Chemoselective Acylation of Amines in Aqueous Media

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Dedicated to Professor Asutosh Nayak[‡]

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Amines are efficiently acylated by both cyclic and acyclic anhydrides by dissolving them in an aqueous medium with the help of a surfactant, sodium dodecyl sulfate (SDS). Cyclic and acyclic anhydrides react with equal ease with an amine, and amines with various stereo-electronic factors react at the same rates with an anhydride. Chemoselective acylation of amines in the presence of phenols and thiols and of thiols in the presence of phenols has been achieved. No acidic or basic reagents are used during the reaction. No chromatographic separation is required for isolation of the acylated products. Reactions in a neutral aqueous medium, easy isolation of products, and innocuous by-products make the present method a green chemical process.

Introduction

A crucial factor for green chemical processes in solution involves the choice of cheap, safe and nontoxic solvents. Water, being abundant in nature, is the obvious choice. Water is not just a "green" solvent, but also has special effects on reactions arising from intra- and inter-molecular noncovalent interactions leading to novel solvation and assembly processes. Since Breslow's discovery of a positive effect on the reaction rates and selectivities of the Diels–Alder reaction, which is otherwise known to be insensitive to solvent effects, special attention has been focused on the origin of the aqueous acceleration.[1] Despite the solubility problems of organic substrates in water, after this seminal contribution there has been an upsurge in interest in using water as the solvent, not only to enhance the reaction rates but also to perform organic reactions that would otherwise be impossible. Several books and reviews have been devoted to such uses.[2] Thus, development of an efficient and convenient synthetic method in water is an important subject.

Acylation of amines is a fundamental process in organic chemistry. Owing to the nucleophilic and basic character of amines they must be blocked with a protecting group during a multi-step synthesis, e.g. in the synthesis of a diverse array of biological molecules such as amino acids, peptides, glycopeptides, aminoglycosides, β-lactams, nucleosides, sphingosines and alkaloids. *N*-Acyl derivatives are well-known protecting groups for the amines.[3] Acylation of amines is sometimes carried out using acyl transfer reagents[4] and at other times with acetic acid,[5] but acylating reagents such as acyl halides and acid anhydrides are usually employed in the presence of either acidic[6] or basic catalysts.[7] These reactions have advantages and drawbacks, extensively described recently by Katritzky.[8] Most of the acetyl transfer reagents are expensive and are obtained by acetylation with acetylating agents making them unsuitable for large-scale reactions. Some of these reagents and catalysts lead to waste and some reactions involve organic solvents, often toxic and polluting, both unacceptable in these environmentally conscious days. Thus, desirable features for these reactions would be a neutral medium, innocuous by-products, mild reaction conditions and greater tolerance towards other nucleophilic centers. Considering the importance of acylation and environmental factors, as well as our interest in green chemical processes,[9] we report here the acylation of amines in an aqueous medium, which fulfils many of the above-mentioned requirements.

Results and Discussion

Acetylation of aromatic amines has been carried out in an aqueous medium using amine, hydrochloric acid, a concentrated solution of sodium acetate and acetic anhydride.[10] In addition, there are a few other methods of aqueous acylation reported in the literature.[11] All the known aqueous acylation methods use either acids, bases or combinations of both. One of the reasons for using an acid in an aqueous medium is to convert the amine into a

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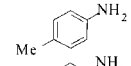
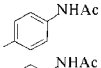
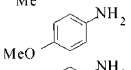
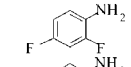
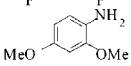
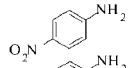
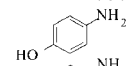
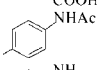
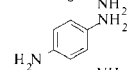
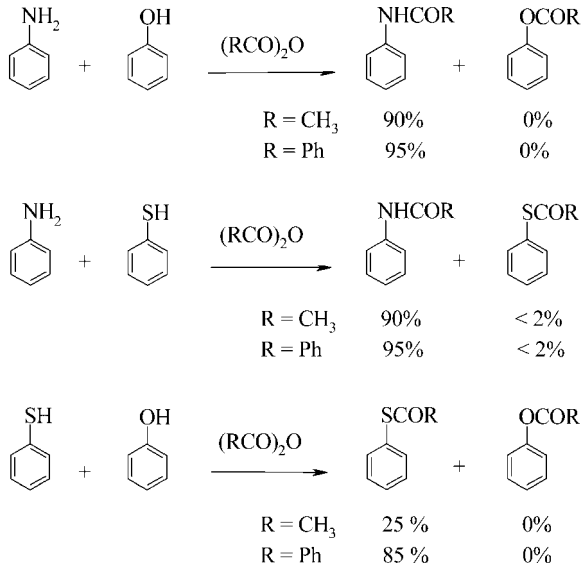
water-soluble ammonium salt and the base is to neutralize the acid liberated from the anhydride. The use of mineral acids or bases makes the above method less attractive. Considering the environmental aspects, we looked for a greener alternative, devoid of any acidic or basic reagents. In one of our ongoing projects we noticed the solubility of several aromatic and aliphatic amines in an aqueous medium in the presence of sodium dodecyl sulfate (SDS). The SDS concentration (2.31×10^{-4} M) required for the dissolution of several aromatic amines is much lower than the critical micelle concentration (8.3×10^{-3} M) of SDS, thus ruling out the possibility of micelle formation for the dissolution of amines. Initially, we speculated that the dissolution of the hydrogen donor amino group might be due to interaction with the hydrogen acceptor sulfonic acid group of SDS. But when the sodium salt of methane sulfonic acid was used instead of SDS, the amine did not dissolve at all; hence the possibility of the above type of interaction is ruled out. Other surfactants such as triton-X 100 and hexadodecyl ammonium bromide and phase transfer reagents such as tetrabutylammonium bromide can be used instead of SDS, thereby supporting the presence of hydrophobic-type interactions.

