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Communications to the Editor

Formation of Acrylanilides, Acrylamides, and Amides Directly from Carboxylic Acids Using Thionyl Chloride in Dimethylacetamide in the Absence of Bases

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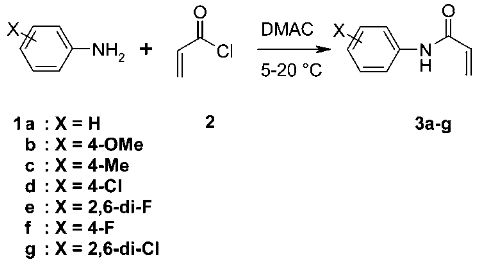
Abstract:

A general one-pot procedure is described that rapidly converts acrylic acid to anilides upon sequential treatment of the acid in dimethylacetamide (DMAC) with thionyl chloride and stoichiometric amounts of anilines in 88−98% yields, with DMAC offering rate and stability advantages over the use of DMF. The use of DMAC was extended to other organic acids in forming anilides. Benzylamine amides can also be formed using stoichiometric amounts of benzylamine and brought to completion by warming in the absence of additional base. In addition, it was shown that *tert*-butylamides can be easily formed with the addition of excess *tert*-butylamine at 20 °C.

The need to prepare a variety of acrylanilides from anilines **1** and acryloyl chloride **2**, in particular 2,6-dichloroacrylanilide **3g**, in support of a large-scale synthesis project was initially satisfied by the addition of aniline **1g** to acryloyl chloride in Et_2O or CH_2Cl_2 with amine bases, providing isolated yields of only 40%,[1] even in the presence of excess base or acryloyl chloride. This was due to the insolubility of 2,6-dichloroaniline HCl salt that formed in the reaction. Requiring kilogram quantities of acrylanilide **3g**, the low yield of this procedure necessitated the exploration of alternative procedures. It was found that when acryloyl chloride in DMF at 0−5 °C was treated with 1 equiv of aniline **1g** in the absence of base, a slow reaction ensued at 20 °C that required warming to 60 °C to achieve complete reaction. This procedure gave a 90% yield of acrylanilide **3g**. It was observed, however, that at 60−70 °C polymerization of product can occur under these highly acidic conditions. When dimethylacetamide (DMAC) was used in place of DMF, a slightly exothermic reaction occurred at 5 °C, which when warmed to 15−20 °C resulted in the complete formation of acrylanilide **3g**. Product was isolated by crystallization in 90% yield with the simple addition of water to the reaction. The series of anilines **1a−g** were all successfully converted to acrylanilides **3a−g** and isolated in 88−98% isolated yields as crystalline solids (Scheme 1).

Scheme 1. **Synthesis of acrylanilides 3a−g from acryloyl chloride**



Although excellent yields of anilides were recently reported by Chen et al.[2] using acryloyl chloride in acetone/water/base, the cost of acryloyl chloride (∼$300/kg for multikilogram orders) relative to the cost of acrylic acid (<$6/kg) and thionyl chloride (<$3/kg) led us to directly convert acrylic acid to acrylanilide **3g** in a one-pot reaction in DMAC with thionyl chloride and aniline **1g**.[3] Indeed, when acrylic acid was dissolved in DMAC at −5 °C and treated sequentially with thionyl chloride [**Note: thionyl chloride reacts with DMAC at 20 °C; therefore, thionyl chloride should be added neat.]** and 2,6-dichloroaniline and warmed to 20 °C and then crystallized with water, a 95% yield of acrylanilide **3g** was isolated.[4]

A solvent comparison between DMAC, DMF, and NMP[5] using anilines **1a** and **1g** was conducted. In DMF, coupling with aniline **1g** required warming and was prone to polymerization, as stated above, while aniline **1a** gave anilide **3a** rapidly at 0−20 °C but in only 37% yield. In NMP, aniline **1g** gave anilide **3g** in 92% yield, similar to DMAC in reaction rate and yield, but aniline **1a** gave anilide **3a** in only 63% yield.

The generality of anilide formation in DMAC with this simple procedure with other acids (**4−9**) was tested and is

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(1) (a) Falbe, J.; Korte, F. *Chem. Ber.* **1962**, *95*, 2680.

