"On-water" conjugate additions of anilines†

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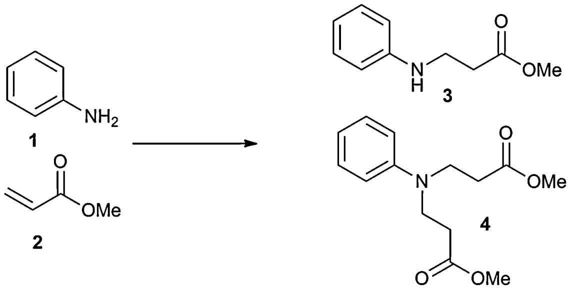
The conjugate addition of anilines onto unsaturated ketones, esters and *N*-acylpyrroles was investigated. Based on a recently proposed explanation for the phenomenon of on-water catalysis, operationally simple and mild reaction conditions for effecting these addition reactions have been developed. The success of these additions provides further support for the acid-catalysed nature of on-water chemistry.

Given the ubiquity of amines and nitrogen heterocycles in the natural and built environments, it is unsurprising that methods to construct the C–N bond have been intensively studied. One general method that has been widely adopted is the Michael addition of amines onto α,β-unsaturated carbonyl compounds. Whilst it is known that the rate of addition of *aliphatic* amines can be increased by acid or base catalysis in organic solvents,[1–8] several reports have been disclosed that utilise water as the solvent where no catalyst is required.[9–11] In contrast to those aliphatic cases, the Michael addition of substituted anilines onto enones and enoates has traditionally been a difficult transformation to effect, with only highly activated Michael acceptors participating in the non-catalysed reaction.[12] This is somewhat surprising given that the nucleophilicity (in contrast to the basicity) of aniline has been measured experimentally to be similar to that of other primary amines.[13] The use of Lewis acids,[3,14,15] metal promoters,[16,17] surfactants[18–21] and other additives[2,22] have all been proffered as a means to overcoming this inherent lack of reactivity. For example, Chen *et al.*[23] and Surendra *et al.*[24] reported the conjugate addition of aniline onto methyl acrylate at room temperature in water catalysed by tungstophosphoric acid and β-cyclodextrin respectively. Even under those catalyst-promoted conditions the reactions were sluggish, requiring up to 40 h to reach completion.

Recently, Legros, Crousse and co-workers reported the uncatalysed addition of aniline (**1**) onto methyl acrylate (**2**) using hot water (80 °C) as the solvent (Scheme 1).[16] When a 1 : 1 ratio of aniline : methyl acrylate was employed the desired reaction proceeded to only 15% conversion. When a threefold excess of methyl acrylate was employed the Michael adduct **3** was produced in 34% yield. Revealingly, the use of the more acidic trifluoroethanol (pK_a 12.5) as a co-solvent at 80 °C, gave the product **3** in 85% yield. Increasing the acidity of the solvent still further by employing hexafluoroisopropanol (pK_a 9.3) allowed the bis-alkylated compound **4** to be generated in good yield at a slightly lower temperature (54 °C). Rather than being uncatalysed, the conjugate addition of anilines in those instances appears to be acid catalysed.



Scheme 1 Conjugate addition of aniline to methyl acrylate.

We recently proposed a mechanism that explains the phenomenon of on-water catalysis.[25] Protonation of organic substrates at the oil–water interface is driven by the strong adsorption of hydroxide ions to the interface.[26,27] The protonated species is available to undergo acid-catalysed reactions while the hydroxide ion is sequestered in a deep thermodynamic well. This mechanism is consistent with the observed on-water rate enhancements for the conjugate addition of nitromethane to enones.[28–30] Based on this new understanding of acid catalysis on neutral water, we anticipated that the rate of conjugate addition of aniline to methyl acrylate could be accelerated by conducting the reaction as a heterogeneous suspension of organic droplets in water (the reaction conditions described by Sharpless *et al.* as "on-water").[31] This would provide a straightforward and economical route for effecting the acid catalysed additions. As detailed below, this supposition proved correct.

