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Europium(III) Triflate-Catalyzed Trofimov Synthesis of Polyfunctionalized Pyrroles

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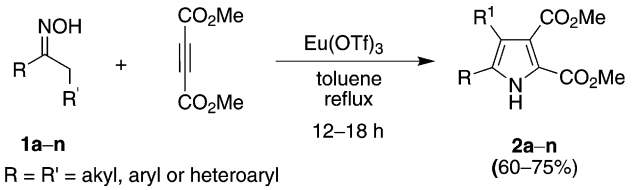
Abstract: The synthesis of polyfunctionalized pyrroles by reaction of a ketoxime with dimethyl acetylenedicarboxylate using europium(III) triflate as the catalyst is described.

Keywords: europium(III) triflate; ketoximes; Lewis acid catalysis; pyrroles; Trofimov reaction

Polyfunctionalized pyrroles are ubiquitous in natural products,[1] pharmaceuticals[2] and agrochemicals.[3] In recent years, they have found applications also in the preparation of organic semiconductors, light-emitting diodes and solar batteries.[4] The classical methods available for preparation of pyrroles include Knorr,[5] Paal–Knorr,[6] Hantzsch reactions,[7] in addition to a variety of cycloadditions,[8] transition metal-catalyzed cyclizations,[9] multicomponent[10] and tandem reactions.[11]

In recent years, the Trofimov[12] method for the preparation of pyrroles by condensation of a ketoxime with an acetylene using the super base MOH (M = Li, Na or K)-dimethyl sulfoxide, as the catalyst has received high attention as this method allows the preparation of a variety of previously inaccesible pyrroles. Although this reaction was initially carried out using inorganic bases, recently, Ngwerume et al.,[13] described a modified procedure for the Trofimov reaction using organic bases such as triphenylphosphine, 1,4-diazabicyclo[2.2.2]octane(DABCO) and 4-dimethylaminopyridine(DMAP). In our study, we observed an efficient Trofimov reaction also under Lewis acid catalysis and herein we report, for the first time, an efficient method for the synthesis of pyrroles by reaction of a ketoxime and dimethyl acetylenedicarboxylate (DMAD) using europium(III) triflate as a catalyst to obtain polyfunctionalized pyrroles in 60–75% yields as shown in Scheme 1.



Scheme 1. Europium(III) triflate-catalyzed synthesis of pyrroles by the Trofimov reaction.

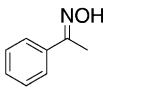
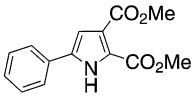
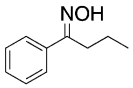
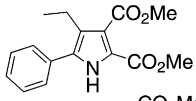
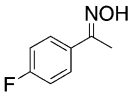
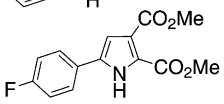
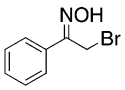
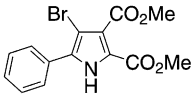
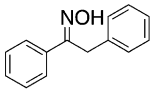
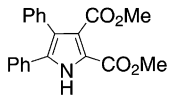
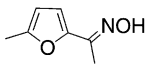
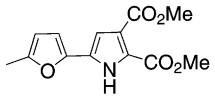
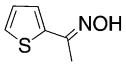
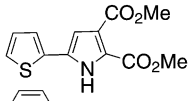
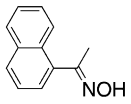
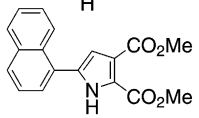
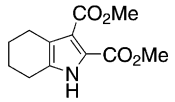
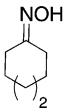
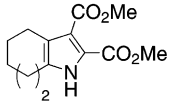
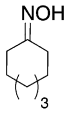
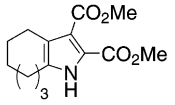
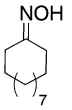
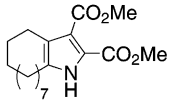
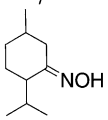
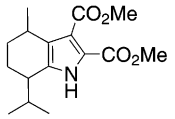
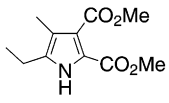
In our preliminary experiments, acetophenone oxime **1a** and DMAD were reacted in the presence of a variety of Lewis acid catalysts such as europium(III) triflate, zinc(II) triflate, lanthanum(III) triflate, copper(II) triflate, ytterbium(III) triflate, yttrium(III) triflate, scandium(III) triflate, praseodymium(III) triflate, antimony(III) chloride, indium(III) chloride,