(2) Chen, I.-L.; Wang, T.-C.; Chen, Y.-L.; Tzeng, C.-C. *J. Chin. Chem. Soc.* **2000**, *47*, 155. (b) Wang, E.-C.; Huang, K.-S.; Lin, G.-W.; Lin, J.-R. *J. Chin. Chem. Soc.* **2001**, *48*, 83.

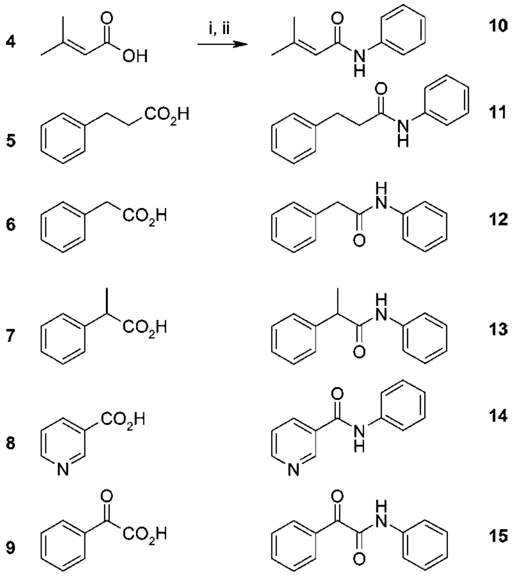
(3) (a) For a comprehensive listing of methods for conversion of carboxylic acids to amides up to 1999, see: Larock, R. C. *Comprehensive Organic Transformations,* 2nd ed.; Wiley-VCH: New York, 1999; pp 1932−1941. More recently: (b) Shiina, I.; Kawakita, Y.-i. *Tetrahedron* **2004**, *60*, 4729 used benzoic anhydrides. (c) Kunishima, M.; Kawachi, C.; Morita, J.; Terao, K.; Iwasaki, F.; Tani, S. *Tetrahedron* **1999**, *55*, 13159 used 2-chloro-4, 6-dimethoxy-1, 3, 5-triazine (CDMT). (d) Sheng, S.-R.; Wang, X.-C.; Liu, X.-L.; Song, C.-S. *Synth. Commun.* **2003**, *33*, 2867 used solid-phase synthesis. (e) Kunishima, M.; Kawachi, C.; Hioki, K.; Terao, K.; Tani, S. *Tetrahedron* **2001**, *57*, 1551 used 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM). (f) Srinivas, K. V. N. S.; Das, B. *J. Org. Chem.* **2003**, *68*, 1165 used Fe^{3+}-K-10 Montmorillonite clay.

(4) Carboxylic acid conversion to aniline-amides in DMAC: see Morris, J. J.; Hughes, L. R.; Glen, A. T.; Taylor, P. J. *J. Med. Chem.* **1991**, *34*, 447.

(5) NMP in methylene chloride was used in making *N*-phenylbenzamide: Higashi, F.; Nishi, T. *J. Polym. Sci., Part A: Polym. Chem.* **1986**, *24*, 701.

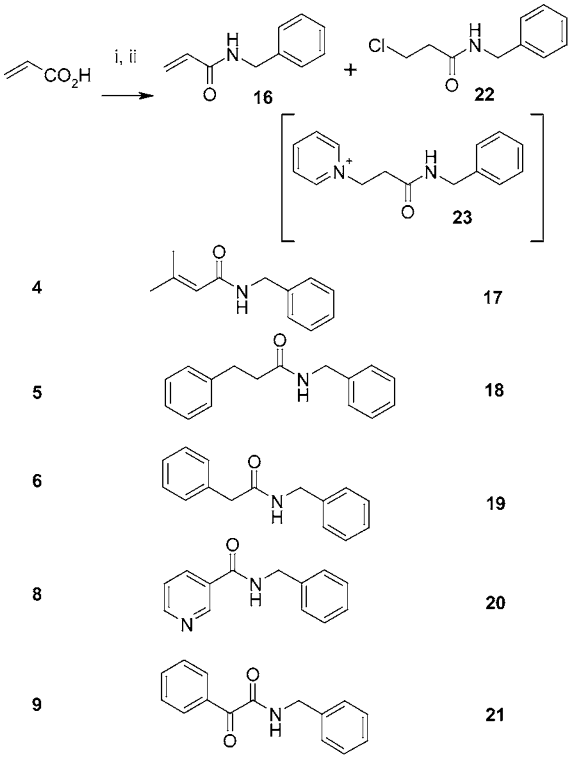
10.1021/op060125+ CCC: $33.50

Scheme 2. **Anilides from carboxylic acids using DMAC and $SOCl_2$**[a]



