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KF/Al$_2$O$_3$ mediated 1,3-dipolar cycloaddition of azomethine ylides: a novel and convenient procedure for the synthesis of highly substituted pyrrolidines

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Abstract—The regio- and diastereoselective synthesis of pyrrolidine derivatives through 1,3-dipolar cycloaddition of an azomethine ylide and dipolarophile mediated by KF/Al$_2$O$_3$, a versatile solid supported reagent, is reported. KF/Al$_2$O$_3$ is sufficiently basic such that it can deprotonate α-imino esters to generate azomethine ylides and it also functions as a solid supported catalyst leading to the cycloadduct rather than the Michael adduct.
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The pyrrolidine ring is present in many biologically active natural products[1] and pharmaceuticals.[2] Pyrrolidines are important building blocks in organic synthesis, and have recently emerged as privileged organo-catalysts.[3] The 1,3-dipolar cycloaddition reaction of an azomethine ylide with an electron deficient dipolarophile is a rapid method to assemble pyrrolidine rings, usually in a regio- and stereocontrolled fashion.[4] However, azomethine ylides are unstable and have to be prepared in situ. Several methods have been developed for the generation of azomethine ylides, but only some of them have general applicability.[5] Among these methods, the imine tautomerization method[6–8] is one of the most commonly used. Typically, azomethine ylides are generated from the corresponding α-imino esters by deprotonation with a base (e.g., Et$_3$N, DBU, etc.) under thermal conditions.[8] Recent research in this area has involved Lewis acid [Ag(I), Li(I), Mg(II), Cu(II), etc.] catalyzed reactions[9] and the use of chiral metal complexes in an asymmetric version.[10] However, the use of solid supported reagents in 1,3-dipolar cycloaddition reactions is less explored.[11]

Recently, the use of solid supported reagents in organic synthesis has received considerable attention due to their eco-friendly nature and unique properties, such as enhanced reactivity, selectivity, mild conditions, avoidance of cumbersome aqueous work-up and decreased solvent handling issues, etc.[12] KF/Al$_2$O$_3$ is a widely used solid supported reagent for catalysis of a variety of reactions. Due to its strongly basic nature it has been used as a replacement for organic bases in a number of organic reactions.[11] The application of KF/Al$_2$O$_3$ was first reported by Bougrin et al.[13] in the 1,3-dipolar cycloaddition of a nitrile imine. To the best of our knowledge, KF/Al$_2$O$_3$ has not been applied to the cycloaddition reaction between an azomethine ylide and a dipolarophile.

In our continuing efforts to develop new methods for the generation of azomethine ylides[14] and their cycloaddition reactions, we have developed a procedure to prepare pyrrolidine derivatives through 1,3-dipolar cycloaddition of azomethine ylides mediated by KF/Al$_2$O$_3$. This solid supported reagent is responsible for the deprotonation of α-imino esters to generate azomethine ylides and also catalyzes the cycloaddition reaction.

As a model study, we investigated the reaction of the dipole generated from imine ester **1a** and methyl acrylate **2a** (1:1.2 equiv) in the presence of KF/Al$_2$O$_3$ (2 g, 40% KF in alumina) in THF at room temperature with stirring for 5 h (Scheme 1). This resulted in the clean formation of *endo*-isomer **3aa** (Scheme 1) in high yield (90% of the total yield).[15] Diastereomer, *exo*-**3aa** was also

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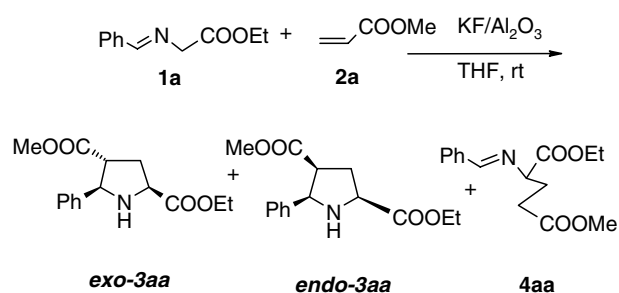
Scheme 1. KF/Al$_2$O$_3$ mediated 1,3-dipolar cycloaddition of an azomethine ylide and a dipolarophile.

formed (10% of the total yield), whereas, the possible Michael adduct, **4aa** was not observed. The stereochemistry of the cycloadduct was determined by spectroscopic analysis. Both ^{1}H NMR and ^{13}C NMR spectra matched well with the literature data.[9a]

To explore the scope of the [3+2] cycloaddition, we investigated various α-imino esters derived from arylaldehydes. The reactions of α-imino esters **1b–f** with methyl acrylate (**2a**) proceeded with high levels of diastereoselectivity, regardless of the electronic properties of the aromatic ring (Table 1). The presence of a chloro or bromo substituent at the *para* position in α-imino esters **1d** and **1e** accelerated the reaction which showed only *endo*-selectivity. In contrast, decreased diastereoselectivity and lower reactivity were observed when a nitro-group was present at the *para* position of the α-imino ester (entry 6). The reaction was carried out in different solvents, but THF proved to be the best solvent in terms of regio- and diastereoselectivity and reaction time.

