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Diazo transfer reaction to 1,3-dicarbonyl compounds with sulfonyl azides catalyzed by molecular sieves

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ABSTRACT

A simple and effective heterogeneous catalyst based on zeolite-type materials has been developed for the diazo transfer reaction involving 1,3-dicarbonyl compounds and tosyl azide. α-Diazo carbonyl compounds were obtained under mild conditions in good to high yields using commercial molecular sieve 4A or analogues as the catalyst. The best catalyst was found to be 4A-1000, a synthetic potassium-free nepheline obtained by heating molecular sieve 4A at 1000 °C. Characterization of the resulting aluminosilicate by XRD, FTIR and SEM-EDS analysis confirmed the change of the crystal structure. Besides being nontoxic and inexpensive, the heterogeneous catalyst was readily removed by filtration and could be reused at least for four runs without any special treatment.

1. Introduction

α-Diazo carbonyl compounds are useful pharmaceutical building blocks since they can undergo a wide variety of chemical transformations such as cyclopropanation, Wolff rearrangement, 1,3-dipolar cycloaddition, and X–H insertion (X = C, N, O, S), often under mild conditions [1–3]. The transfer of the diazo group to an active methylene compound is one of the most prevalent synthetic approaches to the α-diazo carbonyl scaffold [4,5]. The diazo transfer reaction to 1,3-dicarbonyl compounds usually involves a combination of a sulfonyl azide and a base in a given organic solvent to furnish 2-diazo-1,3-dicarbonyl derivatives in good yields (Scheme 1). *para*-Toluenesulfonyl azide (tosyl azide, TsN_3) is commonly used as the transfer reagent due to its easy accessibility (TsN_3 is commercially available or can be readily prepared from tosyl chloride) and relatively high reactivity among sulfonyl azides. In spite of these advantages, the reaction using tosyl azide is frequently associated with problems related to the isolation of the desired diazo product as an equivalent mixture with tosyl amide ($TsNH_2$), which is the byproduct of the diazo transfer using TsN_3. To overcome the drawbacks associated with the use of tosyl azide and its byproduct tosyl amide, several modified diazo transfer reagents have been reported [6–12]. However, some present similar purification issues, the methods for their preparation can be complex and/or the cost of the reagent is high when compared to tosyl azide.

The basic catalyst also requires particular consideration, since it is very often a tertiary amine (triethylamine, DABCO, DBU) or an alkaline hydroxide/carbonate (NaOH, K_2CO_3, Cs_2CO_3) used in excess [5–7,13,14]. The need for an aqueous work-up to separate out the water-soluble bases from the reaction mixture, besides this being a tedious process, precludes any practical recovery of the catalyst and thus represents a main source of residue generation.

The increase in environmental consciousness worldwide has led to a considerable interest in developing more efficient and cleaner methods for chemical synthesis [15–18]. Among them, the use of heterogeneous catalysis (in which the active sites are supported on an insoluble solid) offers many advantages over the use of conventional homogeneous catalysis, even in industrial scale [19–22]. Besides the generally higher reaction ratio and selectivity observed for the heterogeneous process, the insoluble catalysts are easily recovered by filtration and thus can be reused instead of being disposed of as waste. In spite of these benefits, the use of basic inorganic solids as heterogeneous catalysts for the diazo transfer reaction is so far limited to one report, wherein natural clays pretreated with NaOH furnished the α-diazo carbonyl compounds in good yields, although the reaction was slow (1–3 days) for all but one case [23]. Therefore, the development of more effective heterogeneous catalysts for basic catalysis is of considered interest. In this regard, molecular sieves are particularly useful since they are inexpensive and can be modified to attain the desired basic properties [24–29].

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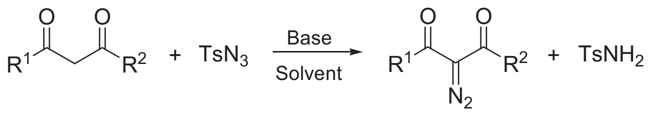


Scheme 1. Diazo transfer reaction of tosyl azide and 1,3-dicarbonyl compounds.

As a continuation of our research interest in synthetic transformations involving α-diazo carbonyl compounds [30–32] and heterogeneous catalysis with molecular sieves [33–35], we report herein a general and more benign approach to the preparation of α-diazo carbonyl compounds **2** through the diazo transfer reaction catalyzed by recyclable molecular sieves.