In the earlier methods,[10,11] the protonated ammonium ion obtained by the dissolution of amines in an acidic medium is nonnucleophilic, requiring a base to regenerate the nucleophilic amine for acylation. However, when SDS is used for its dissolution it retains its nucleophilic character. This was further confirmed by UV spectral analysis. No change in UV absorption was observed at 226 nm and 276 nm when SDS was added to a dilute solution of 2-fluoroaniline (**10**). Thus, when acetic anhydride was added to an SDS solution of an amine, acetylated products were obtained in moderate to good yields as shown in Table 1. It was gratifying to observe that the product also precipitates from the reaction mixture in most of these cases. Increasing the ionic strength of the medium by adding sodium chloride to the reaction medium enhanced the amount of precipitation. To our utter surprise no base was required and the pH of the medium recorded at the end of the reaction was ca.7. Several examples illustrating this novel procedure for acetylation are presented in Table 1. The optimized acetylation reactions were performed by adding acetic anhydride (7.5 mmol) to the substrate amine (5 mmol) dissolved in water (20 mL) with sodium dodecyl sulfate (20 mg). The method works well for aliphatic amines **1** and **2** when the anhydride was added in portions but gave poor yields when it was added in one lot. Benzylamine (**3**) and furfurylamine (**4**) gave the corresponding acetamide in good yields. Chiral amines **5** and **6** can be easily acetylated with complete retention of optical activity. Primary arylamines **7**−**18**, with varying steric and electronic factors, were examined and all gave excellent yields of the corresponding acetamide. In most of these cases the products precipitated in less than 5 min. It has been observed that in acetylation reactions electron-donating groups favor the reaction, whereas electron-withdrawing groups inhibit the reaction when performed in organic reaction media. However, no such effect was observed by the present method and all the substrates react with equal ease. Arylamines gave better yields than alkylamines. Phenol did not react at all and thiophenol reacted slowly under identical conditions, giving moderate (25%) yields of acetylated product. Thus, by taking advantage of the differential reactivity between nucleophiles, we were able to carry out intermolecular chemoselective acetylation of amines over phenol and thiol (Scheme 1). Thus, in a competitive acetylation reaction with an equimolar mixture of an amine (**7**) and a phenol by this procedure, the amine was acetylated selectively leaving the phenol unaffected. In an analogous reaction between an amine (**7**) and a thiophenol, the thiophenol remained untouched (Scheme 1). However, in a competitive reaction between a phenol and a thiophenol, the thiophenol was selectively acetylated over phenol (Scheme 1). This observation is in

Table 1. Acetylation of amines with acetic anhydride

Substrate		Product [a]		Yield % [b]
	**1**		**1a**	71
	**2**		**2a**	74
	3		**3a**	85
	**4**		**4a**	95
	**5**		**5a**	76
	**6**		**6a**	78
	**7**		**7a**	83
	**8**		**8a**	83
	**9**		**9a**	88
	**10**		**10a**	81
	**11**		**11a**	77
	**12**		**12a**	87
	**13**		**13a**	86[c]
	**14**		**14a**	90
	**15**		**15a**	99
	**16**		**16a**	91[d]
	**16**		**16aa**	91[e]
	**17**		**17a**	94[e]
	**18**		**18a**	28[f]

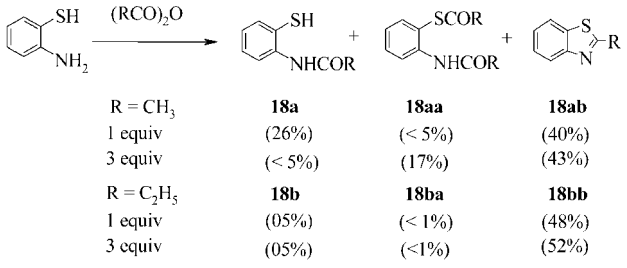
[a] Confirmed by comparison with IR, ^{1}H and ^{13}C NMR of the authentic sample. [b] Isolated yields. [c] The reaction was performed in 1:1 mixture of acetonitrile water. [d] Based on the recovery of starting material. [e] 3 equivalents of Ac_2O was used. [f] Rest of the products being **18aa** and **18ab** (Scheme 2).



