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Unique chemoselective Paal-Knorr reaction catalyzed by MgI_2 etherate under solvent-free conditions

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1. Introduction

Pyrrole derivatives are important species with remarkable biological activities[1] and useful intermediates in the synthesis of natural products and heterocycles.[2] Many methods for the synthesis of pyrrole derivatives have been developed, which involve conjugate addition,[3] Hantzsch procedure,[4] 1,3-dipolar cycloaddition reaction,[5] transition metal-mediated cyclization,[6] aza-Wittig reaction,[7] titanium catalyzed hydroamination of diynes,[8] multicomponents reactions[9] and other operations.[10] Among them, the Paal-Knorr reaction remains one of the most significant and simple methods, which consists of the cyclocondensation of primary amines with 1,4-diketones to produce *N*-substituted pyrroles.

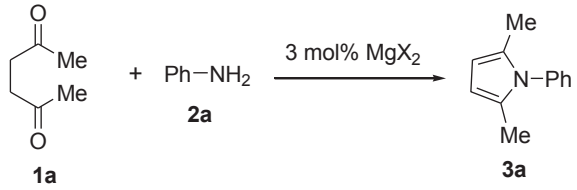
Recently, many methods for the synthesis of pyrroles by Paal-Knorr cyclization of primary amines with 1,4-diketones have been developed in the presence of various Lewis acid catalysts, such as, $Ti(O^iPr)_4$,[13] $ZrOCl_2\cdot 8H_2O$,[14] $Sc(OTf)_3$,[15] $Bi(NO_3)_3\cdot 5H_2O$,[16] $ZrCl_4$,[17] $BiCl_3/SiO_2$,[18] $InCl_3$,[19] and $FeCl_3$.[20] Although, pyrroles can be obtained by the aforementioned strategies, it is highly desirable to develop methods that will overcome the inherent limitations, such as harsh reaction conditions, poor substrate generality, and can introduce a diverse substitution pattern into the heterocyclic core. Therefore, the development of less expensive, environmentally benign, and easily handled promoters for the synthesis of *N*-substituted pyrroles by Paal-Knorr condensation under neutral, mild, and convenient condition is still highly desirable. Magnesium, a practically ideal main group metal, which abundantly exists in nature, has been actively investigated as a catalyst in the field of C–C bond formation and functional group transformation.[21]

In our previous papers,[22] we have demonstrated that MgI_2 etherate could efficiently catalyze the Mukaiyama aldol reaction of aldehydes with trimethylsilyl enolates, allylation of aldehydes with allylstannane, cycloaddition of isocyanates with oxiranes and Clauson-Kass reaction of primary amines with 2,5-dimethoxytetrahydrofuran. In continuation of our ongoing research field, we wish to report a mild, efficient, and highly chemoselective Paal-Knorr condensation of various primary amines with 1,4-diketones catalyzed by 3 mol% MgI_2 etherate under solvent-free conditions.

2. Results and discussion

Initially, we have chosen aniline and 2,5-hexadione **1a** (acetonylacetone) as the model substrates for surveying the reaction parameters in the model reaction. The results are summarized in Table 1. By screening various solvents we have found that CH_2Cl_2 is the best solvent for this reaction (Table 1, entry 1). Moderate yields were given in THF, MeCN, acetone and methanol (Table 1, entries 2–5). Very low yield was given in DMF (Table 1, entries 6). It is worthy to be noted that this Paal-Knorr reaction was carried out very efficiently under solvent-free conditions in a short time. Under solvent-free condition, temperature has a remarkable effect on the yield of compound **3a**. The results showed that the yields were improved by increasing the reaction temperature. The excellent yield was given at 70 °C (Table 1, entry 9). However, the higher temperature could not cause the obvious increase for the yield of product (Table 1, entries 10–11). In addition, the reaction was carried out sluggishly without catalyst under solvent-free condition (Table 1, entry 12). To examine the halide anion effect, halogen analogs of MgI_2 etherate, $MgBr_2$ etherate, $MgCl_2$, $Mg(ClO_4)_2$ and $Mg(OTf)_2$ were compared under parallel reaction conditions, respectively. The best result has been observed with MgI_2 etherate as the catalyst (Table 1, entry 9). Good yield was given by using 3 mol% of $MgClO_4$ (Table 1, entry 13). $MgCl_2$ and $MgBr_2$ etherate are also effective to this reaction and produced the moderate yields (Table 1,

Table 1
Optimization of reaction conditions for MgX_2-catalyzed Paal-Knorr reaction[a]



Entry	Solvent	Catalyst	Temp (°C)	Time (h)	Yields (%)[b]
1	DCM	$MgI_2\bullet(OEt_2)_n$	40	5	94
2	MeCN	$MgI_2\bullet(OEt_2)_n$	70	5	75
3	THF	$MgI_2\bullet(OEt_2)_n$	70	5	70
4	MeOH	$MgI_2\bullet(OEt_2)_n$	65	5	78
5	Acetone	$MgI_2\bullet(OEt_2)_n$	55	5	60
6	DMF	$MgI_2\bullet(OEt_2)_n$	70	5	20
7	None	$MgI_2\bullet(OEt_2)_n$	30	1	70
8	None	$MgI_2\bullet(OEt_2)_n$	50	1	76
9	None	$MgI_2\bullet(OEt_2)_n$	70	1	96
10	None	$MgI_2\bullet(OEt_2)_n$	90	1	89
11	None	$MgI_2\bullet(OEt_2)_n$	110	1	89
12	None	None	70	5	48
13	None	$Mg(ClO_4)_2$	70	2	85
14	None	$MgCl_2$	70	2	75
15	None	$MgBr_2\bullet(OEt_2)_n$	70	2	78
16	None	$Mg(OTf)_2$	70	2	50

[a] The reaction was carried out by the condensation of aniline(5.0 mmol) and 2,5-hexadione (6.0 mmol) in the presence of MgX_2 under the above reaction conditions.
[b] Isolated yield by silica gel flash chromatography.