2. Experimental

2.1. General

The FTIR spectra for the samples were recorded on a Bruker spectrophotometer in the 4000–600 cm^{-1} range with 32 scans. The samples were prepared in KBr pellets. The X-ray diffractograms were measured in the angular range of $2\theta = 5–80°$, using a Philips X'Pert diffractometer equipped with a copper tube (Cu $K\alpha$, $\lambda = 1.54056$ Å). Scanning electron microscopy (SEM) images were acquired with a Jeol JSM-6701F microscope. The elemental analysis was based on the scan area of the SEM and the identification was carried our by energy dispersive X-ray spectroscopy (EDS) at an accelerating voltage of 15 kV and magnification of 13000×. Samples were prepared as suspensions in ultrapure water (1 g/L) applying sonication at 500 W for 20 min. The suspensions were added dropwise to aluminum stubs, dried at 70 °C and sputter-coated with gold.

The molecular sieves (MS) 3A, 4A, 5A and 13X were commercially available and obtained from Sigma-Aldrich. Potassium-exchanged MS 4A/KCl and 13X/KCl were prepared by the diffusion method using aqueous KCl as previously reported [34,35]. Thermally-modified 4A-600, 4A-1000, 4A/KCl-1000 and 13X-1000 samples were prepared by heating the corresponding MS in an electric furnace at 1000 °C (for 4A-1000, 4A/KCl-1000 and 13X-1000) or at 600 °C (for 4A-600) for 1 h. After the samples had been cooled, the final solids were transferred to a desiccator and stored for months without any significant loss of activity.

2.2. General procedure for the diazo transfer reaction

To a solution of the 1,3-dicarbonyl compound **1** (1.00 mmol) and *p*-toluenesulfonyl azide (0.197 g, 1.00 mmol) in THF (2.0 mL) was added the MS (0.300 g) and the mixture was stirred at 25 °C for the time stated in Table 2. After the reaction was completed (monitored by TLC [8:2 hexane:EtOAc] by following the consumption of the starting 1,3-dicarbonyl compound **1**), the catalyst was separated by filtration followed by sequential washing with 10 mL CH_2Cl_2 and 10 mL EtOAc. The filtrate was concentrated under reduced pressure and the residue was taken up in ethyl ether. The mixture was concentrated again and the final residue was triturated with hexane (3 × 20 mL). The solid material formed ($TsNH_2$) was filtered and the solvent was removed under reduced pressure to give the diazo carbonyl compound **2** in >95% purity. Diazo compounds **2a–d**, **f–k** are known and their spectroscopic characterizations were in agreement with published data [7,12,32,36–39]. Spectroscopic data for the novel ethyl 2-diazo-3-(4-nitrophenyl)-3-oxopropanoate (**2e**): colorless oil; IR (neat): ν_{max} = 3110, 2985, 2147, 1718, 1629, 1523, 1314, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, *J* = 8.6 Hz, 2*H*), 7.74 (d, *J* = 8.6 Hz, 2*H*), 4.24 (q, *J* = 7.0 Hz, 2*H*), 1.26 (t, *J* = 7.0 Hz, 3*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.4 (C), 160.1 (C), 149.3 (C), 142.4 (C), 129.1 (2 × CH), 122.8 (2 × CH), 61.8 (CH_2), 14.0 (CH_3).

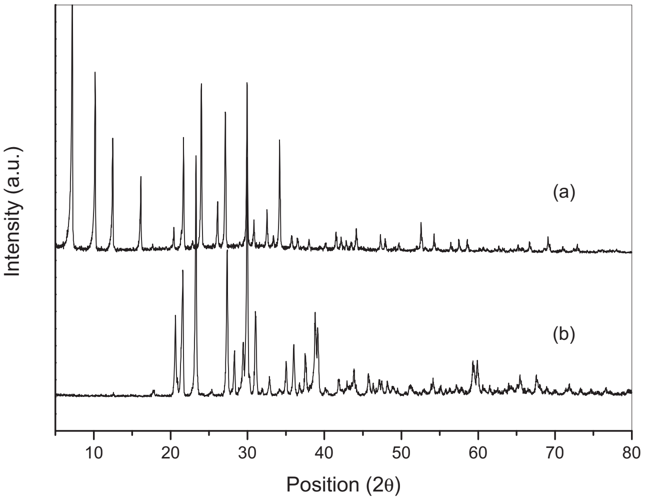


Fig. 1. XRD patterns for MS 4A (a) and 4A-1000 (b).

