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Tributylphosphine-catalyzed Stetter reaction of *N*,*N*-dimethylacrylamide: synthesis of *N*,*N*-dimethyl-3-aroylpropionamides

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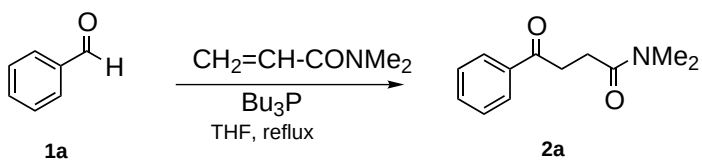
Abstract—The reaction of arylaldehydes **1** and *N*,*N*-dimethylacrylamide in the presence of tributylphosphine afforded *N*,*N*-dimethyl-3-aroylpropionamides **2** in moderate yields. The reaction might involve the formation of α-oxo ylide **A**.

The Baylis–Hillman reaction is well known as a coupling reaction of aldehydes and activated alkenes catalyzed by tertiary amines or tertiary phosphines.[1] Activated alkenes involve ethyl acrylate, acrylonitrile, alkyl vinyl ketone, aryl vinyl sulfone, etc.[1] However, acrylamides cannot be used as a electrophile in the Baylis–Hillman reaction in usual reaction conditions due to the diminished electrophilicity of the β-position of acrylamides.[1,2] The Baylis–Hillman adduct of acrylamide was obtained in low yield in certain reaction conditions such as under high pressure or under microwave irradiation conditions.[2]

Recently, mild cooperative catalytic activity of phenol derivatives in the Baylis–Hillman reaction with tributylphosphine (Bu_3P) was reported.[3] Phenol acts as a Brϕnstead acid to activate the carbonyl group of an aldehyde and a polarized alkene in the reaction. Thus, we envisioned that the use of phenol in the Baylis–Hillman reaction of *N*,*N*-dimethylacrylamide and benzaldehyde could afford the Baylis–Hillman adduct. We examined the reaction of benzaldehyde (**1a**) and *N*,*N*-dimethylacrylamide in THF in the presence of Bu_3P and phenol as our continuing program on the Baylis–Hillman reaction.[4] However, no expected Baylis–Hillman adduct was obtained in the reaction. Instead, we could isolate *N*,*N*-dimethyl-3-benzoylpropionamide (**2a**)[5] in 52% yield as an oil. The reaction could also be conducted without phenol (Scheme 1).

The reaction mechanism could be suggested as follows as Stetter have proposed in a similar reaction.[6] Tributylphosphine attacked benzaldehyde to generate the tautomeric betaine-ylide species **A**,[7] which was added to *N*,*N*-dimethylacrylamide in a 1,4-fashion to give the product after elimination of Bu_3P (pathway (i) in Scheme 2). The catalyzed nucleophilic addition of aldehyde to electrophilic double bond, known as Stetter reaction, is a rapid and efficient method for the preparation of 1,4-dicarbonyl compounds.[6] Cyanide ion and thiazolium salt were used as the catalyst in the Stetter reaction. Although almost all of the electrophilic double bonds have been used in the Stetter reaction, the reaction of acrylamides was not mentioned in the litera-



Scheme 1.