Table 1. Lewis acid-promoted Trofimov reaction of acetophenone oxime and DMAD.

Entry	Lewis acid[a]	Reaction time [h]	Yield[b] [%] **2a**
1	$Eu(OTf)_3$	18	75
2	$Zn(OTf)_2$	24	58
3	$La(OTf)_3$	24	65
4	$Cu(OTf)_2$	30	20
5	$Yb(OTf)_3$	30	46
6	$Y(OTf)_3$	30	15
7	$Sc(OTf)_3$	30	20
8	$Pr(OTf)_3$	30	54
9	$SbCl_3$	30	35
10	$InCl_3$	30	10
11	InF_3	30	18
12	$ZnCl_2$	30	30

[a] 10 mol%.
[b] Yields of isolated prooducts.

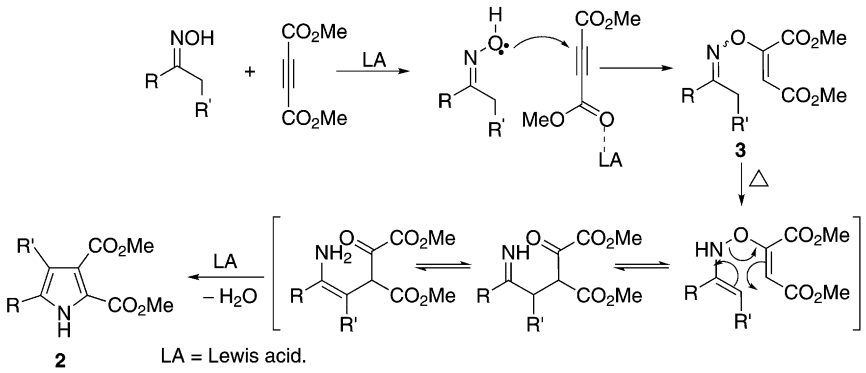
Table 2. Europium(III) triflate-catalyzed Trofimov reaction of a ketoxime and DMAD.

Entry	Ketoxime, **1**	Pyrrole **2**	Reaction time [h]	Yield [%][a]	mp [°C]
a			18	75	134-136
b			12	72	101-103
c			18	65	133-135
d			18	60	128-130
e			14	72	187-189
f			16	64	106-108
g			14	68	108-110
h			12	60	113-115
i			12	62	134-136
j			12	70	114-116
k			12	75	118-120
l			16	72	158-160
m			14	63	139-140
n			14	65	liquid

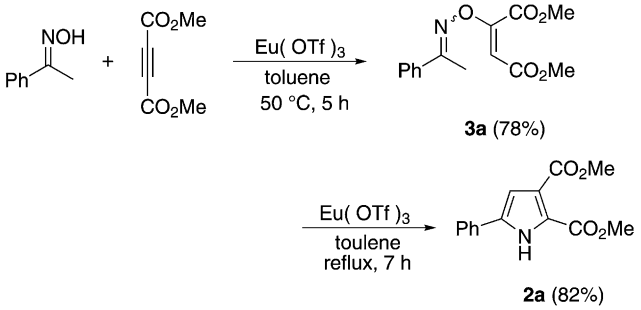
[a] Yields of isolated products. All compoundss were characterized by ^{1}H, ^{13}C NMR, IR and mass spectral data.

indium(III) fluoride and zinc(II) chloride under reflux conditions using toluene as the solvent as shown in Table 1.