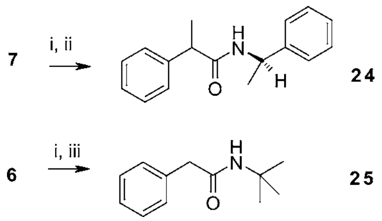
[a] Reagents and conditions: i, DMAC, −5 °C, $SOCl_2$; ii, aniline, 0−20 °C.

Scheme 3. **Benzyl amides from acids using DMAC and $SOCl_2$**[a]



[a] Reagents and conditions: i, DMAC, −5 °C, $SOCl_2$; ii, benzylamine, 0−60 °C.

Scheme 4. **Hindered amides using DMAC and $SOCl_2$**[a]



[a] Reagents and conditions: i, DMAC, $SOCl_2$; ii, (*R*)-methyl benzylamine; iii, *t*-butylamine.

shown in Scheme 2. In each case, reactions were complete within 1 h and gave >90% isolated yields of anilides **10**−**15**.

It was anticipated that the use of stoichiometric amounts of primary amines such as benzylamine, which are stronger bases than aniline, would lead to only 50% conversion to amides. Indeed, after addition of benzylamine to a mixture of acid **5**, DMAC, and $SOCl_2$ at −5 °C a 1:1 mixture of acid:amide was observed. However, after warming to 50 °C, the reaction achieved 100% conversion and resulted in a 90% isolated yield of amide **18**. In this way, acrylic acid and acids **4**, **5**, **6**, **8**, and **9** were readily converted to benzylamides **16**−**21**, each in >80% yield, except for acrylic acid, which produced a mixture (80:20) of acrylamide **16** and chloropropylamide **22** (Scheme 3).

The most rapid conversion to amide occurred with nicotinic acid **8**. When pyridine was added to acrylic acid after the addition of benzylamine, the conversion proceeded rapidly at 20 °C to produce a mixture of amide **16** and pyridine adduct **23** (observed and analyzed by HPLC and LC/MS). When the reaction was quenched with water and adjusted to pH 10, this species converted to amide **16**, which was isolated in 75% yield.

When acid **7** was treated with thionylchloride and (*R*)-methylbenzylamine, similar to benzyl amine, the reaction proceeded to 50% conversion to amide **24**[3b] at −5 to 0 °C and then was completed when heated to 55 °C (Scheme 4).

The preparation of *tert*-butylamides was also accomplished but required the use of excess *tert*-butylamine. After warming to 20 °C, amide **25**[3c] was obtained in an 80% yield from acid **6** (see Scheme 4). The need for excess *tert*-butylamine, in this case, is due to *tert*-butylamine HCl salt insolubility in DMAC.

Summary

Acrylic acid and a variety of other carboxylic acids were smoothly converted to anilides, benzyl amides, and *tert*-butyl amides in high isolated yields by the action of thionyl chloride and the aniline/amine in dimethylacetamide. Complete reactions can be achieved using stoichiometric quantities of acid and amine in the *absence* of bases (i.e., neither excess aniline/amine nor other bases such as TEA, pyridine), with the exception of *tert*-butylamine.

Experimental

Formation of Acrylanilides, General Procedure from Acryloylchloride. Aniline (0.25 mol) was dissolved in *N*,*N*-dimethylacetamide (80 mL) and cooled to −5 °C in a mechanically stirred round-bottom flask equipped with a nitogen inlet and an aqueous NaOH scrubber. Acryloyl chloride (22 mL, 0.27 mol) was added dropwise over 45 min while maintaining the reaction temperature at <0 °C. **[Note: the atmosphere above the reaction contains HCl, and the reaction should be vented to a scrubber.]** After stirring for 15 min, the near homogeneous mixture was warmed to 20 °C and stirred for 1 h. Water (300 mL) was added dropwise over 1 h while stirring with a mechanical stirrer. The reaction mixture initially became homogeneous then produced a thick crystalline slurry. After stirring for 1 h at 20 °C the product was recovered by filtration, washed with water (3 × 20 mL), and then dried in vacuo at 50 °C.

