Green synthesis of nitrogen-containing heterocyclic compounds

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ABSTRACT

A novel environment-friendly vapour phase synthesis of different classes of nitrogen-containing heterocyclic compounds was developed using non-hazardous, commercially available and low cost feeds. 2-Methyl-8-ethylquinoline (MEQUI) was obtained from 2-ethylaniline (2-ETAN) and ethylene glycol (EG) or chloroethanol (CE), operating at high temperature in the presence of acid-treated K10 montmorillonite or $ZnCl_2$/K10 montmorillonite. At lower temperatures and using copper chromite catalysts, 7-ethylindole (7-ETI) or 5-ethylindole (5-ETI) were obtained from 2-ETAN or 4-ethylaniline (4-ETAN), respectively, and EG; excess of alkylaniline was required to avoid the formation of polyalkylated by-products. Mixing SiO_2 with the best copper chromite, made it possible to operate with higher LHSV values, thus improving the yield in alkylindoles. Finally, *N*-(2-ethylphenyl)pyrrole (EPP) and *N*-(2-ethylphenyl)pyrrolidine (EPD) were synthesised using a commercial copper chromite catalyst and feeding 2-ETAN and 2,3-dihydrofuran (DHF), EPP being favoured by high temperatures and absence of water in the feed. The possible reaction pathway for each synthesis is proposed, to evidence the key features of the best catalysts identified..

Keywords: Vapour phase synthesis; Quinoline; Indole; Pyrrole; Pyrrolidine; Solid acids; Copper chromites; SiO_2; Green chemistry

1. Introduction

Nitrogen-containing heterocyclic compounds, such as quinoline, indoles, pyrroles and pyrrolidines (and their alkylated homologues) are of high industrial interest, for applications as intermediates to produce pharmaceuticals, herbicides, fungicides, dyes, etc.[1–3]. Currently, most of these compounds are recovered by distillation of coal tar, although this source is no longer able to cover the market demand. Alternatively, they can also be obtained by well-known liquid-phase syntheses (Skraup's, Fisher's, Madelung's, etc. reactions), which, however, have many important drawbacks, such as use of hazardous reaction conditions, expensive or toxic feeds, large waste production, etc.[4–6]. Recently, novel reactions and/or processes have been investigated, shifting the balance from an exclusive focus on yield to one that places economic value on minimising wasteful by-products, operating in more safe conditions or producing environment-friendly compounds[7,8]. Increasing attention is being focused on vapour phase syntheses of nitrogen-containing compounds with heterogeneous catalysts that exhibit significant advantages in comparison to homogeneous catalysts (continuous production, simplified product recovery, catalyst regenerability, absence of liquid waste streams, etc.)[9–11].

The aim of the research reported here was to study preliminary vapour phase synthesis of 2-methyl-8-ethylquinoline (MEQUI), 7-ethylindole (7-ETI), 5-ethylindole (5-ETI), *N*-(-2-ethylphenyl) pyrrole (EPP) and *N*-(2-ethylphenyl)pyrrolidine (EPD), as significant examples of useful classes of nitrogen-containing heterocyclic compounds.

2. Experimental

The syntheses were carried out starting from low cost and widely available feeds, such as 2-ethylaniline (2-ETAN), 4-ethylaniline (4-ETAN), ethylene glycol (EG), 2-chloroethanol (CE) or 2,3-dihydrofuran (DHF). All the reagents were commercial samples (Aldrich) and were used without any previous purification. To collect data of more general interest, widely employed commercial catalysts or similar catalysts produced in the laboratory, already claimed for reactions of industrial interest, were used.

2.1. Commercial catalysts

CAT1: acid-treated K10 montmorillonite. On the basis of the current literature, K10 is by far the most commercially available acid-treated clay investigated ([12] and references therein). The acid strength of K10 surpasses the acidity of the usual catalyst supports and is

similar to that of concentrated nitric acid[13]. Finally, K10 exhibits a mixed acid character, as indicated by the relative intensities of the infrared bands of adsorbed pyridine (Lewis acidity: 1.91 and Brønsted acidity: 2.23, respectively)[14].

CAT2: Cu/Cr/Ba/Si/Ca (36:34:4:22:4 at.% ratio).