3. Results and discussion

In the search for a catalyst of basic character that is able to mediate the diazo transfer reaction of model substrates (see Section 3.2) we selected ten molecular sieves and zeolite-type derivatives for this study, comprising four commercially available (3A, 4A, 5A, 13X), two exchanged with potassium ion (4A/KCl, 13X/KCl) [34,35] and four thermally-treated (4A-1000, 4A/KCl-1000 and 13X-1000 heated at 1000 °C, and 4A-600 heated at 600 °C) materials. The treatment of MS with a KCl solution causes the partial replacement of Na ions with K ions, which is usually associated with the enhancement of the basic character due to an increase in the negative charge over the peripheral oxygen atoms [24]. Another strategy to modify zeolite-type materials involves conventional heating at high temperatures (600 or 1000 °C), which induces various structural changes in the crystalline materials, including phase transitions and amorphization which can lead to enhanced properties or even novel features.

3.1. Characterization of catalysts

The analysis of the X-ray diffraction (XRD) data for MS 4A and 4A-1000 (Fig. 1) revealed that changes occurred in the crystalline system of 4A heated at 1000 °C. The crystalline arrangement of cubic zeolite 4A was modified to a hexagonal mode, which was identified as the nepheline mineral (JCPDS card N. 88-1231) [40]. Nepheline [$(Na,K)AlSiO_4$] is a natural mineral comprised of aluminosilicate, sodium and potassium which is closely related to feldspar [41,42]. Nepheline has been previously synthesized by heating 4A-type zeolites in an electric furnace or under microwave irradiation at around 1000 °C [43–45].

Energy-dispersive X-ray spectroscopy (EDS) analysis furnished the chemical composition for representative 4A-type materials. The mineral obtained by treating MS 4A at 1000 °C (4A-1000) showed essentially the same composition of Si and Al found for the commercial 4A used as the precursor (Fig. 2a and b). A small decrease (<1.5%) in the oxygen content was observed for the 4A-1000 composition. The Si/Al ratio of 1 was maintained, which means that the basic character of the material may have been retained due to the high number of available Al–O^- sites. In contrast to the natural nepheline, 4A-1000 is potassium-free and also absent of other common metallic impurities such as iron. Therefore, 4A-1000 can

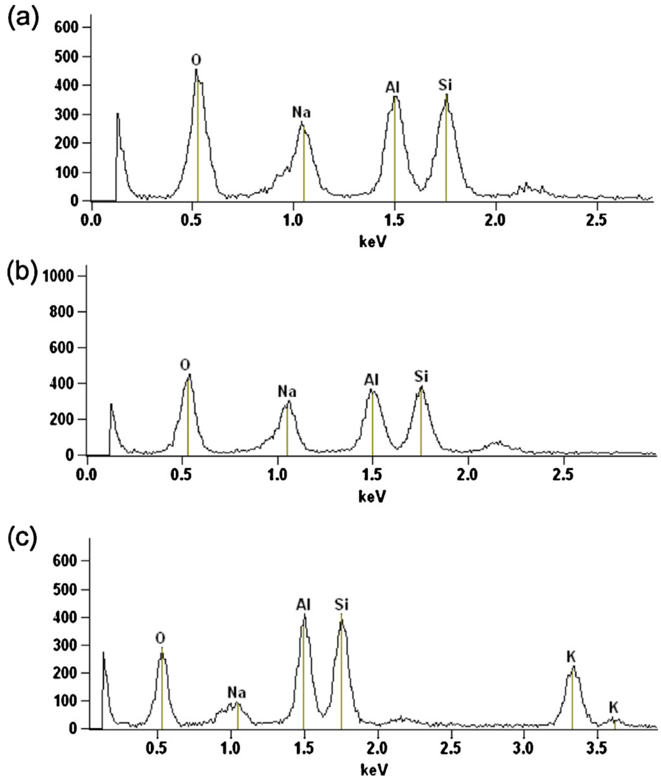


Fig. 2. EDS data for 4A (a), 4A-1000 (b) and 4A/KCl-1000 (c).

be considered as a synthetic nepheline, but with improved purity. The EDS analysis was also useful for confirming the introduction of potassium by Na/K-exchange in the 4A/KCl-1000 sample, at levels comparable to those found in natural nepheline (Fig. 2c).