Scheme 1. Chemoselective acetylation of amines

sharp contrast to selective acetylation of phenol over thiophenol in an organic medium.[6g] Thus an exactly opposite selectivity was observed in an aqueous medium.3

Similar chemoselectivity was observed for intramolecular reactions. Thus, acetylation of 4-aminophenol (**15**) and 2-aminothiophenol (**18**) produced the corresponding acetamides; the phenolic and thiophenolic moieties remaining unaffected with one equivalent of the reagent. Selective acetylation is of significant interest for the preparation of the antipyretic and analgesic drug paracetamol (**15a**). Substrate 1,2-phenylenediamine (**16**) gave exclusively the monoacetylated product **15a** with one equivalent of acetic anhydride. However, similar chemoselectivity could not be achieved for substrate 1,4-phenylenediamine (**17**), which gave exclusively the diacetylated product even with only one equivalent of the acetylating agent. An interesting heterocyclic product, 2-methyl-benzothiazole (**18ab**), was obtained in > 40% isolated yield, the rest being *N*-(2-mercapto-phenyl)acetamide (**18a**) and *S*-[2-(acetylamino)-phenyl] thioacetic acid ester (**18aa**), when 2-aminothiophenol (**18**) was acetylated as shown in Scheme 3. The formation of 2-methyl-benzothiazole (**18ab**) further demonstrates the chemoselective acetylation of amines over thiols. The proposed mechanism is shown in Scheme 2. It may be mentioned here that the compound 2-methylbenzothiazole (**18ab**) is used in the synthesis of polycarbocyanine and thiocyanine dyes, as well as for (arylfuryl)benzothiazoles. In most cases, the acetylated product precipitates from the aqueous reaction medium but in a few cases it was extracted with ethyl acetate to yield the pure product. However, in the case of substrates **16** and **18**, the products required chromatographic separation. It was found that primary amines underwent smooth acetylation whereas secondary amines and tertiary amines remained inert under the present experimental conditions.



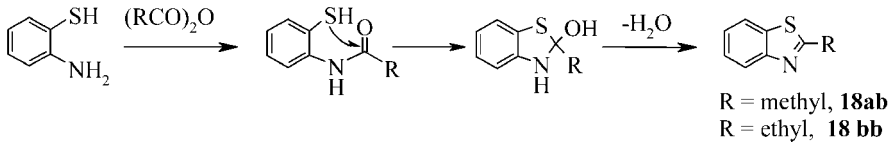
Scheme 2. Chemoselective acylation of amines

In order to extend the scope of the method further, the acylation of amines with propionic anhydride was carried out under identical conditions to those described for acetic anhydride. Thus a variety of amines could be efficiently propionylated in good yields as shown in Table 2. Amine has been chemoselectively propionylated over phenol and thiol as demonstrated for *p*-aminophenol (**15**) and 2-aminothiol (**18**) respectively. No chemoselectivity could be achieved

Table 2. Reaction of amines with propionic anhydride

Substrate		Product [a]		Yield %[b]
	**7**		**7b**	87
	**11**		**11b**	84
	**15**		**15b**	97
	**16**		**16b**	88[c]
	**17**		**17b**	94[c]
	**18**		**18b**	05[d]
	**19**		**19b**	84

[a] Confirmed by comparison with IR, ^{1}H and ^{13}C NMR of the authentic sample. [b] Isolated yields. [c] 3 equivalent of propionic anhydride was used. [d] The rest of the products were **18ba** and **18bb** (Scheme 2).



Scheme 3. Proposed mechanism for the formation of 2-(methyl)benzothiazole (**18ab**) and 2-(ethyl)benzothiazole (**18bb**)

with the symmetrical diamines *o*-phenylenediamine (**16**) and *p*-phenylenediamine (**17**) even with one equivalent of the anhydride. Substrate 2-aminothiol (**18**) gave 2-(ethyl)-benzothiazole (**18bb**, Scheme 2) as the major product and *N*-(2-mercaptophenyl)propionamide (**18b**) as the minor product suggesting chemoselective propionylation of amines over thiols.

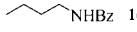
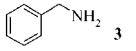
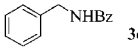
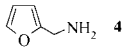
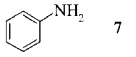
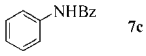
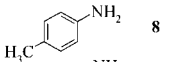
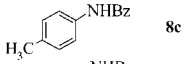
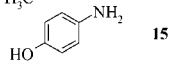
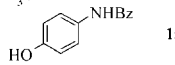
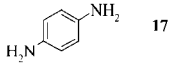
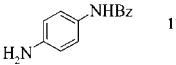
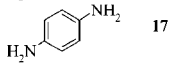
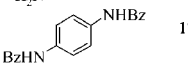
N-Benzoylated products are normally obtained from benzoic acid, benzoyl halides, benzoic anhydride, esters of benzoic acid, and benzoyl transfer reagents under different experimental conditions.[12] Employing our aqueous method, various amines could be benzoylated in excellent yields. Although benzoic anhydride can be directly added to an aqueous solution of the amine, the reaction times are normally longer and some benzoic anhydride remained unchanged, giving lower yields and an impure product. However, better yields and pure product could be obtained by adding an acetonitrile (2 mL) solution of benzoic anhydride (5 mmol) to an aqueous solution of amine (5 mmol) dissolved in water and SDS. The reaction was usually completed within 5 min. Removal of acetonitrile under reduced pressure led to precipitation of the benzoylated product along with benzoic acid. The precipitated benzoic acid was converted into water-soluble sodium benzoate by adding solid sodium hydrogen carbonate until effervescence ceases. The benzoylated product was filtered off to yield the pure compound. Sodium benzoate can be quantitatively recovered from the aqueous filtrate on concentration if required.