CAT3: Cu/Cr/Mn/Ba (44:47:8:1 at.% ratio).

CAT4: Cu/Cr (52:48 at.% ratio).

2.2. Catalyst produced in the laboratory

CAT5: Cu/Cr/Mg (40:50:10 at.% ratio), CAT6: Cu/Cr/Co (40:50:10 at.% ratio). CAT5 and CAT6 consist of cubic non-stoichiometric spinel-type (NSS) phases containing excess copper ions inside the structure. NSS phases are obtained by controlled oxidation of homogeneous precipitates via intermediate chromate-type phases and the partial substitution of the copper ions with other divalent ions gives rise to considerable modifications in both thermal stability and physico-chemical properties[15,16]. These highly active and stable catalysts, which do not require physical or chemical promoters, have been claimed for selective hydrogenation reactions[17,18].

CAT7: $ZnCl_2$ (50 wt.%) supported on acid-treated K10 montmorillonite (*clayzic*). This catalyst, claimed for Friedel–Crafts alkylation reactions, has a greater number of Lewis acid sites than CAT1[19,20]. Maximum activity requires "tuning" of the support for individual adsorbed salts or organic substrates[21,22].

The tests were carried out for 4 h using 2.0 ml of catalyst (particle size, 425–850 mm) in a fixed-bed glass microreactor (i.d. 7 mm, total length 400 mm), placed in an electronically controlled oven and operating at atmospheric pressure. The isothermal axial temperature profile of the catalytic bed was determined using a 0.5-mm J-type thermocouple, sliding in an internal glass capillary tube. The activation of the catalysts was carried out directly in the reactor for 3 h, using $6\,l\,h^{-1}$ of a N_2/H_2 mixture (90:10 v/v) and increasing the temperature in the 573–603K range. An Infors Precidor 5003 infusion pump was used to introduce the organic feedstock and products were condensed in two traps cooled to 268K and collected in methanol; tridecane was added as an internal standard. The analyses were carried out using a C. Erba 4300 GC, equipped with an FID and a wide bore SE 54 column (30m_0.53 mm, film thickness 0.8 mm). The products were preliminarily identified by GC–MS, using a Hewlett–Packard GCD 1800A system. The structures of the main products were determined on the

basis of the ^{1}H-NMR spectra recorded by a 200MHz Varian Gemini 200 spectrometer after separation by preparative layer chromatography[23]. The yield values were calculated with respect to the organic compound fed in the lower amount, i.e. EG or CE in the MEQUI, 7-ETI and 5-ETI syntheses, and DHF in that of EPP and EPD.

3. Results and discussion

The vapour phase synthesis of quinolines or alkylquinolines can be performed using solid acid catalysts such as acid-treated clays or zeolites[23,24]. In particular, using acid-treated K10 montmorillonite (CAT 1), the synthesis of MEQUI from 2-ETAN and

Table 1 Yield in 2-methyl-8-ethylquinoline (MEQUI) obtained feeding ethylene glycol (EG) or 2-chloroethanol (CE) and 2-ethylaniline (2-ETAN)[a]

Catalyst	Organic feed (mol/mol)	Carrier gas (v/v)	LHSV (h^{-1})	Reaction temperature (K)	Yield in MEQUI (%)
CAT1	2-ETAN/EG=10.0/1.0	N_2	0.1	523	11
CAT1	2-ETAN/EG=10.0/1.0	N_2	0.1	563	18
CAT1	2-ETAN/EG=10.0/1.0	N_2	0.1	603	25
CAT1	2-ETAN/EG=5.0/1.0	N_2	0.1	603	33
CAT1	2-ETAN/EG=1.0/2.0	N_2	0.1	603	41
CAT1	2-ETAN/EG=10.0/1.0	N_2/H_2=90/10	0.1	603	31
CAT1	2-ETAN/EG=10.0/1.0	N_2/H_2=90/10	0.2	603	26
CAT1	2-ETAN/CE=10.0/1.0	N_2	0.1	523	15
CAT1	2-ETAN/CE=10.0/1.0	N_2	0.1	603	27
CAT7	2-ETAN/EG=10.0/1.0	N_2/H_2=90/10	0.2	603	30

[a] Reaction conditions: catalyst: GHSV: 3000 h^{-1}.