Keywords: tributylphosphine; Stetter reaction; Baylis–Hillman reaction; acrylamide.
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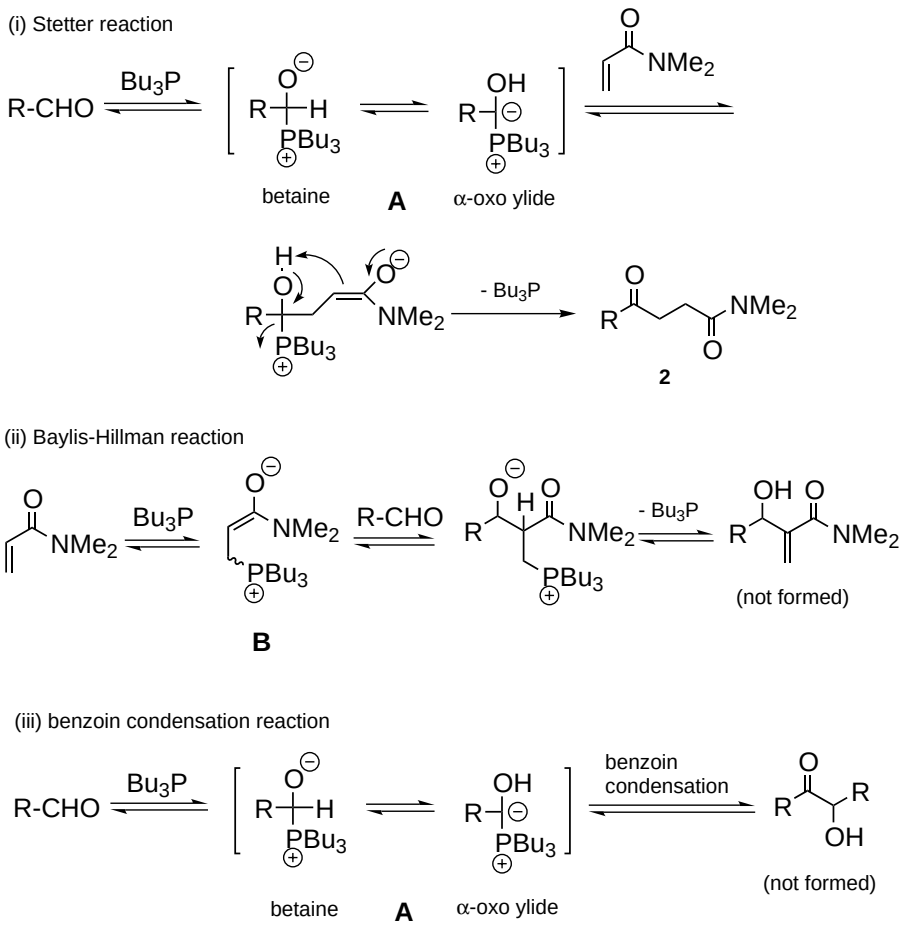
ture.[6] Moreover, Bu_3P catalyzed Stetter reaction have not been reported.

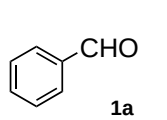
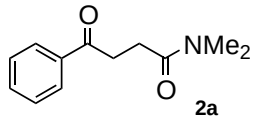
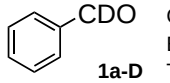
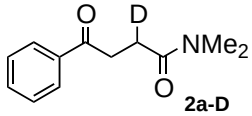
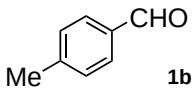
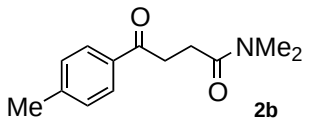
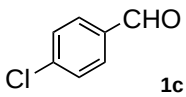
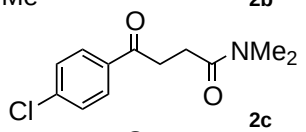
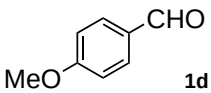
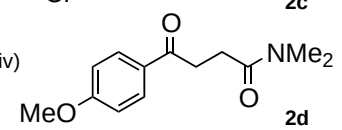
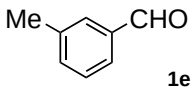
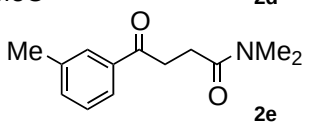
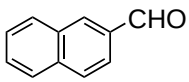
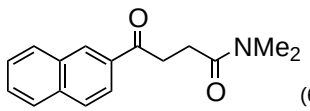
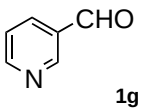
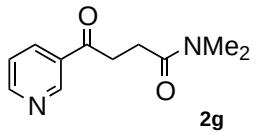
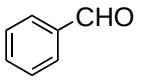
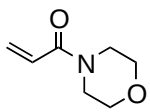
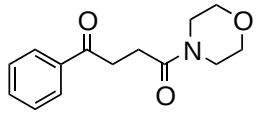
The other possible reaction pathways in the reaction conditions were also depicted in Scheme 2. The reversible addition reactions of Bu_3P either to aldehyde (1,2-fashion, pathway (i) and (iii) in Scheme 2) or *N*,*N*-dimethylacrylamide (1,4-fashion, pathway (ii) in Scheme 2) might be a competition. In our reaction conditions, neither the Baylis–Hillman products nor the benzoin condensation products were observed. The β-position of *N*,*N*-dimethylacrylamide is less electrophilic than the other normally used activated alkenes in the Baylis–Hillman reaction such as ethyl acrylate, acrylonitrile, alkyl vinyl ketone or aryl vinyl sulfone.[1,2] Thus, we could not obtain the Baylis–Hillman adducts. Instead, 1,2-addition of Bu_3P toward benzaldehyde occurred predominantly in our reaction conditions. The initially formed oxyanion (betaine form) was in equilibrium with the tautomeric carbanion (ylide form).[7] The ylide form resembled the carbanion in the benzoin condensation. However, to our disappointment, there was no benzoin condensation product in the reaction mixtures as mentioned before even in the absence of *N*,*N*-dimethylacrylamide. This might be explained as follows. Addition of the carbanion to benzaldehyde leading to the benzoin condensation product is reversible, while the conjugate addition to *N*,*N*-dimethylacrylamide leading to **2** is irreversible as reported.[6] Moreover, it seemed that the sterically hindered **A** could not attack the carbonyl carbon of benzaldehyde. In order to clarify the reaction mechanism we examined the reaction with benz(aldehyde-d) (**1a**–**D**) and obtained the expected deuterium-labeled **2a**–**D** in 41% yield (see entry 2 in Table 1).