We began our investigations by vigorously stirring a 1 : 1.1 mixture of aniline and methyl acrylate on-water for 24 h at ambient temperature. To our delight the desired adduct **3** was collected in 21% isolated yield after chromatography (see Table 1). In agreement with previous work,[16] employing the more nucleophilic *p*-methoxyaniline in the conjugate addition lead to an increased yield (entry 2), whilst the less nucleophilic *p*-bromoaniline disfavoured the coupling reaction (entry 5).

The modest yields can be improved by altering the reaction stoichiometry, but when coupling more complex anilines and acrylates, an excess of either reactant may be undesirable. We therefore repeated the on-water reactions at 50 °C. As shown in Table 1 there was a corresponding increase in the yield of the desired adducts. The yields obtained using this simple protocol were in general superior to the yields obtained using a threefold excess of acrylate at high temperatures in previous work.[16] Even the halogenated aniline (entry 5) which had proven immune to coupling in previous work, provided the 1,4-adduct, albeit in low yield.

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Table 1 On-water conjugate addition of anilines

		Methyl acrylate^a (%)		MVK^b (%)
Entry	Nucleophile	Method A	Method B	Method A
1	Aniline	21	35	100
2	*p*-Methoxyaniline	46	94	70 (30)^c
3	*p*-Methylaniline	18	45	80 (10)^c
4	2,4-Dimethylaniline	6	8	100
5	*p*-Bromoaniline	NR	10	85
6	2,4,5-Trichloroaniline	NR	NR	14^d
7	*p*-Aminophenol	16	55 (25)^c	70 (25)^c
8	Thiophenol	46	—	95
9	*p*-Methylthiophenol	38	—	92
10	*p*-Bromothiophenol	45	—	95

^{a} Yield of isolated product after chromatography, reaction time 24 h. ^{b} Reaction time 1 h. ^{c} Yield of dialkylated product in parentheses. ^{d} Reaction time 2 h. Method A: 1.1 equiv. at rt; Method B: 1.1 equiv. at 50 °C.

The increased yields at lower temperatures that arise from the formation of an oil-in-water emulsion are consistent with the hypothesis of interfacial acid-catalysis to explain the on-water effect.[25]

Legros, Crousse and co-workers reported that substituted anilines participated in uncatalysed conjugate additions onto the highly electrophilic methyl vinyl ketone (MVK) at room temperature under aqueous conditions.[16] We anticipated that performing the same reactions on-water (*i.e.* using a heterogeneous aqueous suspension) would lead to increased yields *via* acid-catalysis. As shown in Table 1 the on-water Michael addition of both electron-rich and electron-poor anilines onto MVK proceeded in excellent yield after short reaction times. Even the deactivated and sterically hindered 2,4,5-trichloroaniline participated in the conjugate addition (entry 6). Only in the case of the electron-rich anilines was double alkylation observed (entries 2, 3 and 7). Legros, Crousse and co-workers demonstrated a clear relationship between the acidity of the solvent and the amount of bis-alkylation.[16] Therefore this result provides yet more evidence that these addition reactions are accelerated by acid-catalysis at the oil–water interface. Unsurprisingly, thiophenols proved to be excellent coupling partners (entries 8–10).

We next turned our attention to designing a system that incorporated the salient synthetic features of both previous conjugate addition reactions. That is, a reaction that was as efficient as the on-water Michael additions using MVK, but that gave products with the same synthetic utility as the on-water Michael additions using methyl acrylate. We anticipated that employing *N*-acryloyl-2,5-dimethylpyrrole (**5**) (Fig. 1) as the electrophilic partner would achieve this goal. Unsaturated *N*-acylpyrroles are known to be more electrophilic than the corresponding esters, and the pyrrole unit serves as a masked ester, acid or amide.[32,33]

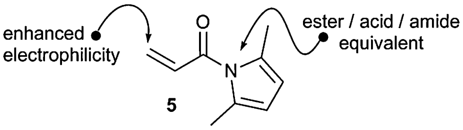

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Fig. 1 *N*-Acryloyl-2,5-dimethylpyrrole.