EG was favoured by increasing the temperature and operating in the presence of small amounts of H_2 in the carrier gas, pure N_2 as the carrier gas gave rise to a significant decrease in activity and, mainly, selectivity (Table 1). The synthesis of MEQUI was also favoured by decreasing the 2-ETAN/EG molar ratio, with the best yield value obtained by feeding the stoichiometric mixture. No evidence of deactivation phenomena due to polymerisation of EG or reaction intermediates was found. Small changes in the yield in MEQUI were observed with increasing liquid hourly space velocity (LHSV) of the organic feed, while a decrease in the gas hourly space velocity (GHSV) up to 900 h−1 lowered the yield in MEQUI, without any effect due to further decreases. The synthesis of MEQUI was also favoured by the addition of a small amount of water in the organic feed, with a positive effect similar to those

previously reported in the literature for some vapour phase organic syntheses and attributed either to tailoring of the surface acidity[25–27] or suppression of coke and tar formation[28].

The substitution of EG with CE (also a low cost and widely available commercial reactant) (Table 1) showed a slight increase in the yield in MEQUI, essentially attributable to its higher stability in the reaction conditions. Finally, an improvement in the yield in MEQUI was observed using the $ZnCl_2/K10$ catalyst (CAT7), showing that although the synthesis is mainly controlled by the Brønsted acidity, Lewis acid sites also play a relevant role.
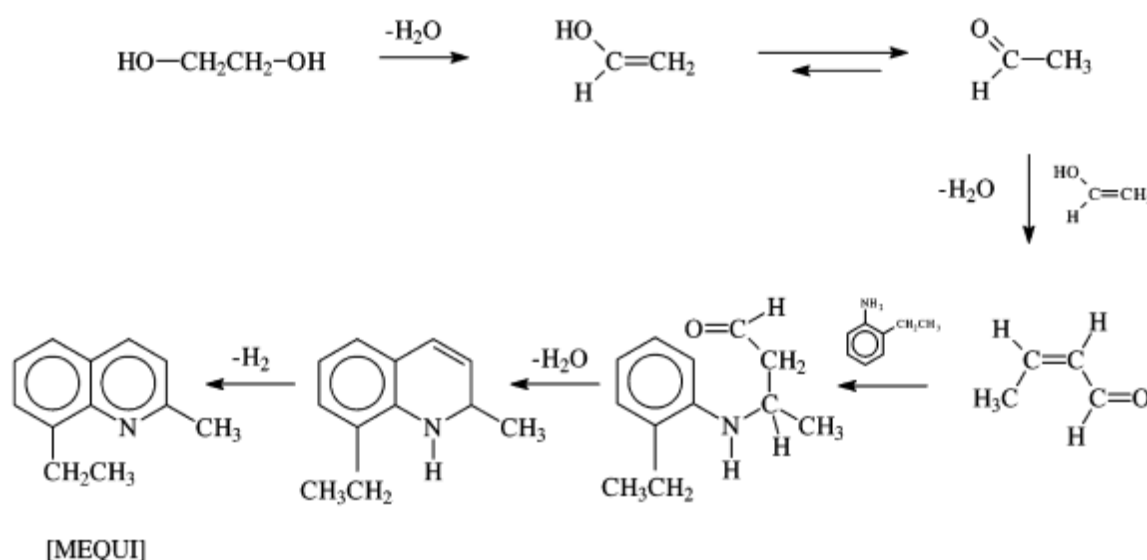

Fig. 1. Proposed reaction pathway for the synthesis of 2-methyl-8-ethylquinoline (MEQUI) using solid acid catalysts.

Table 2 Yield in 7-ethylindole (7-ETI) as a function of the copper chromites investigated [a]

Catalyst	Yield in 7-ETI (%)
CAT2	21.0
CAT3	10.0
CAT4	10.0
CAT5	9.0
CAT6	8.0

[a] Reaction conditions: temperature: 603 K; GHSV: 3000 h^{-1}; LHSV: 0.1 h^{-1}; carrier gas: N_2/H_2 (90:10 v/v).

