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Conjugate Addition of Indoles to Nitroalkenes Promoted by Basic Alumina in Solventless Conditions

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Abstract: Basic alumina is found to promote the conjugate addition of indoles to nitroalkenes in solventless conditions at 60 °C. Nitroalkenes can be replaced by nitro alcohols that are converted into nitroolefins under the reaction conditions. Alternatively, a tandem nitroaldol-dehydration allows the utilization of nitroalkanes and aldehydes as remote precursors of reactive nitroalkenes in a 'one–pot' synthesis of 3-substituted indoles.

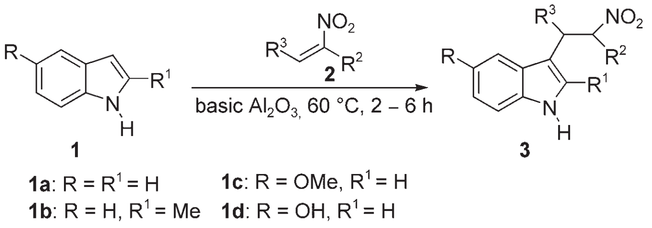
Keywords: basic alumina; conjugate addition; heterogeneous catalysis; indoles; nitroalkenes; solventless reaction

Introduction

Organic reactions on solid supports represent a viable and convenient alternative to traditional synthetic processes realized under homogeneous conditions.[1] In addition, solid catalysts are often able to produce a consistent increase in the reactivity and selectivity of the related processes so that their utilization becomes mandatory for a successful synthetic procedure. Solid supports can be profitably used in different reaction systems that, working in heterogeneous conditions, allow the synthetic process to be carried out by simply mixing the reactants in the absence of any solvent. This opportunity is particularly appealing in the development of environmentally friendly chemical processes avoiding the utilization of harmful solvents. Conjugate addition of nucleophiles to electron-poor alkenes represents a test bench for a considerable number of solid catalysts that may work either by activating the nucleophilic reagent (basic supports) or the alkene moiety (acidic supports).[2] Solid acid catalysis plays a fundamental role in many procedures involving alkylation of indoles *via* 1,4-addition to nitroalkenes that can be regarded more precisely as a Friedel–Crafts alkylation.[3] Nitroalkenes are undoubtedly among the strongest Michael acceptors,[4] and their indole adducts are central intermediates for the synthesis of many biologically active compounds.[5] A similar conjugate addition can also be carried out *via* generation of an indole anion by a suitable base followed by the addition of the nitro olefin. This procedure is less exploited than the acid-catalyzed route and generally involves the utilization of Grignard reagents as basic promoters.[6] Solid base catalysts have found an effective utilization in the reaction of active methylene compounds with Michael acceptors, since the basicity of these heterogeneous systems is usually rather modest. This feature is far from representing a drawback, since it allows a more accurate control of the chemoselectivity of many synthetic processes. In this context, basic alumina has been demonstrated as an effective basic promoter in several reactions involving easily enolizable reagents with electrophiles.[7] In the course of our studies on basic alumina catalysis,[8] we found that this solid base is able to facilitate the addition of indoles to various nitroalkenes leading to the corresponding 3-substituted indoles. This paper presents the results obtained with this procedure that can be extended to the 'one–pot' synthesis of 3-substituted indoles starting directly from nitroalkene precursors.

Results and Discussion

To the best of our knowledge, this procedure represents the first example of such an addition carried out under basic heterogeneous conditions.[9] Indole (**1a**), 2-methylindole (**1b**) and 5-methoxyindole (**1c**) act efficiently as nucleophiles in the reaction with nitroalkenes **2** in the



Scheme 1.

presence of basic alumina at 60 °C giving the corresponding 3-substituted indoles **3** (Scheme 1, Table 1, entries 1–14).

The addition also occurs at room temperature but extensive reaction times (24 h) are required and the isolated yields of products **3** obtained are consistently lower. The electronic density of the heterocycle would play an important role in the reaction since the presence of electron-withdrawing groups in the ring as in 5-bro-

Table 1. Basic alumina catalyzed additions of indoles **1** to nitroalkenes **2** or their precursors **6**, **4** and **5**.

