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An unusual Michael addition–dealkylation or elimination via the reaction of tertiary or secondary amines with a (*Z*)-iodoacrylate

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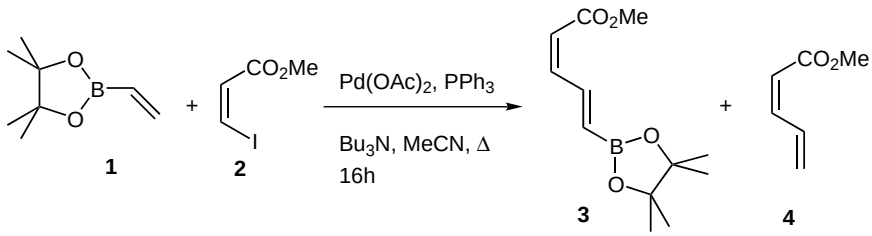
Abstract—A series of (*E*)-ammonium or amino acrylates have been prepared via the Michael addition of methyl (*Z*)-iodoacrylate and several secondary and tertiary alkylamines. Tertiary amines undergo concomitant addition–dealkylation, almost quantitatively producing (*E*)-dialkylamino acrylates.

As part of an ongoing program concerned with the total synthesis of polyene natural products[1] using palladium coupling methodology and vinyl dianion equivalent **1**,[2] we investigated suitable conditions for the coupling of methyl (*Z*)-iodoacrylate[3] **2** with vinylboronate **1** in order to try to obtain the Heck product **3** selectively over the Suzuki product **4** (Eq. (1)).



(1)

Use of phosphine and trialkylamine-free conditions [10 mol% $Pd(Oac)_2$, $AgCO_3$, MeCN, rt, 18 h] resulted in exclusive formation of the Suzuki product **4**, in 68% yield after silica gel chromatography. However, the use of standard Heck conditions (phosphine and trialkylamine-containing, as shown in Eq. (1)), gave neither of the coupled products **3** nor **4**. Instead, a new compound was isolated whose ^{1}H NMR possessed unexpected resonances at δ 4.50 (compared with δ 7.55 and 6.91 for acrylate **2**), together with signals which showed the presence of two *n*-butyl groups. We tentatively assigned this as methyl (*E*)-dibutylaminoacrylate **6b**, which may have arisen from a Michael addition–elimination sequence of tributylamine on iodoacrylate **2**, followed by loss of a butyl group. In order to confirm this series of events, further experiments[4] were performed with both secondary and tertiary amines with iodoacrylate **2**. The results of which are outlined in Eq. (2) and Table 1.

Amino acrylates **6** were typically obtained in near quantitative yields in acetonitrile using 2 equiv. of base, after isolation from the 1:1 mixture with the ammonium salt **7**. The reaction was preferably carried out in toluene, since in most cases this allowed simple separation of the salt **7** (by filtration) from the amino acrylate **6** (Table 1). Assignment of the *E*-alkene geometry of the products was unambiguous by ^{1}H NMR; all of the amino acrylates exhibited a pair of doublets with coupling constants in the range 13.1–13.5 Hz. However, analytical data[5] were in full agreement with those reported in the literature for those amino acrylates that had been previously synthesised.[6]

Our mechanistic rationale for the formation of these adducts involves a reversible addition of the amine **5** to the acrylate **2** forming an intermediate ammonium propenolate zwitterion, analogous to the first step involved in the Baylis–Hillman reaction.[7] This zwitterion would rapidly lose iodide to form a methyl 1-

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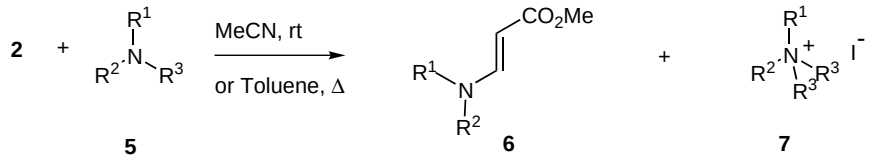