On the basis of the experimental findings a possible reaction pathway is proposed (Fig. 1)[23,29], in which crotonaldehyde (CA) forms at first from two molecules of EG on the Brønsted acid sites, giving rise to MEQUI by alkylation and following dehydrogenation reactions, according to the pioneering work of Doebner and Von Müller[30]. To confirm this pathway, a 2-ETAN/CA (10.0/0.5 mol/mol) mixture was fed, and the yield in MEQUI was analogous to that observed using the 2-ETAN/EG mixture. The different molar ratios in the organic feedstocks took into account the differences in carbon atom number between EG and CA. In the present work only the 2-methyl isomer was found, in contrast to previous studies, where using an aluminosilicate catalyst in the vapour phase synthesis from CA and aniline, mainly 4-methylquinoline has been reported[31,32].

Always feeding 2-ETAN/EG mixtures, but using copper chromite catalysts, 7-ETI can be obtained. Different copper chromite catalysts were first investigated to evidence the role of the composition and/or the physical or chemical promoters (Table 2). The best yield was obtained using a commercial copper chromite containing only promoters improving the physical properties (CAT2). This catalyst was used to define the role of the different reaction parameters. The 7-ETI synthesis was favoured at lower temperatures than those required for the MEQUI synthesis (Table 3), since higher temperatures favoured the polyalkylation of 7-ETI. No significant differences were observed as a function of the H_2 content, while pure H_2 and, even more, pure N_2 as the carrier gas worsened the catalytic activity and, mainly, the selectivity in 7-ETI. Furthermore, unlike that previously reported for the MEQUI synthesis, organic mixtures with 2-ETAN/EG molar ratios _10.0 had to be used to avoid the formation of polyalkylated indoles (mainly 7, N-diethylindole), that cause a reduction in the yield of 7-ETI. Finally, while no difference in the yield of 7-ETI was observed when the GHSV was decreased from 3000 to 180 h^{-1}[33], typical value reported in the literature[34,35], increasing the flow rate of the organic mixture did not show any effect up to an LHSV value of 0.2 h^{-1}, after which the conversion decreased significantly, probably due to saturation of the active sites.

On the basis of the catalytic data collected, a three-step reaction pathway may be proposed (Fig. 2): dehydrogenation of EG to 2-hydroxyacetaldehyde, followed by N-alkylation of 2-ETAN to form a Schiff's base, that cyclises to 7-ETI. Thus, the synthesis of 7-

ETI requires bi-functional catalysts, containing both dehydrogenating and weak-acid active sites (Lewis-type). 5-ETI was obtained feeding 4-ETAN,

Table 3 Yield in 7-ethylindole (7-ETI) obtained feeding EG and 2-ETAN[a]

Organic feed (mol/mol)	Carrier gas (v/v)	LHSV (h^{-1})	Reaction temperature (K)	Yield in 7-ETI (%)
2-ETAN/EG=10.0/1.0	N_2/H_2=90/10	0.1	498	6.0
2-ETAN/EG=10.0/1.0	N_2/H_2=90/10	0.1	523	39.0
2-ETAN/EG=10.0/1.0	N_2/H_2=90/10	0.1	563	29.0
2-ETAN/EG=10.0/1.0	N_2/H_2=90/10	0.1	603	21.0
2-ETAN/EG=10.0/1.0	N_2/H_2=90/10	0.1	633	17.0
2-ETAN/EG=10.0/1.0	N_2	0.1	563	7.0
2-ETAN/EG=10.0/1.0	H_2	0.1	563	22.0
2-ETAN/EG=5.0/1.0	N_2/H_2=90/10	0.2	523	25.0
2-ETAN/EG=10.0/1.0	N_2/H_2=90/10	0.2	523	37.0
2-ETAN/EG=10.0/1.0	N_2/H_2=90/10	0.4	523	11.0