The success of the method has been tested with aliphatic (**1**), benzylic (**3**) and furfurylic (**4**) amines. Arylamines such as **7** and **8** gave the corresponding benzamides in quantitative yields. Excellent intermolecular chemoselective benzoylation of amines over phenols and thiols, and thiols over phenol, has been demonstrated in Scheme 1, further supporting the preferential *S*-acylation over *O*-acylation in an aqueous medium. Again an intramolecular chemoselective benzoylation of amine has been shown with *p*-aminophenol (**15**). No chemoselectivity of the symmetrical diamine 1,4-phenylenediamine (**17**) was achieved when acetic and propionic anhydrides were used (Table 1). However, excellent chemoselectivity could be achieved in the benzoylation of a symmetrical diamine in aqueous medium as shown for substrate **17**. This is probably because the monobenzoylated product **17c** is highly hydrophobic and therefore precipitates from the aqueous medium before it can undergo dibenzoylation if one equivalent of benzoic anhydride is used. However, the dibenzoylated product could be obtained in quantitative yields with two equivalents of benzoic anhydride.

The (arylcarbamoyl)propenoic acids or maleamic acid and propanoic acid or succinamic acid have been prepared by the condensation of amine with maleic anhydride or succinic anhydride using a variety of conditions.[6g,13] The novel aspect of the present method was further applied to cyclic anhydrides such as succinic anhydride and maleic anhydride. In the case of succinic anhydride, the anhydride (1.2 equivalents) was added in portions over a period of ten minutes to an aqueous solution of amine (1 equivalent). The reaction took place readily with concurrent precipitation of the white solid product. This has been tested with a number of aromatic amines and the results are summarized in Table 4. Here again chemoselective succcinylation of amine has been achieved over phenols as shown for *p*-aminophenol (**15**).

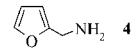
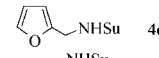
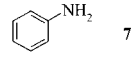
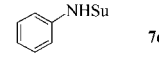
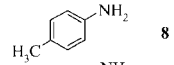
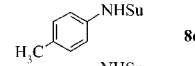
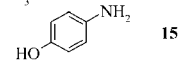
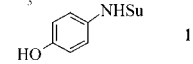
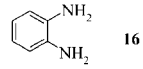
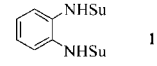
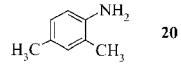
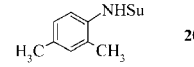
Amines also react successfully with maleic anhydride giving good yields of the desired products under similar conditions (Table 5). All the amines tested could be converted into the corresponding aryl maleamic acid in good yields. These reactions were performed analogously to the reaction using succinic anhydride. It is worth mentioning that maleamic and succinamic acids are important classes of compounds having fungicidal, insecticidal and herbicidal properties.

Table 3. Reaction of amines with benzoic anhydride

Substrate		Product [a]		Yield % [b]
	**1**		**1c**	88
	**3**		**3c**	93
	**4**		**4c**	92
	**7**		**7c**	96
	**8**		**8c**	97
	**15**		**15c**	98
	**17**		**17c**	91
	**17**		**17cc**	98[c]

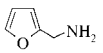
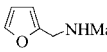
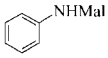
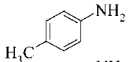
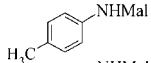
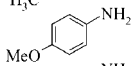
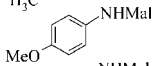
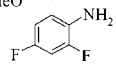
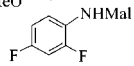
[a] Confirmed by comparison with IR, ^{1}H and ^{13}C NMR of the authentic sample. [b] Isolated yields. [c] 2 equivalent of Bz_2O was used.

Table 4. Reaction of amines with succinic anhydride

Substrate		Product [a]		Yield % [b]
	**4**		**4d**	75
	**7**		**7d**	82
	**8**		**8d**	81
	**15**		**15d**	87
	**16**		**16d**	83[c]
	**20**		**20d**	84

[a] Confirmed by comparison with IR, ^{1}H and ^{13}C NMR of the authentic sample. [b] Isolated yields. [c] 2.4 equivalents of succinic anhydride were used. Su = $COCH_2CH_2COOH$

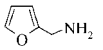
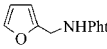
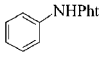
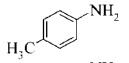
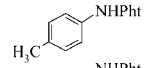
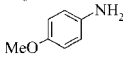
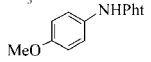
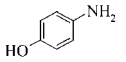
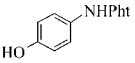
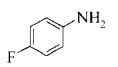
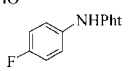
Table 5. Reaction of amines with maleic anhydride