As shown in Table 1 various aromatic aldehydes **1a**–**g** gave the corresponding Stetter type products **2a**–**g** in reasonable yields. Replacement of Bu_3P to Ph_3P did not give the products at all. The use of DABCO was also ineffective. The use of catalytic amounts of Bu_3P required long reaction time to obtain appreciable amounts of products. It is interesting to note that the use of cyanide ion or thiazolium salt (3-benzyl-5-(2-hydroxyethyl)-4-methyl thiazolium chloride) in the reaction was ineffective for the synthesis of **2**. By using 4-acryloylmorpholine the corresponding product **2a′** was obtained similarly (entry 9).[5e,5f] However, when we used sterically hindered aldehydes such as **1h** and **1i**, the formation of intermediate **A** was inhibited and we could not obtain the desired compounds **2h** and **2i**. Instead, we could isolate the allylic alcohol derivatives **3h** and **3i** in moderate yields (Scheme 3).[8] The plausible mechanism for the formation of these compounds was



Scheme 2.

Table 1. Synthesis of *N*,*N*-dimethyl-3-aroylpropionamides **2**

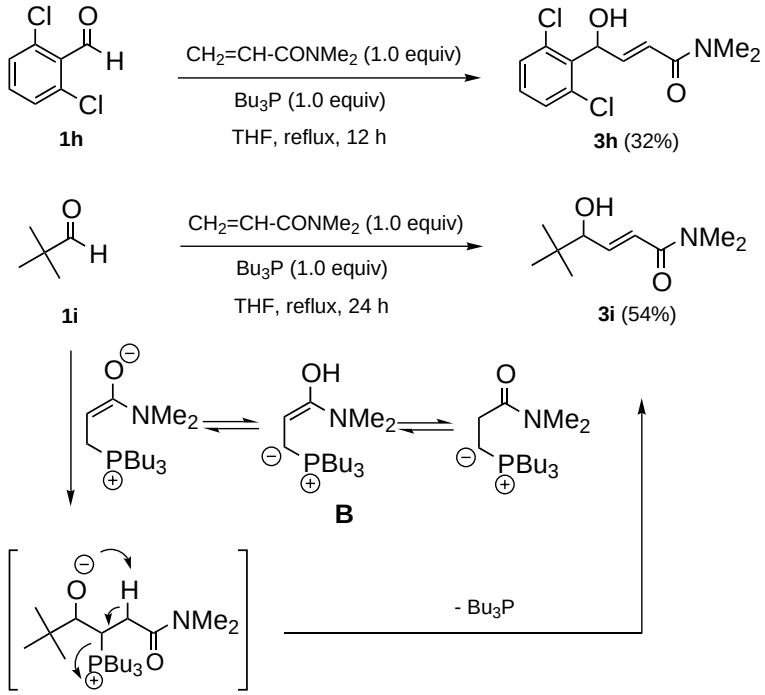
entry	aldehyde (**1**)	conditions	product (**2**)	yield (%)[a]
1	 **1a**	CH_2=CHCONMe$_2$ (1.5 equiv) Bu_3P (1.0 equiv) THF, reflux, 2 h	 **2a**	52 (oil)
2	 **1a-D**	CH_2=CHCONMe$_2$ (1.0 equiv) Bu_3P (1.0 equiv) THF, reflux, 3 h	 **2a-D**	41[b] (oil)
3	 **1b**	CH_2=CHCONMe$_2$ (1.5 equiv) Bu_3P (1.0 equiv) THF, reflux, 2 h	 **2b**	61 (59-61)
4	 **1c**	CH_2=CHCONMe$_2$ (0.5 equiv) Bu_3P (0.5 equiv) THF, 40-50 °C, 3 h	 **2c**	49[c] (101-102)
5	 **1d**	CH_2=CHCONMe$_2$ (0.7 equiv) Bu_3P (0.7 equiv) THF, refulx, 4 h	 **2d**	58[c] (69-70)
6	 **1e**	CH_2=CHCONMe$_2$ (0.5 equiv) Bu_3P (0.5 equiv) THF, reflux, 4 h	 **2e**	53[c] (oil)
7	 **1f**	CH_2=CHCONMe$_2$ (1.0 equiv) Bu_3P (1.0 equiv) THF, 40-50 °C, 3 h	 **2f**	58 (69-71)
8	 **1g**	CH_2=CHCONMe$_2$ (1.0 equiv) Bu_3P (1.0 equiv) THF, reflux, 2 h	 **2g**	68 (oil)
9	 **1a**	 (1.0 equiv) Bu_3P (1.0 equiv) THF, reflux, 2 h	 **2a'**	61 (71-73)