5 6 7

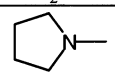
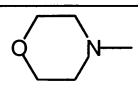
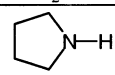
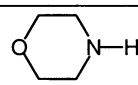
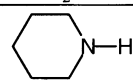
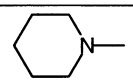
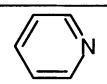
a; $R^1 = R^2 = R^3 = Et$
b; $R^1 = R^2 = R^3 = {}^nBu$
c; $R^1 = Et$, $R^2 = R^3 = {}^iPr$
d; $R^1 = R^2 = -(CH_2)_4-$, $R^3 = Me$
e; $R^1 = R^2 = -(CH_2CH_2)_2O$, $R^3 = Me$
f; $R^1 = R^2 = Et$, $R^3 = H$
g; $R^1 = R^2 = {}^iPr$, $R^3 = H$
h; $R^1 = R^2 = -(CH_2)_4-$, $R^3 = H$
i; $R^1 = R^2 = -(CH_2CH_2)_2O$, $R^3 = H$
j; $R^1 = R^2 = Bn$, $R^3 = H$
k; $R^1 = R^2 = -(CH_2)_5-$, $R^3 = H$
l; $R^1 = R^2 = -(CH_2)_5-$, $R^3 = Me$

a; $R^1 = R^2 = Et$
b; $R^1 = R^2 = {}^nBu$
c; $R^1 = Et$, $R^2 = {}^iPr$
d; $R^1 = R^2 = -(CH_2)_4-$
e; $R^1 = R^2 = -(CH_2CH_2)_2O$
f; $R^1 = R^2 = {}^iPr$
g; $R^1 = R^2 = Bn$
h; $R^1 = R^2 = -(CH_2)_5-$

a; $R^1 = R^2 = R^3 = Et$
b; $R^1 = R^2 = R^3 = {}^nBu$
c; $R^1 = Et$, $R^2 = R^3 = {}^iPr$
d; $R^1 = R^2 = -(CH_2)_4-$, $R^3 = Me$
e; $R^1 = R^2 = -(CH_2CH_2)_2O$, $R^3 = Me$
f; $R^1 = R^2 = Et$, $R^3 = H$
g; $R^1 = R^2 = {}^iPr$, $R^3 = H$
h; $R^1 = R^2 = -(CH_2)_4-$, $R^3 = H$
i; $R^1 = R^2 = -(CH_2CH_2)_2O$, $R^3 = H$
j; $R^1 = R^2 = Bn$, $R^3 = H$
k; $R^1 = R^2 = -(CH_2)_5-$, $R^3 = H$
l; **k**; $R^1 = R^2 = -(CH_2)_5-$, $R^3 = Me$

(2)

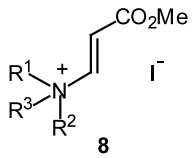
Table 1.

Entry	Amine **5**	Amino Acrylate **6** (Yield/%) in PhMe	Ammonium **7** Salt (Yield/%) in PhMe	Amino Acrylate **6** (Yield/%) in MeCN	Ammonium Salt **7** (Yield/%) in MeCN
1	Et_3N	**6a**[6a] (96)	**7a** (86)	**6a**[6a] (95)	**7a** (77)
2	$^nBu_3N$	**6b** (94)	**7b** (96)	**6b** (94)	**7b** (79)
3	$^iPr_2NEt$	**6c** (93)	**7c** (96)[b]	**6c** (91)	**7c** (70)[b]
4		[a]	[a]	**6d** (92)	**7d** (74)[b]
5		[a]	[a]	**6e** (94)	**7e** (86)
6	Et_2NH	**6a** (92)	**7f** (88)	**6a** (93)	**7f** (83)
7	$^iPr_2NH$	**6f** (94)	**7g** (96)	**6f** (90)	**7g** (77)
8		**6d** (93)	**7h** (94)	**6d** (91)	**7h** (72)
9		**6e** (92)	**7i** (94)	**6e** (93)	**7I** (72)
10	Bn_2NH	**6g** (94)	**7j** (94)	**6g** (95)	**7j** (90)
11		**6h** (91)	**7k** (92)	**6h** (93)	**7k** (91)
12		[a]	[a]	**6h** (94)	**7l** (88)
13		0[c]	0[c]	0[c]	0[c]
14	Et_2NPh	0[d]	0[d]	0[d]	0[d]

[a]Obtained the corresponding methyl *E*-ammoniumpropenoate iodide **8** quantitatively. [b]Salt not isolated; yield was estimated from ^1H NMR of crude reaction. [c]Complex mixture of products results. [d]No reaction observed.