Table 2 On-water conjugate addition of anilines to an *N*-acylpyrrole

Entry	Nucleophile	Yield at rt^a (%)	Yield at 50 °C^a (%)
1	Aniline	96	—
2	*p*-Methoxyaniline	100	—
3	*p*-Methylaniline	100	—
4	2,4-Dimethylaniline	70^b	100^c
5	*p*-Bromoaniline	20	100^c
6	2,4,5-Trichloroaniline	30^c	65^c
7	*p*-Aminophenol	75 (25)	—
8	Thiophenol	95	—
9	*p*-Methylthiophenol	94	—
10	*p*-Bromothiophenol	96	—

^{a} Yield of isolated product after chromatography, reaction time 4 h. ^{b} Reaction time 16 h. ^{c} Reaction time 24 h.

As shown in Table 2, unsubstituted aniline and electron-rich anilines underwent conjugate addition onto *N*-acryloyl-2,5-dimethylpyrrole (**5**) at room temperature in as little as 4 h to give the desired products in preparatively useful yields. The use of the more electrophilic and hydrophobic pyrrolic amide removed the need for heating or excess reagents. Electron-poor anilines required longer reaction times to generate useful yields (entries 4 and 6), but even 2,4,5-trichloroaniline participated in the reaction under ambient conditions. Increasing the reaction temperature to 50 °C facilitated the conjugate addition of electron poor and sterically hindered anilines in excellent yields (entries 4–6). The double alkylation product was only observed for the reaction involving *p*-aminophenol.‡ Again, thiophenols proved to be exceptional coupling partners in the conjugate addition to *N*-acryloyl-2,5-dimethylpyrrole (entries 8–10).

To unambiguously demonstrate that each of the conjugate additions detailed in this communication was subject to on-water catalysis rather than hydrophobic-driven concentration effects, we compared the product yield of the reactions between aniline and the Michael acceptors after a fixed reaction time. As shown in Table 3, each of the reactions was substantially faster on-water than neat, demonstrating that formation of the oil-in-emulsion catalysed the reaction.

In summary, we have used our mechanistic understanding of the phenomenon of on-water catalysis to uncover a general and efficient method for effecting the conjugate addition of anilines (and thiophenols) onto methyl acrylate and *N*-acryloyl-2,5-dimethylpyrrole. The success of this strategy provides evidence in favour of acid-catalysis at the interface being responsible for the "on-water" effect. The use of this new protocol in synthetic settings is underway in our laboratories and will be reported in due course.

Table 3 Comparative rates of reaction

	Neat^a (%)	"On-water"^{a} (%)
Methyl acrylate^b	0	21
Methyl vinyl ketone^c	66	100
N-Acryloyl-2,5 dimethylpyrrole^d	51	70

^{a} Yield of isolated product after chromatography. ^{b} Reaction time of 24 h. ^{c} Reaction time of 11 h. ^{d} Reaction time of 15 min.

Notes and references

‡ This product distribution may reflect a secondary process, as the initial mono-alkylated compound was observed to convert into the bisalkylated compound on standing.