In this study, the formation of pyrrole **2a** was observed in maximum yields (75%) with europium(III) triflate as the catalyst. When this reaction was studied



Scheme 2. A palusible mechanism for the Lewis acid-catalyzed Trofimov reaction.



Scheme 3. Control study of the europium(III) triflate-catalyzed Trofimov reaction.

in other solvents such as 1,2-dichloroethane and tetrahydrofuran under reflux conditions for 24 h, **2a** was formed in 12 and 20% yields, respectively, and in solvents such as acetonitrile and methanol, no reaction was observed. The present Lewis acid-catalyzed Trofimov reaction was found to proceed only with DMAD and this reaction did not proceed with aryl and aliphatic acetylenes under similar conditions.

Next, a variety of ketoximes **1a–n** was reacted with DMAD using europium(III) triflate as the catalyst under reflux in toluene to obtain the corresponding pyrroles **2a–n** in 60–75% yields as shown in Table 2. A plausible pathway for the formation of pyrroles via the Lewis acid-catalyzed Trofimov reaction is shown in Scheme 2. It shows that the initial step of the reaction is the formation of ketoxime **1**/DMAD adduct (ketoxime vinyl ether, **3**), which subsequently transforms into pyrrole **2** through a 3,3-sigmatropic rearrangement under Lewis acid catalysis. In our study, acetophenone oxime **1a** and DMAD gave adduct **3a** in 78% yield under europium(III) triflate catalysis in toluene upon heating at 50 °C for 7 h. When adduct **3a** was refluxed in toluene in the absence of europium(III) triflate, no reaction was observed even after 24 h. In the presence of europium(III) triflate, **3a** was converted into **2a** in 82% yield as shown in Scheme 3, which confirms the mechanism shown in Scheme 2.

In conclusion, the present work describes the first observation of a Lewis acid-catalyzed Trofimov reaction. This work provides an efficient method for the preparation of polyfunctionalized pyrroles by reaction of a ketoxime with dimethyl acetylenedicarboxylate using europium(III) triflate as the catalyst.

Experimental Section

Typical Procedure for Europium(III) Triflate-Catalyzed Synthesis of Pyrroles

Acetophenone oxime **1a** (0.5 g, 3.69 mmol), dimethyl acetylenedicarboxylate (0.52 g, 3.69 mmol), toluene (5 mL) and europium(III) triflate (0.22 g, 0.37 mmol), were charged into a 25-mL round-bottomed flask fitted with a condenser and nitrogen balloon. The mixture was refluxed for 18 h and after completion of the reaction (TLC), the reaction mixture was concentrated under reduced pressure and purified by column chromatography (100–200 mesh silica gel, EtOAc-hexane = 1:10) to afford dimethyl 5-phenyl-1*H*-pyrrole-2,3-dicarboxylate **2a** as a pale yellow solid; yield: 0.72 g (75%); mp 134–136 °C. The product was characterized by the following spectral data : ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 9.69$ (bs, 1H, exchangeable with D_2O), 7.49 (d, 2H, $J = 7.0$ Hz), 7.32 (t, 2H, $J = 8.0$ Hz, 7.0 Hz), 7.23 (t, 1H, $J = 8.0$ Hz, 7.0 Hz), 6.81 (s, 1H), 3.81 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 164.24$, 160.72, 134.90, 130.26, 129.08, 128.30, 124.87, 122.65, 121.48, 110.64, 52.22; IR (KBr): $\nu =$ 3299, 2923, 2853, 1733, 1686, 1513, 1457, 1292, 1257, 1210, 1153, 1068, 927 cm^{-1}; ESI-MS: $m/z = 260$ (M+H), 282 (M+Na); exact mass observed for $C_{14}H_{13}O_4NNa$: 282.0733 (calcd.: 282.0742).

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