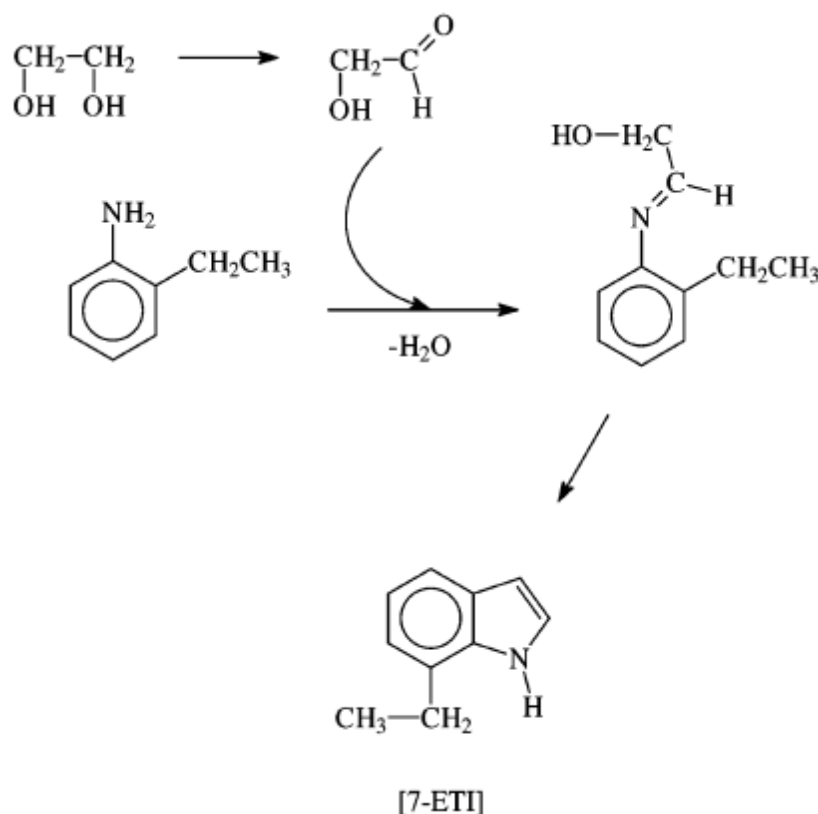[a] Reaction conditions: catalyst: CAT2; GHSV: 3000 h^{-1}.

Fig. 2. Proposed reaction pathway for the synthesis of 7-ethylindole (7-ETI) using copper chromite or copper chromite/SiO_2 catalysts.

but with a yield 70% lower than that observed in 7-ETI synthesis in the same reaction conditions. This result may be explained considering the lower inductive effect on the nitrogen by the ethyl group in the 4 position as compared with, when it is in the 2 position, that is more relevant than the lower steric hindrance in the cyclization step. On the other hand, this result cannot be attributed to a different activity of the two isomers in the electrophilic aromatic substitution, since the cyclization of the Schiff's base takes place in the *meta*-position with respect to the ethyl group and the ethyl is an *ortho*- and *para*-position orienting group.

A preliminary kinetic study was carried out using the method of initial rate, operating at low contact times and with a small amount of catalyst (to avoid complete EG conversion) (Table 4). Since the organic mixture fed contained a large excess of 2-ETAN (2-ETAN/EGD10.0/1.0 mol/mol), the amount of 2-ETAN was assumed constant and included in the kinetic constant. Plotting conversion versus contact time gives a linear correlation (XD74.4tC13.9; regression index D0.98), showing a reaction order equal to zero for the EG. Thus the reaction rate does not seem to depend on the EG concentration, suggesting cyclization of the Schiff's base as the rate limiting step .

Table 4 Kinetic investigation of the 7-ethylindole synthesis using the initial rate method [a]

GHSV (h^{-1})	Contact time, t (s)	EG conversion, X (%)
12000	0.3	40
4800	0.7	59
3600	0.9	80
2880	1.1	100

[a] Reaction conditions: catalyst: CAT2 (0.25 ml); temperature: 523 K; LHSV: 1.6 h^{-1}; carrier gas: N_2/H_2 (90:10 v/v).

Using chromite catalysts it is not possible to increase significantly the hourly productivity in 7-ETI by: (i) increasing the flow rate of the organic mixture or (ii) moving its composition towards the stoichiometric ratio (2-ETAN/EG D10.0/1.0 mol/mol), due to the saturation of the active sites and their high activity in further alkylation of 7-ETI, respectively. On the other hand, although increasing the GHSV to values higher than those reported in the patent literature[34,35], makes it possible to reduce the reactor volume, it also gives rise to a

corresponding increase in the gas flow rate, thus worsening the economy of the recycling loop[29,33].