1 H. Firouzabadi, N. Iranpoor, M. Jafarpour and A. Ghaderi, *J. Mol. Catal. A: Chem.*, 2006, **252**, 150–155.
2 Z. Duan, X. J. Xuan, T. Li, C. F. Yang and Y. J. Wu, *Tetrahedron Lett.*, 2006, **47**, 5433–5436.
3 B. A. Fetterly, N. K. Jana and J. G. Verkade, *Tetrahedron*, 2006, **62**, 440–456.
4 N. Karodia, X. H. Liu, P. Ludley, D. Pletsas and G. Stevenson, *Tetrahedron*, 2006, **62**, 11039–11043.
5 J. Nath and M. K. Chaudhuri, *Catal. Lett.*, 2009, **133**, 388–393.
6 S. S. Pawar, D. V. Dekhane, M. S. Shingare and S. N. Thore, *J. Heterocycl. Chem.*, 2008, **45**, 1869–1873.
7 V. Polshettiwar and R. S. Varma, *Tetrahedron Lett.*, 2007, **48**, 8735–8738.
8 S. P. Singh, T. V. Kumar, M. Chandrasekharam, L. Giribabu and P. Y. Reddy, *Synth. Commun.*, 2009, **39**, 3982–3989.
9 B. C. Ranu and S. Banerjee, *Tetrahedron Lett.*, 2007, **48**, 141–143.
10 M. I. Uddin, K. Nakano, Y. Ichikawa and H. Kotsuki, *Synlett*, 2008, 1402–1406.
11 J. S. Yadav, B. V. S. Reddy, T. Swamy and K. S. Shankar, *Monatsh. Chem.*, 2008, **139**, 1317–1320.
12 S. Yamazaki, M. Yamamoto and A. Sumi, *Tetrahedron*, 2007, **63**, 2320–2327.
13 F. Brotzel, Y. C. Chu and H. Mayr, *J. Org. Chem.*, 2007, **72**, 3679–3688.
14 M. J. Bhanushali, N. S. Nandurkar, S. R. Jagtap and B. M. Bhanage, *Catal. Commun.*, 2008, **9**, 1189–1195.
15 L. W. Xu, L. Li and C. G. Xia, *Helv. Chim. Acta*, 2004, **87**, 1522–1526.
16 K. De, J. Legros, B. Crousse and D. Bonnet-Delpon, *J. Org. Chem.*, 2009, **74**, 6260–6265.
17 L. W. Xu, J. W. Li, C. G. Xia, S. L. Zhou and X. X. Hu, *Synlett*, 2003, 2425–2427.
18 H. Firouzabadi, N. Iranpoor and M. Abbasi, *Adv. Synth. Catal.*, 2009, **351**, 755–766.
19 H. Firouzabadi, N. Iranpoor and A. A. Jafari, *Adv. Synth. Catal.*, 2005, **347**, 655–661.
20 L. Yang, L. W. Xu, W. Zhou, L. Li and C. G. Xia, *Tetrahedron Lett.*, 2006, **47**, 7723–7726.
21 A. G. Ying, L. M. Wang, H. X. Deng, J. H. Chen, X. Z. Chen and W. D. Ye, *ARKIVOC*, 2009, 288–298.
22 A. Scettri, A. Massa, L. Palombi, R. Villano and M. R. Acocella, *Tetrahedron: Asymmetry*, 2008, **19**, 2149–2152.
23 W. B. Chen, Y. H. Liao, X. L. Du, X. M. Zhang and W. C. Yuan, *Green Chem.*, 2009, **11**, 1465–1476.
24 K. Surendra, N. S. Krishnaveni, R. Sridhar and K. R. Rao, *Tetrahedron Lett.*, 2006, **47**, 2125–2127.
25 J. K. Beattie, C. S. P. McErlean and C. B. W. Phippen, *Chem.–Eur. J.*, 2010, **16**, 8972–8974.
26 A. Gray-Weale and J. K. Beattie, *Phys. Chem. Chem. Phys.*, 2009, **11**, 10994–11005.
27 P. Creux, J. Lachaise, A. Graciaa, J. K. Beattie and A. M. Djerdjev, *J. Phys. Chem. B*, 2009, **113**, 14146–14150.
28 R. Ballini, L. Barboni, F. Fringuelli, A. Palmieri, F. Pizzo and L. Vaccaro, *Green Chem.*, 2007, **9**, 823–838.
29 A. Lubineau, J. Auge and Y. Queneau, *Synthesis*, 1994, 741–760.
30 A. Lubineau and J. Auge, *Tetrahedron Lett.*, 1992, **33**, 8073–8074.
31 S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2005, **44**, 3275–3279.
32 D. A. Evans, G. Borg and K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2002, **41**, 3188–3191.
33 S. D. Lee, M. A. Brook and T. H. Chan, *Tetrahedron Lett.*, 1983, **24**, 1569–1572.