H-Bonding Organocatalysed Friedel–Crafts Alkylation of Aromatic and Heteroaromatic Systems with Nitroolefins

Gabriella Dessole,[a] Raquel P. Herrera,*[b] Alfredo Ricci*[a]

[a] Dipartimento di Chimica Organica 'A. Mangini'Facoltà di Chimica Industriale, Via Risorgimento N°4, 40136-Bologna, Italy
Fax +39(051)2093654; E-mail: ricci@ms.fci.unibo.it

[b] Universidad de Alicante, Dpto. Química Orgánica, Apdo.99, 03080-Alicante, Spain

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Abstract: Catalytic amounts (10 mol%) of *bis*-arylureas and -thioureas promote the Friedel–Crafts alkylation with nitroolefins of aromatic and heteroaromatic N-containing derivatives. A sizeable improvement of the yields is noticed on running the reactions in the absence of solvent. When applied to indoles this protocol provides in good to excellent yields and with high selectivity the corresponding Michael adducts. Alkylation at position 2 of the 3-methylindole can be achieved combining solvent-free reaction conditions with microwave (MW) irradiation.

Key words: organocatalysis, nitroolefins, Friedel–Crafts alkylation, indoles

The metal-ion free catalysis of organic reactions is a challenge that just has been taken up by chemists.[1] Though this field is still in its infancy some rough guidelines have already been devised which allow to envisage concepts for further catalysts developments. Chemists have recently very successfully been using the catalytic antibody approach.[2] It is clear that the recognition process in such system relies on hydrogen bonding and hydrophobic interactions.[3] Unlike the action of Lewis acids, based on a strong coordination with a lone pair of the Lewis bases, the binding energies with hydrogen bonds are expected to be much smaller.[4] Name reactions such as the Strecker,[5] the aza-Henry,[6] the Baylis–Hillmann[7]and the aldol[8] reactions have been recently reported to benefit by organocatalysis.

Whereas various versions of the Michael-type addition of nucleophiles to electron deficient olefins have been reported so far using metal catalysts, few examples of this reaction are known regarding the use of organocatalysis. In particular L-proline,[9] *N*-*i*-Pr-2,2′-bipyrrolidine[10] and (*S*)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine[11] have been employed in the Michael addition of unmodified ketones and aldehydes to nitroolefins. Only recently an important paper is appeared dealing with the enantioselective Michael addition of malonates to nitroolefins using thiourea derivatives as a Lewis acidic catalyst.[12]

The addition of aromatic substrates to alkenes, which in many respects may be considered a Friedel–Crafts-type alkylation,[13] is an important reaction in synthetic organic chemistry for the formation of new C-C bonds.[14] So far there are scant reports regarding the reaction between nitroolefins and aromatic and heteroaromatic systems and the reaction appears to be catalysed by Lewis acids like $Yb(OTf)_3 \cdot 3H_2O$,[15] $Sc(OTf)_3$[16] or $Bi(OTf)_3$.[17] In this paper we disclose the application of organocatalysis, using neutral hydrogen bond donors, to the reaction between nitroolefins and a range of aromatic and heteroaromatic electron rich nitrogen-containing systems. The choice towards urea- and thiourea-type catalysts **I** and **II** (Figure 1) was dictated by the fact that in organocatalysis many interactions are dominated by bidentate hydrogen bonding.

The double hydrogen-bonding motif is becoming a powerful tool in organocatalysis since the first application of thiourea-type catalysts in Diels–Alder reactions by Schreiner and Wittkopp.[18] The design of metal-free bidentate hydrogen-bonding based catalysts, has been recently put on a rational basis by these and other authors in several fundamental papers.[4,19] To screen the catalyst efficiency under various conditions, we carried out the reactions in toluene as well as in the absence of solvent (Scheme 1). The relevant results[20] for the alkylation of aromatic and heteroaromatic systems **1**–**6** with nitroolefins **a** and **b** are reported in Table 1.