The FTIR spectrum of MS 4A showed the characteristic bands of the hydrated zeolite (Fig. 3a). The large band at around 3440 cm^{-1} is attributed to the combination of symmetric and asymmetric OH oscillation of the water molecule. The band at 1668 cm^{-1} refers to the interaction of the OH group with the oxygen in the zeolite structure [46,47]. Also, the bands centered around 1000 and 668 cm^{-1} are attributed, respectively, to the asymmetric and symmetric vibration bands of the TO_4 mode (T = Al or Si), which are characteristic of this zeolite [45,47].

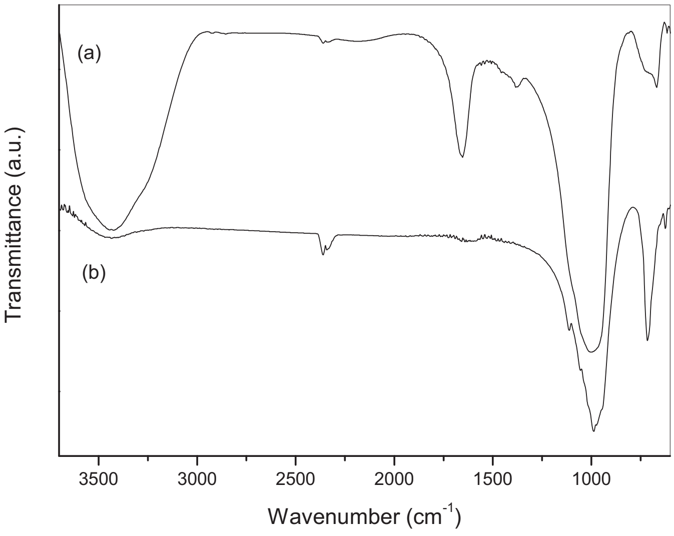
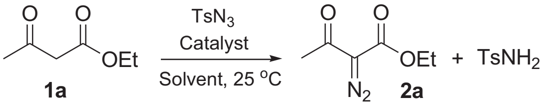


Fig. 3. FTIR spectra for 4A (a) and 4A-1000 (b).

Table 1

Optimizing the reaction conditions for the diazo transfer reaction[a].



No.	Molecular sieve	Solvent	Time (h)	Conversion[b] (%)
1	3A	EtOAc	55	53
2	4A	EtOAc	47	72
3	5A	Acetone	50	14
4	4A	Acetone	48	85
5	13X	THF	24	30
6	4A	THF	48	94
7	4A	CH_3CN	48	91
8	4A	DMF	50	93
9	4A	H_2O	50	10
10	4A	Isopropanol	48	70
11	4A	Hexane	45	75
12	4A	CH_2Cl_2	48	36
13	4A	[c]	50	93
14	4A	[c]	52	96
15	4A	[c]	52	91
16	4A/KCl	THF	24	37
17	13X/KCl	THF	45	35
18	4A-1000	THF	6	95
19	4A-1000	CH_3CN	10	90
20	4A-600	THF	46	24
21	4A/KCl-1000	THF	6	34
22	13X-1000	THF	6	33

[a] Conditions: ethyl acetoacetate (**1a**; 1.00 mmol), TsN_3 (1.00 mmol), MS (300 mg), solvent (2.0 mL).

[b] Conversion (%) was determined by ^1H NMR integration (400 MHz, $CDCl_3$) of the crude mixture.

[c] Solvent-free conditions; mass catalyst (mg) per substrate **1a** (mmol): 300 (entry 13), 200 (entry 14) and 100 (entry 15).

As expected for the 4A-1000 sample, the bands at around 3440 and 1668 cm^{-1}, which are related to the O–H bond, disappeared or dramatically diminished its intensity. This observation supports the possibility that at high temperatures the Brønsted acid sites from the crystal lattice undergo dehydroxylation (loss of O–H groups) with the release of water and the consequent formation of Lewis acid sites [48]. In fact, the most prominent band for the 4A-1000 sample, at around 1000 cm^{-1}, was related to the asymmetrical stretching vibration of Si–O–Si and Si–O–Al modes of the inorganic framework [47,49]. Finally, the appearance of a shoulder in 1104 cm^{-1} and a relatively strong band at around 714 cm^{-1} can be related to the displacement of the original bands of asymmetric and symmetric vibration stretching (TO_4 mode) to longer wavelengths.