Formation of Amides from Acid, General Procedure. A solution of dimethylacetamide (80 mL) and the chosen acid (0.25 mol) was cooled to −5 °C in a mechanically stirred round-bottom flask equipped with a nitogen inlet and an aqueous NaOH scrubber. Thionyl chloride (0.27 mol) was added dropwise (by addition funnel or syringe) over 15 min. [**Note: thionyl chloride reacts with DMAC, so it is added neat.**[7]] After stirring for 10 min, the amine or aniline (0.25 mol) (or 1.0 mol as in the case of *tert*-butylamine), either neat or as a solution in DMAC, was added over 15−30 min. Upon complete addition, the mixture was warmed to 20 °C **[Note: the atmosphere above the reaction contains HCl, and the reaction should be vented to a scrubber.]** and stirred for up to 1 h (or warmed to 50 °C when necessary). With the reaction mixture at 20 °C, water (300 mL) was added dropwise over 1 h while stirring with a mechanical stirrer. After stirring for 1 h at 20 °C the product was recovered by filtration, washed with water (3 × 20 mL), and then dried in vacuo at 50 °C. For amides **11** and **16**, product was precipitated by the addition of 1 N NaOH to bring the pH to 7. In cases where an oil was formed (i.e., **12**), product was extracted with MTBE.

The following compounds are known in the literature: (**3a**, **c**, **d**, **f**),[3d] **3b**,[2b] **3g**,[1] **10**,[6a] **11**,[3b] **12**,[3f] **13**,[3b] **14**,[6b] **15**,[6c] **16**,[3d] **17**,[6d] **18**,[3b] **19**,[3f] **20**,[6e] **21**,[6f] **24**,[3b] **25**.[3c]

***N*-(2,6-Difluorophenyl)acrylamide (3e):** ^{1}H NMR (400.25 MHz) d_6-DMSO: δ 9.90 (s, 1H), 7.36 (om, 1H), 7.18 (om, 2H), 6.47 (dd, $J = 17.1$, 10.2 Hz, 1H), 6.27 (dd, $J = 17.2$, 1.9 Hz, 1H), 5.80 (dd, $J = 10.2$, 1.9 Hz, 1H). ^{13}C NMR (100.65 MHz) $CDCl_3$: δ 163.4, 157.7 (dd, $J = 248.8$, 5.4 Hz, 2C), 130.4, 128.0 (t, $J = 9.9$ Hz), 127.7, 114.3 (t, $J = 16.9$ Hz), 111.8 (dd, $J = 17.9$, 5.1 Hz, 2C). HRMS (ES^+) calcd for $C_9H_7F_2NO$ (M + 1) 184.0568, found 184.0575.

Supporting Information Available

^{1}H NMR and ^{13}C NMR spectra for compounds **3a**−**3g**, **10**−**21**, **24**, and **25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) (a) Evans, D. A.; Wu, J. *J. Am. Chem. Soc.* **2005**, *127*, 8006. (b) Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327. (c) Tani, K.; Suwa, K.; Tanigawa, E.; Ise, T.; Yamagata, T. *J. Organomet. Chem.* **1989**, *370*, 203. (d) Greico, P. A.; Clark, D. S.; Withers, G. P. *J. Org. Chem.* **1979**, *44*, 2945. (e) Pop, I. E.; Deprez, B. P.; Tartar, A. L. *J. Org. Chem.* **1997**, *62*, 2594. (f) Steglich, W.; Schmidt, H.; Hollitzer, O. *Synthesis* **1978**, *78*, 622.

(7) When thionyl chloride (2 ml) is added to DMAC (10 ml) at 20 °C, an exothermic reaction ensues, and the temperature rises to 65 °C over 20 min with the mixture turning dark brown. At −5 °C, no exotherm was observed, but it is preferred to add the thionyl chloride neat.