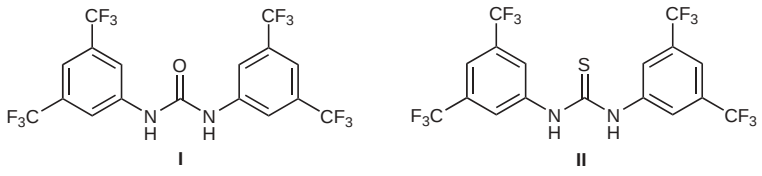

Figure 1

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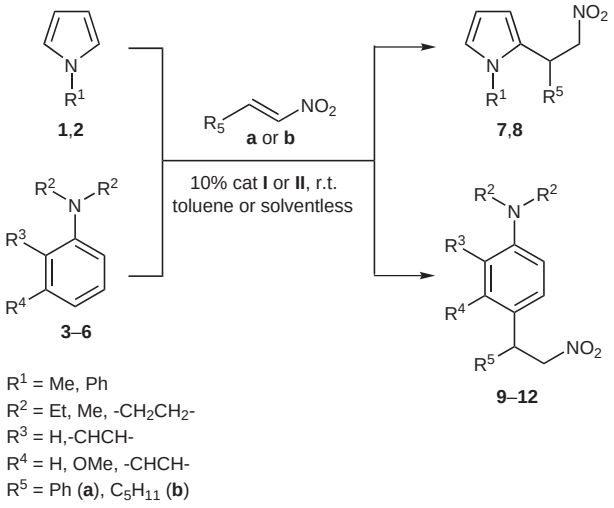


Scheme 1

In control experiments, all compounds listed in Table 1 failed to react with nitroolefins under the standard conditions[20] in the absence of an organocatalyst. The reactivity in the presence of **I** or **II** (a catalyst loading of 10% mol was used throughout) strongly depended upon the structure of the nitrogenated organic substrate. *N*-Methylpyrrole reacted smoothly in toluene to give (entries 1, 3) the 2-substituted product, but the reaction was disappointing in the case of the *N*-aryl derivative (entries 7, 9). Aryl alkylation took place leading in low to moderate yields to the products after prolonged reactions times (entries 11, 13, 15, 17, 23, 25). Only in the presence of an electron releasing function in the aryl moiety, as in the case of *m*-OMe-*N*,*N*′-dimethylaniline, the increase of reactivity was remarkable, quantitative yields of the alkylated product being achieved (entry 21) after only one hour at room temperature using **II** as the catalytic species. In general the efficiency of thiourea-based organocatalyst (**II**) resulted superior with respect to that of the oxygenated analogous (**I**). This trend has been rationalised[4,19] on the grounds of the greater hydrogen-bond donor ability of thiourea derivatives supported by the enhanced differences in acidities (pK_{HA} thiourea = 21.0; pK_{HA} urea = 26.9).[21] Furthermore, the lower electronegativity of sulfur makes self-association, the interaction of the N-H group of one molecule with the carbonyl or thiocarbonyl group of another, less favourable.[22]

A working hypothesis regarding the enhancement of electrophilicity of the nitroolefins due to the interaction of the urea-type derivatives with the nitro group is shown in Figure 2.

A consistent improvement of the reaction efficiency was achieved by running the reactions under solvent-free conditions. In highlighting the solventless approach, an important strategy in the drive towards benign chemical technologies,[23] the Friedel–Crafts alkylation was examined by simply mixing compounds **1**–**6** with nitrostyrene in the presence of **I** and **II**. Adducts **7**–**12** were formed as single products with high degree of conversion after shorter reaction times. Less reactive systems such as **2**–**4**, and **6** took particular advantage of these modified reaction conditions (in Table 1 compare entries 9, 10 or 13, 14 or 17, 18 or 19, 20, or 25, 26). Again the catalytic efficiency of **II** prevailed, and the difference resulted particularly remarkable in the case of **4** (compare entries 16 and 18). Comparison between β-nitrostyrene and an aliphatic nitroolefin, indicated the greater reactivity of the latter (compare entries 2, 5 and 4, 6) in agreement with literature data.[24]