The SEM images show that the morphology of MS 4A (Fig. 4a) consists of cubic particles with sizes ranging from 2 to 5 μm. However, as supported by the XRD analysis (see Fig. 1) the particle morphology was significantly altered from a cubic shape for 4A to a nearly spherical shape for 4A-1000 (Fig. 4b). These spherical-type particles were also observed for the Na/K-exchanged 4A/KCl-1000 (Fig. 4c), as well as for 4A-1000 after four consecutive uses (4A-1000 × 4, Fig. 4d) verifying the recycling potential of this material (see Section 3.2). This morphological alteration may be primarily responsible for differences in the catalytic performance of the catalyst due to the increase in the surface area of the particles on changing from cubic to spherical shapes.

3.2. Catalyst profiles

Ethyl acetoacetate (**1a**) and TsN_3 were selected as the model substrates for screening a variety of molecular sieves as potential catalysts for the diazo transfer reaction under different reaction conditions (Table 1). The formation of the expected α-diazo-β-keto ester **2a** was dependent on both the catalyst and the solvent

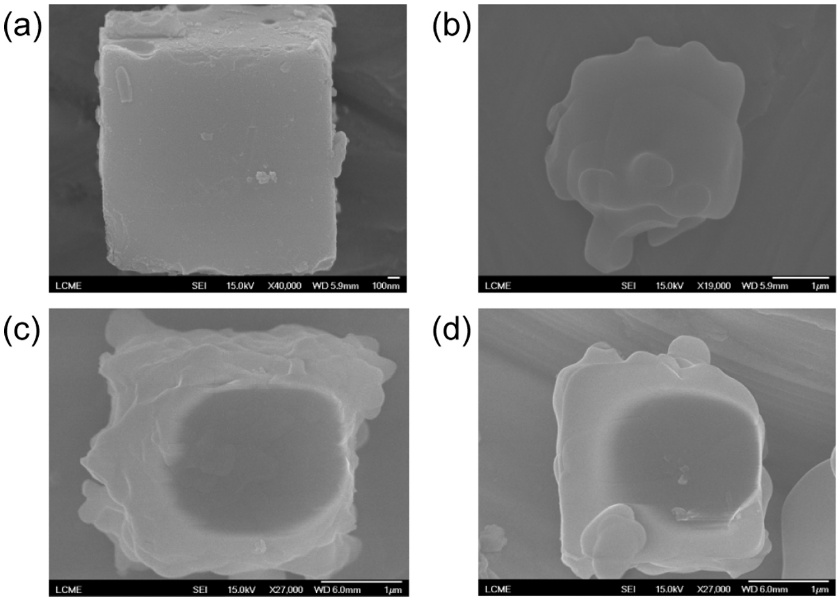


Fig. 4. SEM micrographs for MS 4A (a), 4A-1000 (b), 4A/KCl-1000 (c) and 4A-1000 × 4 (d).

used. Clearly, MS 4A was the most efficient catalyst with all solvents tested (compare entries 1 and 2; 3 and 4; 5 and 6). In combination with 4A, THF and acetonitrile were equally useful solvents for the reaction (entries 6 and 7), although DMF (entry 8) also led to >90% conversion. However, the latter was not selected for further studies due to environmental concerns and toxicity issues [50]. With regard to the other classes of solvents tested, neither the hydroxylic (entries 9 and 10) nor the less polar (entries 11 and 12) solvents gave satisfactory results. On the other hand, solvent-free transformations were successfully achieved (entries 13–15), even with reduced quantities of the catalyst, although for small-scale reactions it was difficult to control the stirring due to the heterogeneous nature of the medium. Therefore, THF (in minimum quantities) was chosen as the preferred solvent for further developments.