These constraints were partially overcome by mixing the commercial copper chromite (CAT2) with commercial SiO_2, i.e. by increasing the number of weak acid sites and thus favouring cyclization of the Schiff's base, the rate limiting step. In this way, it was possible to increase the LHSV to values about eight times higher, without any evidence of deactivation and with an increase in the productivity of 7-ETI. Two different CAT2 /SiO_2 ratios were investigated (16/84 and 66/33 v/v). Better yields in 7-ETI were obtained with

Table 5 Yield in 7-ethylindole (7-ETI) obtained feeding EG and 2-ETAN[a]

Catalyst (v/v)	Reaction temperature (K)	Yield in 7-ETI (%)
CAT2	523	10
CAT2	563	17
CAT2	603	16
CAT2/SiO2=66/33	523	18
CAT2/SiO2=66/33	563	19
CAT2/SiO2=66/33	603	12
CAT2/SiO2=16/84	563	30
CAT2/SiO2=16/84	603	25

[a] Reaction conditions: GHSV: 3000 h^{-1}; LHSV: 1.6 h^{-1}; carrier gas: N_2/H_2 (78:22 v/v).

Table 6 Yield in *N*-(2-ethylphenyl)pyrrole (EPP) and *N*-(2-ethylphenyl)pyrrolidine

(EPD) feeding DHF and 2-ETAN[a]

Organic feed (mol/mol)	Reaction temperature (K)	Yield in EPP (%)	Yield in EPD (%)
2-ETAN/DHF=5.0/1.0	603	43.5	0.0
2-ETAN/DHF/H2O=5.0/1.0/0.1	603	37.0	9.5
2-ETAN/DHF/H2O=5.0/1.0/0.1	523	7.0	14.0

[a] Reaction conditions: catalyst: CAT2; GHSV: 3000 h^{-1}; LHSV: 0.2 h^{-1}; carrier gas: N_2/H_2 (90:10 v/v).

the higher SiO_2 content in the mixed catalyst, thus confirming the key role of weak-acid Lewis sites in the rate determining step (Table 5). With high LHSV values, CAT2 alone showed an improvement in the yield of 7-ETI when the temperature was increased, whereas the CAT2/SiO_2 mixed catalysts exhibited opposite trends. Furthermore, at high LHSV values higher H_2-contents were necessary in the carrier gas to maintain the catalytic activity.

However, a very significant improvement was achieved by developing novel ZrO_2/SiO_2 catalysts[36], able to operate with high LHSV values, almost stoichiometric ratios between 2-ETAN and EG and using water as the main carrier gas. Water can be easily separated by condensation and recycled to the reactor, thus avoiding environmental constraints. These catalysts were investigated with a wide number of substrates (anilines and/or diols), and catalytic results better than those reported in the literature were obtained[33,36].

4. Conclusions

The vapour phase synthesis of nitrogen-containing heterocyclic compounds represents a significant example of an environment-friendly process of high industrial interest, since in comparison with the current liquid-phase syntheses many different compounds can be economically synthesised, with evident advantages (more simple and safe reaction conditions, use of non-toxic, low cost and widely available commercial feeds, simple catalyst recovery or regeneration, easy set-up or work-up, minimum waste production, etc.). Furthermore, vapour phase synthesis is highly flexible, since a wide number of different nitrogen-containing heterocyclic compounds can be obtained as a function of the nature of the feed, catalyst composition and reaction conditions. In particular,

- quinoline or alkylquinolines may be synthesised from aniline/alkylanilines and diols, operating at high temperature and in the presence of strong solid acid catalysts, mainly Brønsted-type (for example acid-treated K10 montmorillonite), although Lewis acid sites also contribute to the reaction;
- indoles or alkylindoles may also be obtained from aniline/alkylanilines and diols, operating at lower temperatures and in the presence of multicomponent catalysts, in which both dehydrogenating and weak-acid sites (Lewis-type) are present (e.g. copper chromites or, better, copper chromite/SiO_2 mixtures);
- using the latter catalysts, but changing the nature of the hydroxyaldehyde-intermediate, e.g. feeding DHF instead of EG, pyrroles and/or pyrrolidines can be obtained, depending on temperature and presence of water in the feed.

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