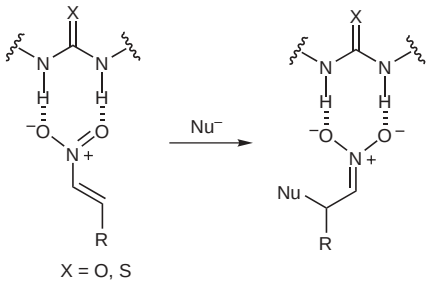


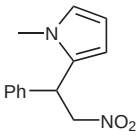
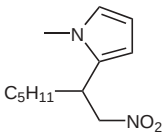
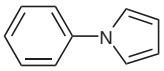
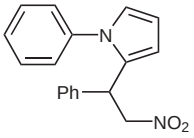
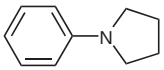
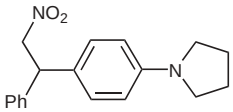
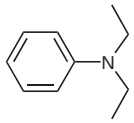
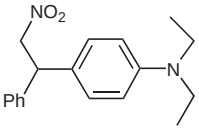
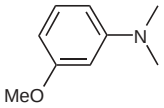
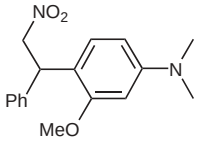
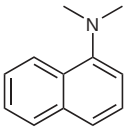
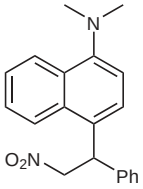
Figure 2

Then we turned our attention to the Friedel–Crafts alkylation of indoles. The indole framework is present in over 3000 isolated natural products and 40 medicinal agents with diverse therapeutic action.[25] The coupling between indoles and Michael acceptors, is known[26] but is subjected to a number of serious constraints such as the need of unhindered acceptors or the tendency to polymerise under acid-catalysed conditions. Only recently a practical and efficient $InBr_3$-catalysed addition of indoles to nitroalkenes in aqueous media has been proposed.[27] On the grounds of results in Table 1 and given the significant nucleophilic character of the indole molecule, alkylation with nitroolefins in the presence of organocatalysts **I** and **II** seemed promising.

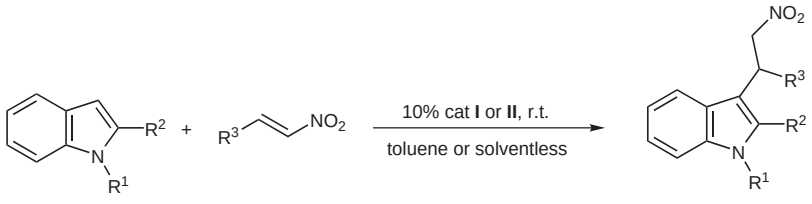
Scheme 2 outlines the reaction between indole, and 1- and 2-methylindole and nitroolefins catalysed by **I** and **II** leading to adducts **16**–**18** precursors of tryptamines of interest for their physiological activity and for being closely related to the β-carboline nucleus.[28] The relevant results are shown in Table 2.

The established reactivity series towards Michael acceptors for the indoles studied is 2-methylindole > indole > 1-methylindole.[24] Accordingly, only 2-methylindole (**14**) under solventless conditions proved to be reactive in the uncatalysed reaction (entries 5 and 10 in Table 2) but still the yields were substantially increased by the presence of the organocatalysts (entries 6–9 and 11, 12 in Table 2). A drastic improvement was noticed on the other hand when less reactive indoles **13** and **15** were used. Under **I** and **II** catalysis, (entries 1, 13, 14, 19) high yields were obtained after the suitable reaction time (72 hours) in the case of the reaction of indole in toluene at room temperature and the addition of 1-methylindole afforded in nearly quantitative yields the expected adducts **18a** and **18b** after short reaction time (4 h). Finally, the reaction at position 2 of 3-methylindole, known to be very difficult, was examined:

Table 1 Friedel–Crafts Alkylation Reactions of Aromatic and Heteroaromatic Systems with Nitroolefins Catalysed by **I** and **II**