Although the use of KCl-exchanged molecular sieves, such as 4A/KCl and 13X/KCl, has been associated with enhanced basic properties [24,35], in this study both catalysts led to low conversions (<40%) even after prolonged periods (Table 1, entries 16 and 17). On the other hand, the reaction efficiency was considerably improved on using 4A-1000 as the catalyst, which is a potassium-free nepheline obtained by heating MS 4A at 1000 °C. In these cases, the conversion was almost completed after only 6 h in THF (entry 18) or 10 h in acetonitrile (entry 19). Furthermore, the separation of the catalyst by filtration was much more convenient with the use of 4A-1000 than with commercial 4A due to the tendency of 4A-1000 to be in the form of large aggregates that are more easily retained by regular paper filter than the powder-like 4A. The higher activity observed for 4A-1000 was unexpected because nepheline-type materials are generally of no interest as catalysts due to their lack of porosity [47]. The application of temperature during the preparation of the catalysts was found to greatly affect their activation, since heating 4A at 600 °C produced a much poorer reaction promoter (4A-600, entry 20). As anticipated, prior K/Na-exchange followed by heating at 1000 °C also failed to furnish a catalyst that was able to promote high conversions to the expected product **2a** (4A/KCl-1000, entry 21), and the same was true for another type of MS heated at 1000 °C (13X-1000, entry 22).

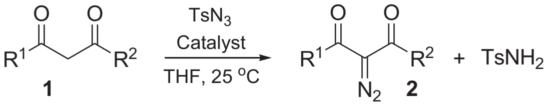
Motivated by this preliminary study, the procedure using 4A-1000 as the catalyst for the diazo transfer reaction was extended to a representative group of 1,3-dicarbonyl compounds. Commercial MS 4A was also included in this study in order to compare their catalytic profile. The results in Table 2 were generated from reactions run on the mmol scale, although scaling up to gram quantities provided comparable results.

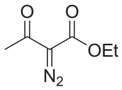
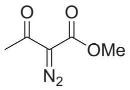
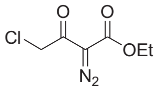
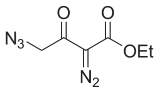
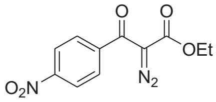
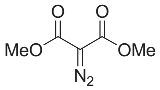
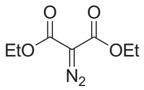
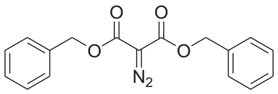
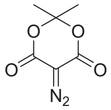
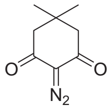
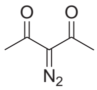
In all cases, the use of 4A-1000 furnished better isolated yields and shorter reaction times compared to 4A. In general, β-keto esters are reactive substrates for the diazo transfer reaction using 4A or 4A-1000, with a clear preference for the latter. Remarkably, in one case (the preparation of the 4-nitrobenzoyl-substituted diazo ester **1e**) the use of 4A-1000 was successful while the commercial 4A was found to be completely inactive. The enhanced reactivity of methyl over ethyl ester was evidenced by comparing β-keto ester **1b** with **1a** and, much more dramatically, the malonate **1f** with **1g**. While this pronounced difference in reactivity may be initially attributed to steric effects (the ethyl group being larger than the methyl group), the preparation of dibenzyl diazomalonate (**1h**) in reasonable yields clearly contradicts this hypothesis. Instead, the difference in the p*K*a of the active α-methylene group and the relative ability to coordinate to Lewis acid sites from the catalyst should be considered (see discussion below).

Cyclic substrates also worked well and gave the corresponding diazo product from the diester (**1i**) and the diketone (**1j**). Similarly, 1,3-pentanodione (**1k**) was very reactive and could be entirely converted to the expected diazo diketone **2k**, although the isolated yield was only moderate due to mass loss during the work-up. This may be ascribed, in part, to the ability of some 1,3-dicarbonyl compounds to become associated with the MS, possibly through coordination with the Al sites as represented in Scheme 2. Control experiments in the absence of TsN_3 showed that the loss of the 1,3-dicarbonyl substrate during the catalyst removal is dependent on both the type of MS and the solvent used in the filtration step. Therefore, it is advisable to wash the catalyst thoroughly with two different solvents of medium polarity, such as dichloromethane and ethyl acetate (see Section 2).