ammoniumpropenoate iodide **8**. In both acetonitrile and toluene, subsequent reaction of iodide ion on salt **8** accomplishes dealkylation, giving rise to an alkyl iodide, which in turn reacts with the second equivalent of amine **5** yielding the salt **7** in almost all cases (see Table 1). The exceptions to this are entries 4, 5 and 12 (Table 1), where *N*-methylated cyclic tertiary amines are employed. For these cases, in acetonitrile, dealkylation occurs as for other amines, however in toluene, the methyl 1-ammoniumpropenoate iodide salt **8** rapidly

precipitates before dealkylation can occur allowing its isolation.[5] In addition, it is interesting that loss of ^{i}Pr occurs in preference to loss of Et when using Hünig's base (entry 3, Table 1), which suggests that in this case an S_N1 reaction is involved in the iodide-mediated dealkylation process. In contrast, the less nucleophilic base, diethylaniline, did not react under the reaction conditions employed, whereas pyridine did react resulting in a complex mixture of products.



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Reported uses for amino acrylates are quite scarce;[6] there are a few examples of them being utilised in natural product chemistry, but in each case they have been prepared through reaction of a secondary amine with a propiolate ester. There are also reports detailing the preparation of *trans*-ammonium halides **8** as stable compounds[8] and their subsequent use as Diels–Alder dienophiles.[9] These salts are usually prepared by reaction of a quaternary ammonium chloride or bromide with a propiolate ester under slightly milder conditions and in these cases there were no reports of amino acrylate formation, suggesting that elimination of iodide leading to amino acrylate formation is a facile process compared with loss of chloride or bromide.

To the best of our knowledge, the reaction presented here represents an unusual example of dealkylation from nitrogen and provides a simple, high-yielding route to a variety of amino acrylates.