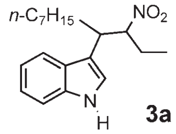
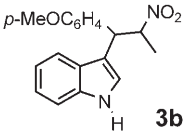
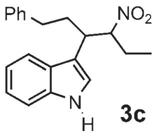
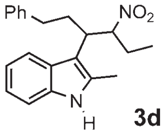
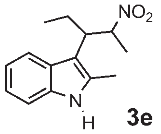
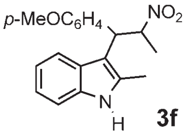
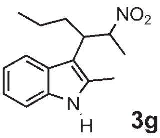
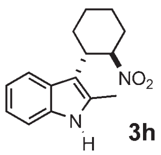
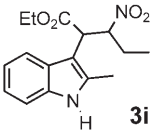
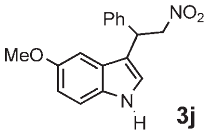
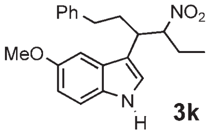
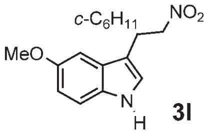
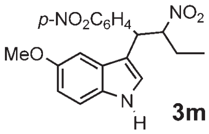
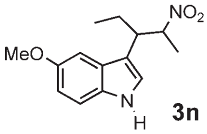
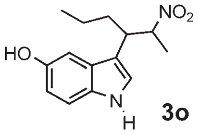
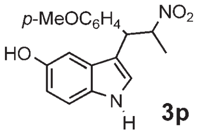
Entry	Indole **1**	Product **3**	Yield (%)[a] of product **3** starting from:		
			Nitro compound **4** and aldehyde **5**[b]	Nitro alcohol[c] **6**	Nitroalkene[d] **2**
1	**1a**	 **3a**			63 (6:4)
2	**1a**	 **3b**			65 (1:1)
3	**1a**	 **3c**			70 (1:1)
4	**1b**	 **3d**	58	62	75 (1:1)
5	**1b**	 **3e**	50	74	80 (1:1)
6	**1b**	 **3f**			66 (7:3)
7	**1b**	 **3g**	68	75	84 (1:1)
8	**1b**	 **3h**			58[e] (95:5)

Table 1 (cont.)

Entry	Indole **1**	Product **3**	Yield (%)[a] of product **3** starting from:		
			Nitro compound **4** and aldehyde **5**[b]	Nitro alcohol[c] **6**	Nitroalkene[d] **2**
9	**1b**	 **3i**			88 (8:2)
10	**1c**	 **3j**			61
11	**1c**	 **3k**	60	76	81 (1:1)
12	**1c**	 **3l**		50	65
13	**1c**	 **3m**			64[e] (1:1)
14	**1c**	 **3n**			84 (1:1)
15	**1d**	 **3o**			43[f] (1:1)
16	**1d**	 **3p**			44[g] (1:1)

[a] Isolated yields after column chromatography. Unless otherwise stated, reaction time was 2 h at 60 °C.

[b] Nitro compound and aldehyde were made to react for 1.5 h at room temperature and then, after addition of the appropriate indole, the solid mixture was heated at 60 °C for 2 h.

[c] Nitro alcohol was used as precursor of nitroalkene. The mixture was heated at 60 °C for 2 h.

[d] The diastereoisomeric ratio was determined by ^{1}H NMR on the crude product.

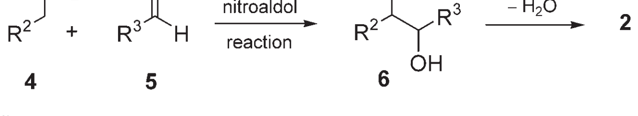
[e] Reaction time: 6 h at 60 °C.

[f] Reaction time: 15 h at 60 °C.

[g] Reaction time: 55 h at 60 °C.