Substrate		Product [a]		Yield % [b]
	**4**		**4e**	70
	**7**		**7e**	84
	**8**		**8e**	84
	**9**		**9e**	84
	**11**		**11e**	79

[a] Confirmed by comparison with IR, ^{1}H and ^{13}C NMR of the authentic sample.[b] Isolated yields. Mal = COCH=CHCOOH

There has been a recent resurgence of interest in *N*-phenylphthalimide derivatives and their analogues because of their potential biological activity, such as amino peptidase inhibition,[14a] anticonvulsant activity,[14b] and promotion of tumor necrosis factor alpha (TNF alpha) production.[14c] Substituted *N*-arylphthalimic acids have been synthesized by the reaction of phthalic anhydride and arylamines under different conditions.[15] Again, owing to the insolubility of phthalic anhydride in water, an acetonitrile (5−6 mL) solution of phthalic anhydride (5 mmol) was added to an aqueous solution of amine (5 mmol). Arylphthalamic acid precipitated on evaporation of acetonitrile. The product was filtered and recrystallized from acetonitrile to yield the crystalline compound in excellent yields. The reaction of phthalic anhydride with various amines is summarized in Table 6. It may be noted here that cyclic anhydrides react considerably more slowly than acyclic anhydrides when the reaction is catalyzed by montmorillonite K-10 in an organic solvent.[6g] As demonstrated here, both acyclic and cyclic anhydrides react with different amines with equal ease when the reaction was performed in an aqueous medium.

Table 6. Reaction of amines with phthalic anhydride

Substrate		Product [a]		Yield % [b]
	**4**		**4f**	78
	**7**		**7f**	87
	**8**		**8f**	85
	**9**		**9f**	89
	**15**		**15f**	91
	**19**		**19f**	93

[a] Confirmed by comparison with IR, ^{1}H and ^{13}C NMR of the authentic sample. [b] Isolated yields. Pht = COC_6H_5COOH

Conclusion

In conclusion, this method represents a tremendous opportunity for the practice of green chemistry. The reactions are, in general, very clean giving good to moderate yields with excellent selectivity, and no side products have been isolated. In addition, chromatographic purification of the acylated product is not required. The method is environmentally friendly with respect to by-products. Although procedures exist for acylation of amines, the simplicity and low cost of our procedure allow it to compete as a better practical alternative to the existing methods for selective acylation of primary amines in the presence of phenols and thiols and particularly of thiols in the presence of phenols. The reverse order of chemoselectivity, thiol over phenol will find useful application in the synthesis of complex natural products where selective protection of thio and amino groups is required in the presence of thiol.

Experimental Section

General Remarks: All the reagents were commercial grade and purified according to established procedures. Organic extracts were dried with anhydrous sodium sulfate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60−120 mesh size) was used for column chromatography. Reactions were monitored by TLC on silica-gel 60 F_{254} (0.25 mm). Elemental analysis was performed with a Perkin−Elmer 2400 elemental analyzer. Melting points were recorded with a Büchi B-540 melting point apparatus. NMR spectra were recorded in $CDCl_3$ or [D_6]DMSO with tetramethylsilane as the internal standard for ^{1}H (200, 300 and 400 MHz) or $CDCl_3$ or [D_6]DMSO solvent as the internal standard for ^{13}C (50, 75 and 100 MHz). For **16a**, **18a**, **18aa**, **18b**, **18ba** and **18bb** the organic solution was concentrated and passed through silica gel (60−120 mesh) using EtOAc/hexane to afforded the analytically pure compound. All the compounds were identified and confirmed by IR and NMR (^{1}H and ^{13}C) spectroscopy and by comparison with authentic samples.

General Procedure for Reaction of Amines with Acetic, Propionic, Succinic and Maleic Anhydride: Sodium dodecyl sulfate (SDS, ca. 20 mg) was added to a stirred heterogeneous suspension of amine (5 mmol) in water (20 mL) until a homogeneous solution was formed, (in case of turbidity, the mixture was warmed to obtain a clear solution). The anhydride (7.5 mmol for acetic and propionic anhydride and 6 mmol for succinic and maleic anhydride) was added to this over a period of 5 min. The acetylated product precipitated within 5−10 min. The precipitated product was filtered, washed with water (2 × 1 mL), dried by pressing between folds of filter paper and finally dried in a vacuum desiccator. In cases where the product did not precipitate, the reaction mixture was extracted with ethyl acetate (2 × 25 mL). The combined organic extracts were dried with anhydrous Na_2SO_4 and the solvent was removed in a rotary evaporator under reduced pressure to yield the pure product which was identified by its NMR and IR spectra and GC pattern, and by GC co-injection with authentic samples prepared by known methods.