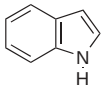
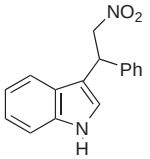
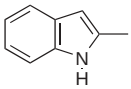
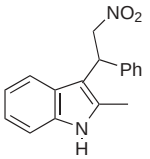
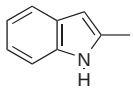
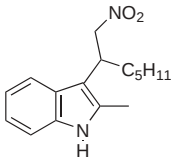
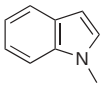
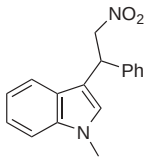
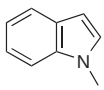
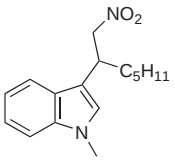
Entry	Substrate	R	Catalyst	Solvent	Time (h)	Product[a]	Yield (%)[b]
1		Ph	**I**	Toluene	18		48
2			**I**	No solvent	3		57
3			**II**	Toluene	18		74 (70)[c]
4	**1**		**II**	No solvent	3		59
						7a	
5		C_5H_{11}	**I**	No solvent	1		70
6			**II**	No solvent			86 (86)[c]
	1						
						7b	
7		Ph	**I**	Toluene	72		5
8			**I**	No solvent			17
9			**II**	Toluene			12
10	**2**		**II**	No solvent			39
						8a	
11		Ph	**I**	Toluene	72		30
12			**I**	No solvent			49
13			**II**	Toluene			53
14	**3**		**II**	No solvent			80 (75)[c]
						9a	
15		Ph	**I**	Toluene	72		25
16			**I**	No solvent	24		26
17			**II**	Toluene	72		55
18			**II**	No solvent	24		100 (97)[c]
	4						
						10a	
19		Ph	**I**	Toluene	1		57
20			**I**	No solvent			100
21			**II**	Toluene			100
22			**II**	No solvent			100 (97)[c]
	5						
						11a	
23		Ph	**I**	Toluene	72		11
24			**I**	No solvent			24
25			**II**	Toluene			27
26			**II**	No solvent			55 (49)[c]
	6						
						12a	

[a] All products were characterized by ^{1}H NMR, ^{13}C NMR, IR and MS.
[b] Conversion as determined by ^{1}H NMR.
[c] Yield of pure, isolated product after flash chromatography.



Scheme 2

Table 2 Friedel–Crafts Alkylation Reactions of Indoles with Nitroolefins Catalysed by **I** and **II**

Entry	Substrate	R	Catalyst	Solvent	Time (h)	Product[a]	Yield (%)[b]
1		Ph	–	Toluene	72		12
2			**I**	Toluene			60 (58)[c]
3			**II**	Toluene			85 (82)[c]
	13					**16a**	
4		Ph	–	Toluene	1		8
5			–	No solvent			45
6			**I**	Toluene			67
7			**I**	No solvent			77 (75)[c]
8	**14**		**II**	Toluene			87
9			**II**	No solvent			87 (83)[c]
						17a	
10		C_5H_{11}	–	No solvent	1		40
11			**I**	No solvent			71
12			**II**	No solvent			80 (80)[c]
	14					**17b**	
13		Ph	–	Toluene	4		3
14			–	No solvent			4
15			**I**	Toluene			77
16			**I**	No solvent			82 (80)[c]
17	**15**		**II**	Toluene			93
18			**II**	No solvent			96 (93)[c]
						18a	
19		C_5H_{11}	–	No solvent	4		19
20			**I**	No solvent			100
21			**II**	No solvent			100 (94)[c]
	15					**18b**	

[a] All products were characterized by ^{1}H NMR, ^{13}C NMR, IR and MS.
[b] Conversion as determined by ^{1}H NMR.
[c] Yield of pure, isolated product after flash chromatography.

even under the most favourable conditions used in this work only traces of the expected adduct were observed after long reaction time. However MW irradiation and the absence of solvent turned out to envisage the right combination for a strong increase of reactivity, and in the presence of **II** as the catalytic species, 3-methylindole led after 20 minutes irradiation at 100 W, and after the usual work-up, to a 49% yield of the Michael adduct.

In the indole series, the double hydrogen bonding catalysis, offers several conspicuous advantages in terms of much milder reaction conditions and higher yields with respect to the traditional methods[24] and appears also to some extent superior to the recently reported alkylations of indoles catalysed by $Yb(OTf)_3$[15] or $Sc(OTf)_3$.[16]

In summary, this metal-free catalytic procedure appears of general applicability to electron rich aromatic and heteroaromatic systems and of particular value in the conjugate addition in the indole series. Issues such as stereochemistry and design of new hydrogen bond donors based catalysts are ongoing developments of this research in our laboratory.