moindole and 5-cyanoindole does not allow any addition with some of the nitroalkenes tested for this purpose. Increasing the size of the substituent close to the reaction center, as occurs in 2-phenylindole, also prevents any efficient electrophilic addition even with simple β-nitrostyrene. In accordance with previous studies, the effect exerted by basic alumina in promoting nucleophilic additions is probably not merely that of a base.[10] Potassium fluoride adsorbed on basic alumina affords a rather basic solid containing no free fluoride anions.[11] This solid catalyst is very efficient in promoting various conjugate additions,[12] but is completely ineffective in the reaction of our indoles with nitroalkenes. As a matter of fact, neutral alumina, although less efficiently, is able to promote the conjugate addition of indoles to nitroalkenes.[13] In any event, the presence of the acidic N–H proton seems mandatory since every attempt to use *N*-methylindole for these reactions sorely failed. When free hydroxy groups are present in the benzene ring of the indoles they are preferentially deprotonated by the basic catalyst leading to a consistent acidity reduction of the pyrrole nucleus. This effect is clearly evident in the behavior of 5-hydroxyindole **1d** that reacts with nitroalkenes giving low yields of the corresponding adducts even after prolonged reaction times (Table 1, entries 15 and 16). Various substituted nitroalkenes can be used for this purpose but generally α,β-disubstituted nitro olefins give the best yields of the corresponding adducts that are obtained as a mixture of stereoisomers with variable degree of diastereoselectivity. A notable exception is represented by product **3 h** that is formed almost exclusively as the *trans* stereoisomer as evidenced by the value of the coupling constant ($J=$ 11.5 Hz) of the corresponding protons. Other basic systems have been tested for the same reaction working in heterogeneous (Amberlyst A21) as well as in homogeneous conditions (TMG, DBU, *t*-BuOK). These basic promoters failed to give adduct **3 g** by reaction of indole **1b** and the appropriate nitroalkene with the exception of *t*-BuOK that gave **3 g** in 27% yield. Nitroalkenes are strong electrophilic reagents that can be readily prepared by means of a two-step procedure involving a preliminary nitroaldol addition (Henry reaction) between a nitroalkane **4** and an aldehyde **5** to give the corresponding nitro alcohol **6** (Scheme 2).[14]

Upon dehydration using appropriate reagents, nitro alcohol **6** can be converted into nitroalkene **2**. Several years ago we found that basic alumina is very effective in promoting the addition of nitro compounds to aldehydes[15] but, under suitable conditions, this solid catalyst is also able to effect the transformation of nitro alcohols into the corresponding nitroalkenes.[16] This feature of basic alumina can be profitably used to realize a tandem procedure allowing the direct synthesis of nitro olefins using a nitroaldol reaction without the need for isolating the intermediate nitro alcohol. As a first attempt we decided to use directly nitro alcohols **6** as precursors of the corresponding nitroalkenes **2** in the reaction with indoles **1**. The aim of these trials was to gain some benefit by the slow conversion of the nitro alcohol into the nitroalkene, since it is known that these electrophiles are prone to polymerization in basic conditions. Furthermore, unlike nitro alcohols, many nitroalkenes are rather toxic and lachrymatory compounds so that direct manipulation of these reactive alkenes is often not advisable. As displayed in Table 1 (entries 4, 5, 7, 11, 12), the yields of adducts **3** obtained from nitro alcohols **6** are generally lower than those observed using nitroalkenes **2** but, in any case, their values are respectable since they refer to a tandem process. Encouraged by these findings, we exploited the possibility to use directly a 'one–pot' nitroaldol-elimination process in order to generate the nitroalkene **2** from their remote precursors namely nitroalkane **4** and aldehyde **5**. Mixing compounds **4** and **5** in the presence of basic alumina resulted, after 1.5 h at room temperature, in the formation of nitro alcohol **6** that upon addition of indoles **1** and heating at 60 °C for 2 h gave adducts **3** in satisfactory yield (Table 1, entries 4, 5, 7, 11). Reaction on the solid support using our procedure makes unnecessary any work-up procedure, since purification of 3-substituted indoles **3** can be easily carried out by direct application of the solid mixture to the head of a chromatographic column followed by elution with an appropriate solvent system.



Scheme 2.

Conclusion

In conclusion, we have disclosed an unprecedented utilization of commercially available basic alumina as solid catalyst for the nucleophilic addition of different indoles to nitroalkenes. The procedure is simple and can be carried out in solventless conditions by mixing the reactants and the catalyst and heating the solid mixture at 60 °C. The direct utilization of nitro olefins as electrophiles can be easily overcome by using nitro alcohols that, in the reaction conditions, are dehydrated to the corresponding nitroalkene. Alternatively, a 'one–pot' nitroaldol-dehydration-addition process can be exploited starting from nitroalkanes and aldehydes as precursors of reactive nitroalkenes. The efficiency of the procedure is witnessed by the satisfactory yields of 3-substituted indoles obtained using basic alumina as solid catalyst.