General Procedure for Reaction of Amines with Benzoic and Phthalic Anhydride: Sodium dodecyl sulfate (SDS, ca. 20 mg) was added to a stirred heterogeneous suspension of amine (5 mmol) in water

(20 mL) until a homogeneous solution was formed, (in case of turbidity, the mixture was warmed to obtain a clear solution). Benzoic or phthalic anhydride (5 mmol) dissolved in acetonitrile (5 mL) was added to this in one lot. After stirring for 5 min the acetonitrile was evaporated and the product precipitated from the aqueous layer. To the aqueous solution containing precipitate, solid sodium hydrogen carbonate was added pinch-wise until the effervescence ceased and the pH was near neutral. The remaining precipitated product was filtered, washed with water (2 × 1 mL), dried by pressing between folds of filter paper and finally dried in a vacuum desiccator. In cases where the product did not precipitate, the reaction mixture was extracted with ethyl acetate (2 × 25 mL). The combined organic extracts were dried with anhydrous Na_2SO_4 and the solvent was removed in a rotary evaporator under reduced pressure to yield the pure product which were identified by its NMR and IR spectra and GC pattern, and by GC co-injection with authentic samples prepared by known methods. Good crystals of the compound can be obtained either from acetonitrile or from ethyl acetate.

Intermolecular Chemoselective Acylation of Aniline and Phenol: Sodium dodecyl sulfate (SDS, ca. 4 mg) was added to a stirred suspension of aniline (1 mmol) and phenol (1 mmol) in water (6 mL). To this was added acetic anhydride (1 mmol). After stirring for 10 min the reaction mixture was extracted with ethyl acetate (2 × 10 mL). The percentage of products formed was determined by gas−liquid chromatography using a crossed-linked methyl silicon gum capillary column (30 m × 0.32 mm × 0.25 μm) fitted with FID.

Chemoselective Acylation of Aniline and Thiophenol: Sodium dodecyl sulfate (SDS, ca. 4 m) was added to a stirred suspension of aniline (1 mmol) and thiophenol (1 mmol) in water (6 mL). To this heterogeneous mixture acetic anhydride (1 mmol) was added. After stirring for 10 min the reaction mixture was extracted with ethyl acetate (2 × 10 mL). The percentage of products formed was determined by gas−liquid chromatography using a crossed-linked methyl silicon gum capillary column (30 m × 0.32 mm × 0.25 μm) fitted with FID.

Chemoselective Acylation of Thiophenol and Phenol: Sodium dodecyl sulfate (SDS, ca. 4 mg) was added to a stirred suspension of aniline (1 mmol) and thiophenol (1 mmol) in water (6 mL). To this heterogeneous mixture acetic anhydride (1 mmol) was added. After stirring for 10 min the reaction mixture was extracted with ethyl acetate (2 × 10 mL). The percentage of products formed was determined by gas−liquid chromatography using a crossed-linked methyl silicon gum capillary column (30 m × 0.32 mm × 0.25 μm) fitted with FID.

Spectral Data: *N*-[2-(3-Carboxypropionylamino)phenyl]succinamic Acid (16d): M.p. 240−241 °C. IR (KBr): $\tilde{\nu}$ = 3529, 3428, 3375, 3334, 2930, 1707, 1680, 1646, 1620, 1597, 1535, 1513, 1481, 1456, 1398, 1351, 1300, 1245, 1209, 1158, 1061, 927, 846, 758 cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO): δ = 2.50 (m, 8 H), 7.08 (m, 2 H), 7.49 (m, 2 H), 9.21(s, 2 H), 12.14 (br. s, 2 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 29.06, 30.86, 124.60, 124.80, 130.44, 170.64, 174.07 ppm. $C_{14}H_{16}N_2O_6$ (308.09): calcd. C 54.54, H 5.23, N 9.09; found C 54.65, H 5.28, N 9.01%.