Acknowledgements

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4. Representative procedure: A mixture of iodoacrylate **2** (200 mg, 0.943 mmol) and $^{i}Pr_2NEt$ (314 μL, 2 equiv.) were refluxed in dry toluene (5 ml) under argon until TLC indicated consumption of **2**. The cooled reaction was filtered and the filtrate washed with 5% HCl and distilled water. The organic phase was dried over $MgSO_4$ and concentrated in vacuo to give the crude amino acrylate. Purification by silica gel chromatography (petroleum ether 40–60:ethyl acetate, 4:1 as eluant) gave methyl (*E*)-3-[ethyl(isopropyl)amino]-2-propenoate **6c** (93%, yellow oil): ν_{max} (film)/cm^{-1} 2966, 1685, 1600, 1420, 1188, 1106, 785; δ_H (300 MHz, $CDCl_3$) 1.10–1.25 (9H, m, 3×Me), 3.12 (2H, q, *J* 7.5, CH_2), 3.50 (1H, m, *J* 7.5, CH), 3.65 (3H, s, OCH_3), 4.55 (1H, d, *J* 13.7, =CH), 7.50 (1H, d, *J* 13.7, =CH); δ_C (75.5 MHz) 11.7 (CH_3), 21.3 [$CH(CH_3)_2$], 40.0 (NCH_2CH_3), 47.0 [$CH(CH_3)_2$], 49.3 (OCH_3), 82.1 (=CH), 148.4 (=CH), 169.4 (C=O); accurate *m*/*z* (ES+) 172.1335 (100%, MH^+, $C_9H_{18}NO_2^+$ requires *m*/*z* 172.1337).
5. All new compounds gave satisfactory NMR, IR and HRMS data. Selected data: **6b** δ_H (300 MHz, $CDCl_3$) 0.9 (6H, t, *J* 7.5, 2×CH_3), 1.27 (4H, m, 2×CH_2), 1.50 (4H, m, 2×CH_2), 3.1 (4H, bm, 2×CH_2), 3.62 (3H, s, OCH_3), 4.50 (1H, d, *J* 13.2, =CH), 7.40 (1H, d, *J* 13.2, =CH); δ_C (75.5 MHz, $CDCl_3$) 14.3 (CH_3), 20.3 (CH_2), 29.3 (CH_2), 50.6 (OCH_3), 55.5 (CH_2), 83.6 (=CH), 152.1(=CH), 170.5 (C=O), 170.7 (C=O); **6d** δ_H (300 MHz, $CDCl_3$) 1.90 (4H, bm, 2×CH_2), 3.10 (4H, bm, 2×CH_2), 3.60 (3H, s, OCH_3), 4.45 (1H, d, *J* 13.1, =CH), 7.60 (1H, d, *J* 13.1, =CH); δ_C (75.5 MHz, $CDCl_3$) 24.2 (CH_2), 49.3 (CH_2), 83.2 (=CH), 147.7 (=CH), 168.9 (C=O); **6e** δ_H (300 MHz, $CDCl_3$) 3.17 (4H, t, *J* 7.0, 2×CH_2), 3.65 (7H, m, OCH_3 and 2×CH_2), 4.67 (1H, d, *J* 13.4, =CH), 7.33 (1H, d, *J* 13.4, =CH); δ_C (75.5 MHz, $CDCl_3$) 47.6 (CH_2), 50.3 (OCH_3), 65.1 (CH_2), 84.9 (=CH), 150.8 (=CH), 168.8 (C=O); **6f** δ_H (300 MHz, $CDCl_3$) 1.15 (12H, s, 2×-$(CH_3)_2$), 3.60 (5H, bs, OCH_3 and 2×CH), 4.65 (1H, d, *J* 13.5, =CH), 7.55 (1H, d, *J* 13.5, =CH); δ_C (75.5 MHz, $CDCl_3$) 20.5 (b, CH_3), 47.0 (CH), 49.3 (OCH_3), 82.1 (=CH), 146.2 (=CH), 169.4 (C=O); **6g** δ_H (300 MHz, $CDCl_3$) 3.68 (3H, s, OCH_3), 4.30 (4H, bs, 2×CH_2), 4.83 (1H, d, *J* 13.1, =CH), 7.40–7.10 (10H, m, ArH), 7.83 (1H, d, *J* 13.1, =CH); δ_C (75.5 MHz, $CDCl_3$) 37.6 (CH_2), 51.7 (OCH_3), 85.9 (=CH), 126.9 (ArC), 128.8 (ArC), 130.1 (ArC), 138.2 (ArCq), 153.2 (=CH), 170.6 (C=O); **6h** δ_H (400 MHz, $CDCl_3$) 1.60 (6H, bs, 3×CH_2), 3.19 (4H, bs, 2×CH_2), 3.65 (3H, s, OCH_3), 4.61 (1H, d, *J* 13.1, =CH), 7.40 (1H, d, *J* 13.1, =CH); δ_C (75.5 MHz, $CDCl_3$) 24.5 (CH_2), 25.8 (CH_2), 50.8 (OCH_3), 52.0 (CH_2), 83.6 (=CH), 152.5 (=CH), 170.9 (C=O); **8** ($R^1=R^2=(CH_2)_4$, R^3=Me) δ_H (400 MHz, D_2O) 2.18 (4H, bm, CH_2), 3.44 (3H, s, NMe), 3.78 (3H, s, OMe), 3.89 (4H, bm, CH_2), 6.19 (1H, d, *J* 9.7, =CH), 6.65 (1H, d, *J* 9.7 Hz, =CH); δ_C (75.5 MHz, D_2O) 21.8 (CH_2), 50.9 (NMe), 53.7 (OMe), 68.9 (CH_2), 120.3 (=CH), 147.4 (=CH), 164.6 (C=O); ($R^1=R^2=(CH_2CH_2)_2O$, R^3=Me) δ_H (400 MHz, D_2O) 3.53 (3H, s, NMe), 3.73 (3H, s, OMe), 3.89–4.12 (8H, bm, 4×CH_2), 6.32 (1H, d, *J* 10.4, =CH), 6.58 (1H, d, *J* 10.4, =CH); δ_C (75.5 MHz, D_2O) 53.7 (NMe), 54.2 (OMe), 62.1 (CH_2), 64.1 (CH_2), 122.0 (=CH), 140.5 (=CH), 164.3 (C=O); ($R^1=R^2=(CH_2)_5$, R^3=Me) δ_H (400 MHz, D_2O) 1.48 (2H, bm, CH_2) 1.66–1.82 (4H, bm, CH_2), 3.40 (3H, s, NMe), 3.37–3.46 (4H, bm, CH_2), 3.74 (3H, s, OMe), 6.24 (1H, d, *J* 10.4, =CH), 6.43 (1H, d, *J* 10.4, =CH); δ_C (75.5 MHz, D_2O) 20.2 (CH_2), 21.3 (CH_2), 53.8 (NMe), 54.1 (OMe), 65.7 (CH_2), 121.0 (=CH), 140.6 (=CH), 164.8 (C=O).
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