The presence of a diversity of functional groups is well tolerated, including chloro, azido and nitro groups (Table 2, entries **1c**, **1d** and **1e**, respectively). The preparation of γ-halo-α-diazo-β-keto esters is of particular interest as they are useful building blocks for the synthesis of a great variety of multifunctionalized compounds [30–32]. However, the prior synthesis of a γ-bromo-α-diazo-β-keto ester derivative involved potentially toxic mercury-based reagents and the highly sensitive bromoacetyl bromide [32], which restricts

Table 2
Diazo transfer reaction[a] promoted by 4A and 4A-1000.



No.	Product **2**	MS 4A		MS 4A-1000	
		Time (h)	Yield (%)	Time (h)	Yield (%)
1a		25	80	6	95
1b		6	70	5	81
1c		24	75	18	80
1d		46	64	26	76
1e		40	0[b]	26	83
1f		27	80	25	94
1 g		50 [25][c]	10 [15][c]	80	12
1 h		80	48[d]	46	73
1i		24	51[d]	22	68
1j		20	75	12	82
1k		5	65	4	69

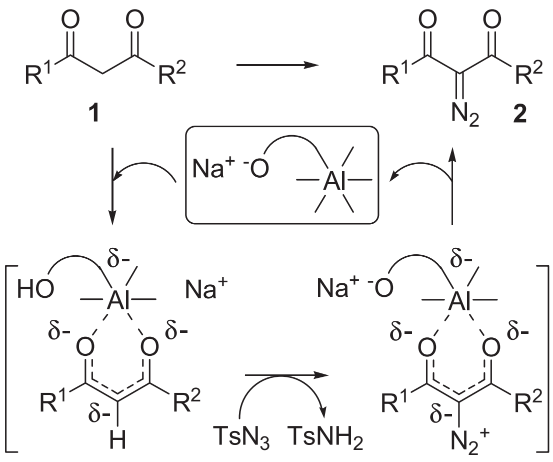
[a] Conditions: **1** (1.00 mmol), TsN_3 (0.197 g, 1.00 mmol), catalyst (0.300 g), THF (2.0 mL), 25 °C.

[b] Recovery of >90% starting material **1**.

[c] Numbers in brackets refer to the results obtained under conventional heating at 65 °C.

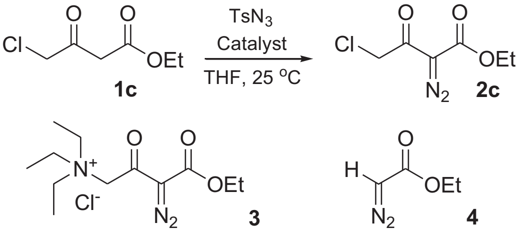
[d] Under these conditions the compound was obtained in ca. 50% conversion (by ^{1}H NMR).

its broader application. Accordingly, a one-step synthesis of the related γ-chloro-α-diazo-β-keto ester **2c** from the commercially available keto ester **1c** in gram scale is now feasible via an MS-catalyzed diazo transfer reaction (Table 3). As expected, the use of 4A and 4A-1000 led to **2c** in high yields under mild conditions. It is worth noting that, in our study, the conventional method using triethylamine as the catalyst led to unsatisfactory results due to the extensive formation of water-soluble ammonium salt **3** through chlorine displacement from **2c** (Table 3). The nucleophilic character of the base could be severely diminished by replacing triethylamine with DIPEA (*N*,*N*-diisopropylethylamine). Although better results were achieved with the bulkier base, in this case the use of an organic catalyst required an aqueous work-up, which was not only tedious but led to acyl cleavage of the diazo product **2c** to give ethyl



Scheme 2. Plausible mechanism for the diazo transfer reaction catalyzed by 4A-1000.

Table 3
Preparation of γ-chloro-α-diazo-β-keto ester **2c** from the diazo transfer reaction with different catalysts (TEA = triethylamine; DIPEA = *N*,*N*-diisopropylethylamine).



Catalyst	Time (h)	Yield **2c** (%)
TEA	20	<30
DIPEA	21	65
4A	24	75
4A-1000	18	80

diazoacetate (**4**) as a side product, thus having a negative impact on the yield.

The use of 4A-1000 allowed the facile separation of the heterogeneous catalyst from the reaction mixture, which is not only economically advantageous and environmentally benign but also bypass the aqueous work-up, which may cause purification issues. After recovering the catalyst through the filtration and evaporation of the solvents, it was easy to separate out the $TsNH_2$ formed as the byproduct, which is usually associated with difficulties when the conventional work-up is employed [9,12–14]. Our simple and reproducible protocol involved the trituration of the crude product mixture with ether followed by hexane (see Section 2), which causes the precipitation of $TsNH_2$ while the diazo product **2** remains soluble and can be isolated in high purity.