Acknowledgments

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[1] D. C. Rideout, R. Breslow, *J. Am. Chem. Soc.* **1980**, *102*, 7816−7817.
[2] [2a] R. Breslow, *Acc. Chem. Res.* **1991**, *24*, 159−164. [2b] C.-J. Li, *Chem. Rev.* **1993**, *93*, 2023−2035. [2c] W. A. Herrmann, C. W. Kohlpaintner, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1524−1544. [2d] A. Lubineau, J. Auge, Y. Queneau, *Synthesis* **1994**, 741−760. [2e] C.-J. Li, *Tetrahedron* **1996**, *52*, 5643−5668. [2f] S. Kobayashi, *Synlett* **1994**, 689−701. [2g] U. M. Lindström, *Chem. Rev.* **2002**, *102*, 2751−2771. [2h] K Shu, M. Kei, *Acc. Chem. Res.* **2002**, *35*, 209−217. [2i] T. Okuhara, *Chem. Rev.* **2002**, *102*, 3641−3666. [2j] A. N. Pae, Y. S. Cho, *Current Organic Chemistry* **2002**, *6*, 715−737.
[3] [3a] T. W. Greene, P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 3rd ed., John Wiley & Sons: New York, **1999**. [3b] P. J. Kocieński, *Protecting Groups*, Georg Thieme Verlag: New York, **1994**.
[4] [4a] Y. Murakami, K. Kondo, K. Miki, Y. Akiyama, T. Watanabe, Y. Yokoyama, *Tetrahedron Lett.* **1997**, *38*, 3751−3754. [4b] R. S. Atkinson, E. Barker, M. J. Sutcliffe, *Chem. Commun.* **1996**, 1051−1052. [4c] Y.-J. Kang, H.-A. Chung, J.-J. Kim, Y.-J. Yoon, *Synthesis* **2002**, 733−738. [4d] C. E. Humphrey, M. A. M. Easson, J. P. Tierney, N. J. Turner, *Org. Lett.* **2003**, *5*, 849−852. [4e] K. Kondo, T. Kurosaki, Y. Murakami, *Synlett* **1998**, 725−726. [4f] V. K. Haridasan, A. Ajayghosh, V. N. R Pillai, *J. Org. Chem.* **1987**, *52*, 2662−2665. [4g] Y. H. Jois, H. W. Gibson, *J. Org. Chem.* **1991**, *56*, 865−867. [4h] A. Ohta, Y. Inagawa, Y. Okuwaki, M. Shimazaki, *Heterocycles* **1984**, *22*, 2369−2373. [4i] I. H. Chung, K. S. Cha, J. H. Seo, J. H. Kim, B. Y. Chung, C. S. Kim, *Heterocycles* **2000**, *53*, 529−533. [4j] E. Petricci, M. Botta, F. Corelli, C. Mugnaini, *Tetrahedron Lett.* **2002**, *43*, 6507−6509. [4k] C. Helgen, C. G. Bochet, *Synlett* **2001**, 1968−1970.
[5] [5a] N. Narender, P. Srinivasu, S. J. Kulkarni, K. V. Raghavan, *Green Chemistry* **2000**, *2*, 104−105. [5b] B. C. Ranu, P. Dutta, A. Sarkar, *J. Chem. Soc., Perkin Trans. 1* **2000**, 2223−2226. [5c] Y. Ishii, M. Takeno, Y. Kawasaki, A. Muromachi, Y. Nishiyama, S. Sakaguchi, *J. Org. Chem.* **1996**, *61*, 3088−3092. [5d] B. S. Balaji, M. Sasidharan, R. Kumar, B. Chanda, *Chem. Commun.* **1996**, 707−708. [5e] P. Ilankumaran, J. G. Verkade, *J. Org. Chem.* **1999**, *64*, 9063−9066.
[6] [6a] C.-T. Chen, J.-H. Kuo, C.-H. Li, N. B. Barhate, S.-W. Hon, T.-W. Li, S.-D. Chao, C.-C. Liu, Y.-C. Li, I.-H. Chang, J.-S. Lin, C.-J. Liu, Y.-C. Chou, *Org. Lett.* **2001**, *3*, 3729−3732. [6b] P. A. Procopiou, S. P. D. Baugh, S. S. Flack, G. G. A. Inglis, *J. Org. Chem.* **1998**, *63*, 2342−2347. [6c] P. Saravanan, V. K. Singh, *Tetrahedron Lett.* **1999**, *40*, 2611−2614. [6d] K. K. Chauhan, C. G. Frost, I. Love, D. Waite, *Synlett* **1999**, 1743−1744. [6e] H. Zhou, A. Pendri, R. B. Greenwald, *J. Org. Chem.* **1998**, *63*, 7559−7562. [6f] P. M. Bhaskar, D. Loganathan, *Tetrahedron Lett.* **1998**, *39*, 2215−2218. [6g] T.-S. Li, A.-X. Li, *J. Chem. Soc., Perkin Trans. 1* **1998**, 1913−1918. [6h] S. P. Chavan, R. Anand, K. Pasupathy, B. S. Rao, *Green Chemistry* **2001**, 320−322. [6i] P. Kumar, R. K. Pandey, M. S. Bodas, M. K. Dangare, *Synlett* **2001**, 206−209. [6j] G. Sabitha, B. V. S. Reddy, R. Srividya, J. S. Yadav, *Synth. Commun.* **1999**, *29*, 2311−2316. [6k] A. Oitia, C. Tanahashi, A. Kakuda, J. Otera, *Angew. Chem. Int. Ed.* **2000**, *39*, 2877−2879. [6l] B. M. Choudary, M. L. Kantam, B. Bharati, V. C. R. Reddy, *J. Mol Cat. A.* **2001**, *168*, 69−73. [6m] A-X. Li, T-S. Li, T-H. Ding, *Chem. Commun.* **1997**, 1389−1390. [6n] S. Ahmed, J. Iqbal, *J. Chem. Soc., Chem. Commun.* **1987**, 114−115.
[7] [7a] E. Vedejs, S. T. Diver, *J. Am. Chem. Soc.* **1993**, *115*, 3358−3359. [7b] E. Vedejs, O. Daugulis, *J. Org. Chem.* **1996**, *61*, 5702−5703. [7c] B. A. D'Sa, J. G. Verkade, *J. Org. Chem.* **1996**, *61*, 2963−2966. [7d] V. K. Yadav, K. G. Babu, M. Mittal, *Tetrahedron* **2001**, *57*, 7047−7051. [7e] S. Paul, P. Nanda, R. Gupta, A. Laupy, *Tetrahedron Lett.* **2002**, *43*, 4261−4265.