We also investigated the 1,3-dipolar cycloaddition reaction of the azomethine ylide generated from **1a** with various dipolarophiles as outlined in Table 1. Only the *endo*-products were isolated in all cases. The imino ester

1a reacted smoothly with *N*-phenylmaleimide (**2d**) and showed complete *endo*-selectivity. Dimethyl maleate (**2e**) and ethyl cinnamate (**2f**) gave *endo*-adducts as the major products, whereas, low reactivity and regioselectivity were observed with vinyl ketone **2c**. The cycloaddition reaction with acrylonitrile (**2b**) gave poor *endo–exo* selectivity in a ratio of 1.6/1 but high regioselectivity with a total yield of 80%.

Weinstock et al.[11b] have argued that KF/Al$_2$O$_3$ derives its basicity from the formation of KOH in the initial preparation of the solid supported material by reaction of KF with the alumina support. However, deprotonation of α-imino esters has been investigated by several groups,[5b,16] where imines are deprotonated with sodium or potassium alkoxide or Triton B in protic or aprotic solvent. When the resulting species are trapped with electron deficient olefins, the products are mainly the corresponding Michael adducts. Competitive formation of Michael adducts and stereoselective cycloadducts is also known.[16d] The base catalyzed cyclization of the Michael adduct was ruled out as a possible route to the cycloadduct and a concerted 1,3-dipolar cycloaddition is the proposed mechanism. Moreover, olefins with electron withdrawing groups undergo polymerization under highly basic conditions more readily than cycloaddition. Therefore, most of the reported methods used weak organic bases for deprotonation. Only Nájera and co-workers[17] have reported the use of KOH/NaOH (10 mol %) in this reaction in the presence of a Lewis acid (i.e., AgOAc) and phase transfer catalyst (PTC). However, in the KF/Al$_2$O$_3$ mediated cycloaddition reaction, a mildly basic environment is present which avoids polymerization of the olefin. In addition, it is believed that the solid support binds the substrate to its surface[18] and catalyzes the cycloaddition reaction rather than that delivering the Michael adduct.

In conclusion, we have described a novel and efficient method for the 1,3-dipolar cycloaddition reaction of

Table 1. 1,3-Dipolar cycloaddition reaction of azomethine ylides derived from imines **1a–f** with dipolarophiles **2a–f**

Entry	Imine/dipolarophile	Ar	R^1	R^2	Time (h)	Yield[a]	*endo*-3[a,b]
1	**1a/2a**	Ph	COOMe	H	5	80	90
2	**1b/2a**	CH$_3$–C$_6$H$_5$	COOMe	H	5	75	93
3	**1c/2a**	*p*-MeOC$_6$H$_4$	COOMe	H	5.5	65	88
4	**1d/2a**	*p*-ClC$_6$H$_4$	COOMe	H	4	85	96
5	**1e/2a**	*p*-BrC$_6$H$_4$	COOMe	H	4.5	90	98
6	**1f/2a**	*p*-NO$_2$C$_6$H$_4$	COOMe	H	8	70	80
7	**1a/2b**	Ph	CN	H	6	80	62
8	**1a/2c**	Ph	–COCH$_3$	H	10	65	60
9	**1a/2d**	Ph	*N*-Phenylmaleimide		4	90	100
10	**1a/2e**	Ph	COOMe	COOMe	5	94	92
11	**1a/2f**	Ph	Ph	COOEt	8	90	86

[a] Isolated yield, determined by GC and based on reactant **1a**.
[b] Stereochemistry determined by ^{1}H NMR.

azomethine ylides obtained via imine tautomerization with electron deficient dipolarophiles mediated by solid supported KF/Al$_2$O$_3$. This cycloaddition produced the corresponding pyrrolidine derivatives with high stereo- and regioselectivity in reasonable yields under mild reaction conditions.

Acknowledgements

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15. *Typical experimental procedure for the KF/Al$_2$O$_3$ mediated 1,3-dipolar cycloaddition*: To a stirred solution of α-imino ester **1a** (0.25 mmol) in THF (10 mL) was added KF/Al$_2$O$_3$ (2 g, 40% by weight) and methyl acrylate **2a** (0.28 mmol). The reaction mixture was vigorously stirred for 5 h and then the solid was filtered from the reaction mixture. THF was evaporated in vacuum, and the residue was dissolved in EtOAc (20 mL). The EtOAc layer was washed with water (10 mL × 3), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography to give **3aa** in 80% yield. Analytical data for *endo-***3aa**[9a]: IR (CHCl$_3$): 3372 and 1736 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 1.35 (t, $J = 7.3$ Hz, 3H, COOCH$_2$CH$_3$); 2.39 (2H, m, 3-H$_2$), 2.67 (1H, s, NH), 3.19 (3H, s, 4-COOMe), 3.28 (1H, dt, $J_{4-3} = 6.7$ and $J_{4-5} = 7.9$ Hz, 4-H), 3.95 (1H, t, $J_{2-3} = 8.4$ Hz, 2-H), 4.25 (m, 2H, –COOCH$_2$CH$_3$), 4.49 (1H, d, $J_{5-4} = 7.9$ Hz, 5-H), 7.31–7.25 (5H, m, Ph); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 33.60, 50.01, 52.30, 60.00, 65.90, 68.04, 127.0, 127.74, 128.32, 133.2, 139.5, 173.30, 174.00 MS (m/z): 277 (M$^+$). Elemental Anal. Calcd C, 64.98; H, 6.86; N, 5.05%. Found: C, 65.05; H, 6.97; N, 4.85.

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