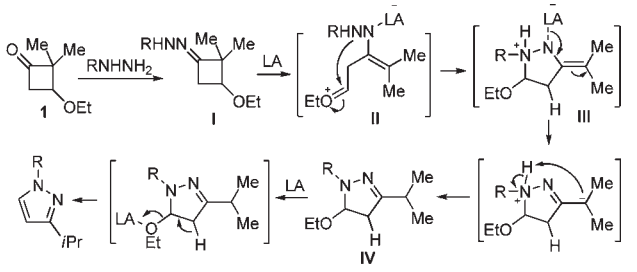
[a] Isolated yield.

to apply these conditions to substituted aryl hydrazines such as $PhNHNH_2$, however, were not as successful as in the case of $TsNHNH_2$. After further screening of the conditions, we discovered that 0.5 equiv of $BF_3 \cdot OEt_2$ provided the most suitable conditions for forming the pyrazole product with $PhNHNH_2$.

Having identified these optimal conditions, we set out to explore the scope for this new ring-opening−cyclization reaction. As shown in Table 2, a variety of monosubstituted hydrazines were reacted with 2,2-dimethyl 3-ethoxycyclobutanone in the presence of either $SnCl_4$ or $BF_3 \cdot OEt_2$. It was found that both $CbzNHNH_2$ and $BzNHNH_2$ reacted readily to furnish the corresponding pyrazole derivatives.[15] Notably, different aryl hydrazines produced the desired pyrazole products smoothly in good to excellent yields (Compounds **6**−**10**,

(15) Highly sterically demanding tBuNHNH$_2$ was also tried with different Lewis acid catalysts. Only a trace amount of possible product was observed by LC-MS analysis.

Scheme 3. Plausible Mechanism



LA: Lewis Acid.

Table 2). In all cases, only one single product was isolated, and no other regioisomer was obtained.

As illustrated in Table 3, the optimum reaction conditions proved to be compatible with a variety of 3-ethoxycyclobutanones which reacted with monosubstituted hydrazines to readily provide different di- and trisubstituted pyrazole derivatives in good to excellent yields. In particular, a consistent complete regioselectivity of the reaction was observed. Only single isomers were obtained in all examples.

A possible mechanism is demonstrated in Scheme 3. Upon activation of the *in situ* generated hydrazone intermediate **I** from 2,2-dimethyl 3-ethoxycyclobutanone (**1**) with Lewis acids, the more substituted C2−C3 bond of the hydrazone intermediate is broken down preferentially to form a zwitterionic intermediate **II**. Subsequently the intermediate **II** ring-closes to form the less strained five-membered ring intermediate **III**. Following this intramolecular cyclization, a proton transfer provides intermediate **IV**. Finally, elimination of one molecue of EtOH from **IV** furnishes the pyrazole products.

In conclusion, a concise, one-pot method has been developed for the rapid synthesis of functionalized pyrazoles from easily accessible starting materials at ambient temperature. This method has been found to be generally useful for the preparation of a variety of pyrazole derivatives some of which are difficult to make via conventional approaches. The reaction demonstrates excellent reactivity, complete regioselectivity,[16] and high yields. By employing 3-ethoxycyclobutanones as synthons for a Lewis acid catalyzed union with monosubstituted hydrazines, we have shown, for the first time, that this 1,3-dicarbonyl synthon acts as a complement to the four-carbon synthon of 3-ethoxycyclobutanones in [4 + 2] cycloadditions.[13] Further investigations using 3-ethoxycyclobutanones as a three-carbon component in other chemical transformations are currently underway.

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Supporting Information Available. Experimental procedures and characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(16) Although NMR analysis of crude products did not reveal the presence of the other regioisomers, theoretically the reaction could be regioselective.