[8] A. R. Katritzky, H. -Y. He, K. Suzuki, *J. Org. Chem.* **2000**, *65*, 8210−8213.

[9] [9a] R. Gopinath, B. Barkakaty, B. Talukdar, B. K. Patel, *J. Org. Chem.* **2003**, *68*, 2944−2974. [9b] R. Gopinath, Sk. J. Haque, B. K. Patel, *J. Org. Chem.* **2002**, *67*, 5842−5845. [9c] R. Gopinath, A. R. Paital, B. K. Patel, *Tetrahedron Lett.* **2002**, *43*, 5123−5126. [9d] S. Naik, R. Gopinath, B. K. Patel, *Tetrahedron Lett.* **2001**, *42*, 7679−7681. [9e] R. Gopinath, B. K. Patel, *Org. Lett.* **2000**, *2*, 4177−4180. [9f] R. Gopinath, B. K. Patel, *Org. Lett.* **2000**, *2*, 577−579.

[10] B. S. Furniss, A. J. Hannaford, P. W. G. Smith, A. R. Tatchell, *Vogel's Textbook of Practical Organic Chemistry.,* 5th ed.; Longman: Singapore, **1989**.

[11] [11a] H. D. DeWitt, A. W. Indersoll, *J. Am. Chem. Soc.* **1951**, *73*, 3359−3360. [11b] S. Roseman, J. Ludowieg, *J. Am. Chem. Soc.* **1954**, *76*, 301−302. [11c] A. C. Richardson, K. A. McLauchlan, *J. Chem. Soc.* **1962**, 2499−2506. [11d] D.-H. Kim, H-S. Rho, J. W. You, J. C. Lee, *Tetrahedron Lett.* **2002**, *43*, 277−279. [11e] V. Srivastava, A. Tandon, S. Ray, *Synth. Commun.* **1992**, *22*, 2703−2710. [11f] T. Sakakibara, Y. Watabe, M. Yamada, R. Sudoh, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 247−254.

[12] [12a] J-G. Rordíguez, R. Martín-Villamil, S. Ramos, *New. J. Chem.* **1998**, 865−868. [12b] K. Kikukawa, K. Kono, K. Nagira, F. Wada, T. Matsuda, *J. Org. Chem.* **1981**, *46*, 4413−4416. [12c] R. S. Varma, K. P. Naicker, *Tetrahedron. Lett.* **1999**, *40*, 6177−6180. [12d] T. Ooi, E. Tayama, M. Yamada, K. Maruoka, *Synlett* **1999**, 729−730. [12e] T. B. Sim, N. M. Yoon, *Synlett* **1994**, 827−828. [12f] L. Perreux, A. Loupy, F. Volatron, *Tetrahedron* **2002**, *58*, 2155−2161. [12g] P. Li, J.-C. Xu, *Tetrahedron* **2000**, *56*, 4437−4445. [12h] B. N. Goswami, N. Borthakur, A. C. Ghosh, *J. Chem. Res. Synop.* **1998**, 268−269.

[13] [13a] V. O. T. Omuaru, *Indian J. Chem.* **1998**, *37B*, 814−816. [13b] A. D. Gholap, V. M. Patel, R. C. Patil, P. Balasubramaniyan, V. Balasubramaniyan, *Indian J. Chem. Edn.* **1980**, *7*, 26−27. [13c] V. M. Patel, V. Balasubramaniyan, *Indian J. Chem.* **1977**, *15B*, 1142−1143.

[14] [14a] R. Shimazawa, H. Takayama, Y. Fujimoto, M. Komoda, K. Dodo, R. Yamasaki, R. Shirai, Y. Koiso, K. Miyata, F. Kato, M. Kato, H. Miyachi, Y. Hashimoto, *J. Enzyme Inhib.* **1999**, *14*, 259−263. [14b] V. Bailleux, L. Vallee, J. P. Nuyts, J. Vamecq, *Chem. Pharm. Bull.* **1994**, *42*, 1817−1821. [14c] Y. Shibata, K. Sasaki, Y. Hashimoto, S. Iwasaki, *Chem. Pharm. Bull.* **1996**, *44*, 156−159.

[15] [15a] V. L. M. Sena, R. M. Srivastava, S. P. Oliveira, V. L. M. Lima, *Biorg. Med. Chem. Lett.* **1998**, *8*, 2671−2674. [15b] C. J. Perry, Z. Parveen, *J. Chem. Soc., Perkin Trans. 2* **2001**, 512−521. [15c] V. O. T. Omuara, N. Boisa, G. U. Obuzor, *Indian J. Chem.* **1998**, *37B*, 704−706.

[16] *The Aldrich Library of* ^{13}C *and* ^{1}H *FT NMR Spectra*, Aldrich Chemical Company, Inc., Milwaukee, **1993**, ed. I.

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