Other substrates containing active methylene groups (Fig. 5) were also tested in the diazo transfer reaction but were not reactive under the stated conditions. The lack of reactivity for the cyano ester **1l** is probably related to the absence of a 1,3-dicarbonyl moiety which excluded the postulated pathway involving the formation of a catalyst-substrate coordination complex (Scheme 2). In the case of the diacid **1m**, the presence of acidic protons might lead to extensive inactivation of the basic sites in the catalyst. However, no reasonable explanation was so far been found for the complete lack of reactivity of the trifluoromethyl-substituted 1,3-diketone **1n**, since other diketones (Table 2, **1j** and **1k**) and aryl-containing substrates (**1e** and **1h**) were readily transformed to the corresponding diazo products **2**.

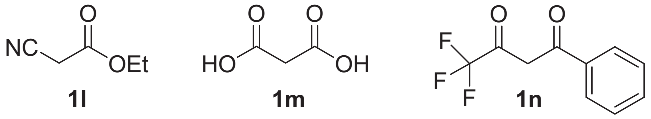


Fig. 5. Substrates that failed to react with TsN_3 and 4A or 4A-1000 as the catalyst.

Table 4
Recovery of the 4A-1000 catalyst for the preparation of diazo ester **2a**.

Entry	Recycle number	Time (h)	Yield (%)
1	Fresh	6	95
2	Recycle 1	6	92
3	Recycle 2	7	84
4	Recycle 3	8	75
5	Recycle 4	8	67

Catalyst reuse is a highly desirable feature in industrial processes and thus we turned our attention to the possibility of reusing 4A-1000 as the catalyst for the diazo transfer reaction with ethyl acetoacetate (**1a**) and TsN_3 under the conditions given in Table 1. Thus, after the first reaction cycle the catalyst was separated by filtration, washed with CH_2Cl_2 and EtOAc, dried in an oven (100 °C) and used in the next run at least twice without appreciable loss of catalytic activity (Table 4). However, it was necessary to progressively extend the reaction time in order to sustain the high product yields obtained in the first two runs. Attempts to reestablish the high catalyst activity by reheating a few recycled samples of the 4A-1000 catalyst at 1000 °C did not give any improvement in the efficiency.

The partial inactivation of the catalyst is possibly related, in part, to the persistence of small quantities of substrate through coordination of the 1,3-dicarbonyl group with the Al sites which act as Lewis acids (Scheme 2).

In combination, the observations described herein support the dual role of the catalyst as a Lewis acid and also a Brønsted base promoter. Of particular importance is the finding that in the case of the 4A-1000 catalyst the heating at 1000 °C enhanced its performance both as a Lewis acid and as a Brønsted base. Complexation of the bidentate 1,3-dicarbonyl substrate at the acidic Al site is facilitated by the concurrent deprotonation in the presence of a Brønsted base such as the electron-rich oxygen atom in close proximity (Scheme 2). Reaction of the substrate-catalyst complex with the diazo transfer reagent followed by product release ultimately led to the α-diazo carbonyl compound **2** with the regeneration of the heterogeneous catalyst.

4. Conclusions

Heterogeneous catalysts based on zeolite-type materials were developed for the diazo transfer reaction from a variety of substrates under mild conditions in good to high yields. Due to the simplicity of the process, the work-up and purification steps were also straightforward and provided high-quality diazo products in the gram scale. Subtle changes in the substrate structure may lead to considerable differences in the reactivity; however, the reactions were generally carried out within 4–24 h when 4A-1000 (a synthetic K-free nepheline) was used as the catalyst. In fact, heating the commercially available MS 4A at 1000 °C did generate a more efficient catalyst, not only enhancing its activity but allowing it to be more easily separated from the reaction medium by filtration. In addition, the reuse of 4A-1000 was found to be potentially viable at least for a few runs without any special treatment. Besides being useful due to its catalytic activity and overall efficiency, 4A-1000 is an aluminosilicate which is nontoxic and inexpensive. These are important features to be considered in relation to the development of more sustainable processes involving acid-base catalysis.

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