Experimental Section

General Remarks

GLC analyses were performed with an SE-54 fused silica capillary column (25 m, 0.32 mm internal diameter), FID detector and nitrogen as carrier gas. GS-MS analyses were carried out by means of the EI technique (70 eV). All chemicals, included 2-nitrostyrene and nitrocyclohexene were purchased and used without further purifications. Nitroalkenes **2** were prepared by dehydration from the corresponding nitro alcohols using known procedures.[17] Commercial basic alumina (Fluka) was activated by heating at 150 °C/1 mmHg for 5 h before utilization. 3-Substituted indoles **3 h, j** are known compounds.[3d, f]

Typical Procedure for Addition of Indoles to Nitroalkenes or Nitro Alcohols

To a mixture of indole **1** (1.0 mmol) and nitroalkene **2** (1.2 mmol) [or nitro alcohol **6** (1.4 mmol)] activated basic alumina (1.2 g) was added at room temperature and the mixture was warmed at 60 °C. After stirring for the appropriate time (see Table 1) the solid mixture was directly charged on a chromatography column and eluted (hexane-ethyl acetate, 9:1) to afford pure product **3**.

Typical Procedure for the 'One-Pot' Nitroaldol-Elimination-Addition Sequence

To a mixture of nitro compound **4** (1.4 mmol) and aldehyde **5** (1.4 mmol), activated basic alumina (1.2 g) was added at 0 °C. The resulting mixture was stirred for 1.5 h at room temperature and after consumption of the reactants (reaction progress was monitored by TLC or GLC) the appropriate indole **1** (1.0 mmol), was added. The solid mixture was warmed at 60 °C and stirred for the appropriate time (see Table 1). Upon reaction completion, the solid mixture was directly charged on a chromatography column and eluted (hexane-ethyl acetate, 9:1) to afford pure product **3**.

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References and Notes

[1] a) K. Rueck-Braun, T. H. E. Freysoldt, F. Wierschem, *Chem. Soc. Rev.* **2005**, *34*, 507–516; b) G. Sartori, R. Ballini, F. Bigi, G. Bosica, R. Maggi, P. Righi, *Chem. Rev.* **2004**, *104*, 199–250; c) C. Chung, Y. Wan, P. H. Toy, *Tetrahedron: Asymmetry* **2004**, *15*, 387–399; d) M. H. Valkenberg, C. de Castro, W. F. Hoelderich, *Green Chem.* **2002**, *4*, 88–93; e) J. H. Clark, *Acc. Chem. Res.* **2002**, *35*, 791–797.

[2] a) P. Perlmutter, *Conjugate Addition Reactions in Organic Synthesis* Pergamon, Oxford, **1992**; b) B. E. Rossiter, N. M. Swingle, *Chem. Rev.* **1992**, *92*, 771–806.

[3] a) M. Bandini, A. Melloni, S. Tommasi, A. Umani-Ronchi, *Synlett* **2005**, 1199–1222; b) M. Bandini, M. Fagioli, A. Umani-Ronchi, *Adv. Synth. Catal.* **2004**, *346*, 545–548; Metal salts on solid supports have also found some utilization: c) Z.-P. Zhan, K. Lang, *Synlett* **2005**, 1551–1554; d) G. Bartoli, M. Bosco, S. Giuli, A. Giuliani, L. Lucarelli, E. Marcantoni, L. Sambri, E. Torregiani, *J. Org. Chem.* **2005**, *70*, 1941–1944; e) G. Bartoli, M. Bartolacci, M. Bosco, G. Foglia, A. Giuliani, E. Marcantoni, L. Sambri, E. Torregiani, *J. Org. Chem.* **2003**, *68*, 4594–4597.

[4] a) O. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877–1894; b) V. V. Perekalin, E. S. Lipina, V. M. Berestovitskaya, D. A. Efremov, *Nitroalkenes Conjugated Nitro Compounds*, Wiley, Chichester, **1994**.