[a]Isolated yield based on aldehyde, mp was written below. [b]Small amounts of **2a** was contaminated, which might be produced due to trace amounts of moisture in the reaction mixture.[8] [c]Based on *N,N*-dimethylacrylamide.

shown for **3i**. For the sterically hindered aldehydes, addition of Bu_3P occurred firstly in a 1,4-fashion to give the intermediate **B** (pathway (ii) in Scheme 2). The reaction of **B** and **1i** gave **3i** after elimination of Bu_3P. However, the reaction with other aliphatic aldehydes such as hexanal and isobutyraldehyde shows complex mixtures on TLC. The reaction with other acrylamides such as *N*-*tert*-butylacrylamide and acrylamide shows sluggish reaction. Thus, we could isolate neither the Stetter type products nor the allylic alcohol derivatives in reasonable yields.

The reaction of benzaldehyde (entry 1 in Table 1) is typical: A mixture of benzaldehyde (212 mg, 2.0 mmol), Bu_3P (405 mg, 2.0 mmol) and *N*,*N*-dimethylacrylamide (297 mg, 3.0 mmol) in THF (10 mL) was heated to reflux for 2 h. After the usual workup process and column chromatographic purification (CH_2Cl_2/ether, 2:1) pure **2a** was isolated as a colorless oil, 214 mg (52%).[5,8]

In conclusion, we disclosed the facile synthesis of *N*,*N*-dimethyl-3-aroylpropionamides in moderate yields by the tributylphosphine catalyzed Stetter type reaction for the first time. The studies on the general applicability of the reaction with various acrylamides and the intramolecular version of the reaction are currently underway.



Scheme 3.

Acknowledgements

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8. Some representative spectroscopic data of **2a**, **2a**–**D** and **3h** are as follows.

2a: 214 mg (52%); colorless oil; IR (KBr) 2925, 1685, 1647 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.77 (t, $J=6.6$ Hz, 2H), 2.95 (s, 3H), 3.09 (s, 3H), 3.35 (t, $J=6.6$ Hz, 2H), 7.42–8.03 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 27.23, 33.68, 35.62, 37.22, 128.12, 128.53, 133.09, 136.75, 172.02, 199.37; mass (70 eV) m/z (rel. intensity) 77 (47), 105 (100), 133 (29), 161 (87), 205 (M^+, 31). **2a–D**: colorless oil; ^1H NMR (500 MHz, $CDCl_3$) δ 2.78 (t, $J=6.5$ Hz, 1H), 2.96 (s, 3H), 3.10 (s, 3H), 3.35 (d, $J=6.5$ Hz, 2H), 7.46 (t, $J=7.5$ Hz, 2H), 7.55 (t, $J=7.5$ Hz, 1H), 8.02 (d, $J=7.5$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.89 (t, $J=19.6$ Hz, CH), 33.50 (CH_2), 35.40 (CH_3), 37.00 (CH_3), 127.99 (CH), 128.41 (CH), 132.90 (CH), 136.79 (C), 171.58 (C), 199.21 (C); mass (70 eV) m/z (rel. intensity) 72 (53), 101 (23), 105 (100), 134 (17), 162 (43), 206 (M^+, 19). **3h**: white solid; mp 119–120°C; IR (KBr) 3259, 2927, 1657, 1591 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.00 (s, 3H), 3.08 (s, 3H), 3.55 (d, $J=9.5$ Hz, 1H, D_2O exchangeable), 6.14 (ddd, $J=9.5$, 4.2 and 2.1 Hz, 1H), 6.57 (dd, $J=15.2$ and 2.1 Hz, 1H), 6.99 (dd, $J=15.2$ and 4.2 Hz, 1H), 7.17 (t, $J=7.9$ Hz, 1H), 7.30 (d, $J=7.9$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 35.75, 37.45, 70.91, 120.62, 129.33, 129.62, 134.63, 135.63, 143.03, 166.23; mass (70 eV) m/z (rel. intensity) 72 (49), 100 (100), 173 (84), 175 (55), 201 (16), 244 (18), 273 (M^+, 10), 275 (M^++2, 7).