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(20) **General Experimental Procedure.** In a Schlenk tube, a mixture of nitroolefin (**a** or **b**, 0.10 mmol), nitrogen-containing aromatic or heteroaromatic compound (**1**–**6**, **13**–**15**, 0.15 mmol) and catalyst (**I** and **II**, 0.01 mmol) in toluene (1 mL) or without solvent, was vigorously stirred at ambient temperature for the appropriate time (Table 1 or Table 2). After completion of the reaction as indicated by ^{1}H NMR, the reaction mixture was diluted with H_2O and extracted with Et_2O. The organic phases were combined, dried over Na_2SO_4 and concentrated under reduced pressure, and the crude mixture was purified by column chromatography. All the new compounds gave satisfactory analytical and spectral data. Typical data for representative compounds:
Analytical data of compound **10a**: IR (CCl_4): 3047, 2893, 1614, 1552, 1376, 1277, 895 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 (t, ^3J = 7.1 Hz, 6 H, 2 × CH_3CH$_2$), 3.24 (c, ^3J = 7.2 Hz, 4 H, 2 × CH$_3$CH_2), 4.71 (dd, ^3J = 8.8 Hz, ^3J = 7.5 Hz, 1 H, NO$_2$CH$_2$C*H*), 4.78–4.93 (m, 2 H, NO$_2$CH$_2$), 6.53 (d, ^3J = 8.7 Hz, 2 H, Ph), 6.97 (d, ^3J = 8.7 Hz, 2 H, Ph), 7.08–7.40 (m, 5 H, Ph). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 12.48 (2 × *C*H$_3$CH$_2$), 44.25 (NO$_2$CH$_2$*C*H), 48.21 (CH$_2$NCH$_2$), 79.66 (NO$_2$CH$_2$), 111.85 (C^{Ph}), 125.40 (C$_q^{Ph}$), 127.26, 127.50, 127.57, 140.03, 128.55, 128.86, (5 × C^{Ph}) 139.97, 147.01 (2 × C$_q^{Ph}$). MS (70 eV): *m/z* (%) = 298 [M$^+$], 284 (17), 283 (86), 252 (50), 238 (100), 237 (19), 236 (56), 208 (28). HRMS: *m/z* calcd for $C_{18}H_{22}N_2O_2$: 298.1681; found: 298.1684.
Analytical data of compound **18b**: IR (CCl_4): 3061, 2860, 1555, 1468, 1426, 1377 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83 (t, *J* = 7.1 Hz, 3 H, CH$_2$C*H*$_3$), 1.12–1.36 (m, 6 H, 3 × CH$_2$), 1.68–1.92 (m, 2 H, NO$_2$CH$_2$CHC*H*$_2$), 3.76 (s, 3 H, NCH$_3$), 3.70–3.81 (m, 1 H, NO$_2$CH$_2$C*H*), 4.61 (dd, ^2J = 11.9 Hz, ^3J = 7.8 Hz, 1 H, NO$_2$C*H*H), 4.66 (dd, ^2J = 11.9 Hz, ^3J = 7.4 Hz, 1 H, NO$_2$CH*H*), 6.89 (s, 1 H, CH$_3$NC*H*), 7.13 (t, ^3J = 7.8 Hz, 1 H, Ph), 7.25 (t, ^3J = 7.8 Hz, 1 H, Ph), 7.31 (d, ^3J = 8.2 Hz, 1 H, Ph), 7.61 (d, ^3J = 8.2 Hz, 1 H, Ph). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 13.99 (CH$_2$*C*H$_3$), 22.43, 26.88, 31.61, 32.49 (4 × CH$_2$), 32.77 (NCH$_3$), 36.29 (NO$_2$CH$_2$*C*H), 80.72 (NO$_2$CH$_2$), 109.56 (C^{Ph}), 112.54 (C$_q^{Ph}$), 118.83, 119.20, 121.92 (3 × C^{Ph}), 126.55 (CH$_3$NCH*C*), 126.64, 137.23 (2 × C$_q^{Ph}$). MS (70 eV): *m/z* (%) = 274 [M$^+$], 228 (17), 214 (42), 171 (34), 158 (21), 157 (100), 156 (16). HRMS: *m/z* calcd for $C_{16}H_{22}N_2O_2$: 274.1681; found: 274.1687.
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