[5] a) R. J. Sundberg, *The Chemistry of Indoles*, Academic Press, New York, **1996**; b) H. Harada, Y. Hirokawa, K. Suzuki, Y. Hiyama, M. Oue, H. Kawashima, H. Kato, N. Yoshida, Y. Furutani, S. Kato, *Chem. Pharm. Bull.* **2005**, *53*, 184–198; c) R. P. Herrera, V. Sgarzani, L. Bernardi, A. Ricci, *Angew. Chem.* **2005**, *117*, 6734–6737; *Angew. Chem. Int. Ed.* **2005**, *44*, 6576–6579; d) E. D. Cox, H. Diaz-Arauzo, Q. Huang, M. S. Reddy, C. Ma, B. Harris, R. McKernan, P. Skolnick, J. M. Cook, *J. Med. Chem.* **1998**, *41*, 2537–2552.

[6] a) S. Mahboobi, W. Wiegrebe, A. Popp, *J. Nat. Prod.* **1999**, *62*, 577–579. b) T. Koike, N. Takeuchi, M. Hagiwara, K. Yamazaki, S. Tobinaga, *Heterocycles* **1999**, *51*, 1271–1280; c) T. Koike, M. Hagiwara, N. Takeuchi, S. Tobinaga, *Heterocycles* **1997**, *45*, 1271–1280.

[7] a) G. W. Kabalka, R. M. Pagni, *Tetrahedron* **1997**, *53*, 7999–8065; b) G. H. Posner, *Angew. Chem.* **1978**, *90*, 527–536; *Angew. Chem. Int. Ed.* **1978**, *17*, 487–496.

[8] a) R. Maggi, R. Ballini, G. Sartori, R. Sartorio, *Tetrahedron Lett.* **2004**, *45*, 2297–2299; b) R. Ballini, G. Bosica, *Synthesis* **1994**, 723–726; c) R. Ballini, G. Bartoli, *Synthesis* **1993**, 965–967.

[9] Neutral and basic alumina have been occasionally used in alkylation of indoles using alkyl halides, 1-alkylation: a) M. A. Tius, J. Busch-Petersen, *Synlett* **1997**, 531–533; b) W. J. Smith III, J. S. Sawyer, *Tetrahedron Lett.* **1996**, *37*, 299–302; 3-alkylation: c) H. Ishibashi, K. Nishida, M. Ikeda, *Synth. Commun.* **1993**, *23*, 2381–2387; d) H. Ishibashi, N. Mita, N. Matsuba, T. Kubo, M. Nakanishi, M. Ikeda, *J. Chem. Soc. Perkin Trans. 1* **1992**, 2821–2825.

[10] G. H. Posner, in: *Preparative Chemistry Using Supported Reagents*, (Ed.: P. Laszlo), Academic Press, San Diego, **1987**.

[11] J. H. Clark, *Catalysis of Organic Reactions by Supported Inorganic Reagents*, VCH, New York, **1994**.

[12] a) D. E Bergbreiter, J. J. Lalonde, *J. Org. Chem.* **1987**, *52*, 1601–1603; b) R. Giovannini, M. Petrini, *Chem. Commun.* **1997**, 1829–1830; c) J.-T. Li, W.-Z. Xu, L.-C. Yang, T.-S. Li, *Synth. Commun.* **2004**, *34*, 4565–4571.

[13] The activity of neutral alumina as catalyst in these additions is probably due to the Lewis and Brønsted acid sites that co-exist on the surface: W. H. Dawson, S. W. Kaiser, P. D. Ellis, R. R. Inners, *J. Am. Chem. Soc.* **1981**, *103*, 6780–6781.

[14] a) G. Rosini, in: *Comprehensive Organic Synthesis*, Vol.2, (Ed.: B. M. Trost), Pergamon, Oxford, **1991**, p. 321–340; b) F. A. Luzio, *Tetrahedron* **2001**, *57*, 915–945.

[15] a) G. Rosini, R. Ballini, P. Sorrenti, *Synthesis* **1983**, 1014–1016; b) G. Rosini, R. Ballini, M. Petrini, P. Sorrenti, *Synthesis* **1985**, 515–517; for a more recent paper, see: c) R. Ballini, G. Bosica, D. Fiorini, A. Palmieri, *Synthesis* **2004**, 1938–1940.

[16] R. Ballini, R. Castagnani, M. Petrini, *J. Org. Chem.* **1992**, *57*, 2160–2162.

[17] a) J. Melton, J. E. Mc Murry, *J. Org. Chem.* **1975**, *40*, 2138–2139; b) S. E. Denmark, L. R. Marcin, *J. Org. Chem.* **1993**, *58*, 3850–3856.