National Institutes of Health (CA49084) and the National Science Foundation (CHE89-10821).

Supplementary Material Available: ^1H NMR spectra of 5-8 and 13 and ^{13}C NMR spectra of 5-8 (9 pages). Ordering information is given on any current masthead page.

Synthesis of 2-Aminobenzophenones via Rapid Halogen-Lithium Exchange in the Presence of a 2-Amino-*N*-methoxy-*N*-methylbenzamide

Stephen V. Frye,* Marty C. Johnson, and Nicole L. Valvano

Glaxo Inc. Research Institute, Five Moore Drive, Research Triangle Park, North Carolina 27709

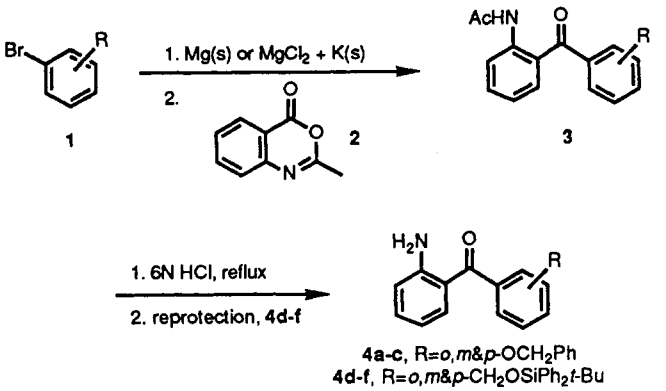
Received December 3, 1990

2-Aminobenzophenones are important precursors to 1,4-benzodiazepines.[1] The continued discovery of novel 1,4-benzodiazepines with new biological activities[2] makes versatile routes for the synthesis of 2-aminobenzophenones essential to further investigations of the structure-activity relationships of these seemingly ubiquitous receptor ligands.[3]

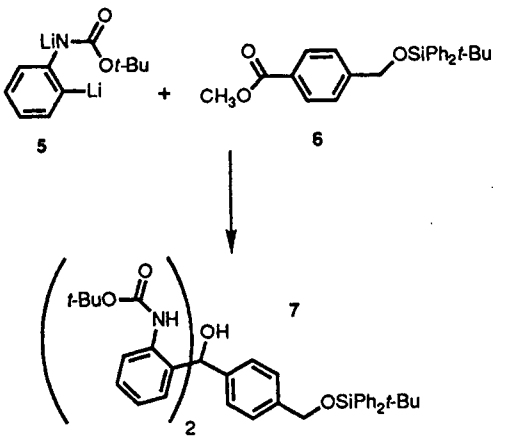
We were interested in preparing 2-aminobenzophenones of general structure **4** (Scheme I) as precursors to a novel series of 1,4-benzodiazepines. The initial approach to these compounds was based upon the route depicted in Scheme I.[4] There were two major drawbacks to this approach: (1) the formation of the requisite Grignard reagents in some cases were low yielding and highly irreproducible (even under the conditions described by Rieke[5]), giving at best a 50% yield of the desired adduct; (2) the silicon protecting groups that were desirable for protection of the benzyl alcohol functionality of **4d-f** were unstable toward the acidic hydrolysis required to deprotect the aniline nitrogen. In an attempt to combine a more reproducible anion-forming reaction and a facile nitrogen deprotection, the condensation of the anion of *N*-(*tert*-butoxycarbonyl)-aniline **5**[6] with methyl ester **6** was examined (Scheme II). However, overaddition of the aryllithium gave **7** as the major product. This result contrasts with the success of monoaddition of lithiopivaloylanilines to methyl benzoate.[4]

The problems encountered with the routes mentioned above, as well as considerations of availability of starting materials, led to the synthetic approach outlined in Scheme III. Reaction of isatoic anhydride (**8**) with *N,O*-dimethylhydroxylamine[7] followed by silica gel chromatography and distillation gave **9** in 75% yield.[8] When a 1:1 mixture of **9** and an aryl bromide (**1a-q**) is treated with 2 equiv of *n*-butyllithium at -78 to -100 °C, many of the desired 2-aminobenzophenones are produced directly in moderate to good yield in a matter of minutes (Table I). The reaction of **9** with **1a-c** has been carried out on up to a 0.1 mol scale with no dimunition in yield and, as anticipated, no products of overaddition are detected.[8] Advantages of this synthetic approach include (1) its brevity; (2) the ability to carry out the reaction without protection of the aniline nitrogen; (3) the ready availability of a large variety of aryl bromides; (4) the mild conditions and ease of workup relative to previous routes often involving high-temperature Friedal-Crafts reactions.[4] As noted in Table I the reaction fails in cases where there is an electrophilic substituent ortho to the incipient anion in the aryl bromides, in bromides containing an acidic hydrogen (even though 3 equiv of *n*-butyllithium was used), and for *o*-chloro- and *o*- and *p*-nitrobromobenzene. The diminished effectiveness of these substrates in this reaction may be due to the attenuation of the nucleophilicity of the derived anion since formation of the anions is expected to be facile.[9] If 1 equiv of *n*-butyllithium is used, very little product formation is detected by TLC. The reaction

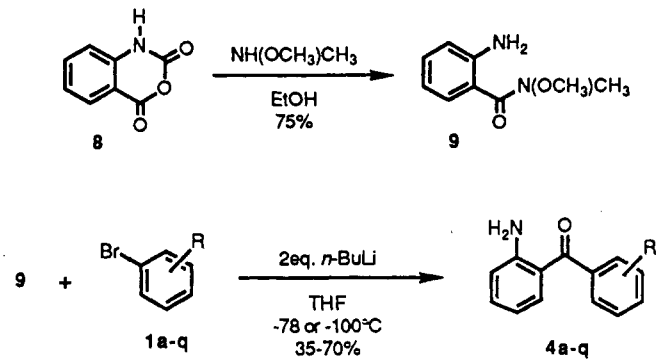
Scheme I



Scheme II



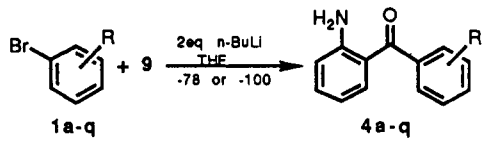
Scheme III



(1) Sternbach, L. H. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 34.
(2) Huang, S. C.; Zhang, L.; Chiang, H.-C. V.; Wank, S. A.; Maton, P. N.; Gardner, J. D.; Jensen, R. T. *Am. J. Physiol.* **1989**, *257*, G169. Bock, M. G.; DiPardo, R. M.; Evans, B. E.; Rittle, K. E.; Freidinger, R. M.; Change, R. S. L.; Lotti, V. J. *J. Med. Chem.* **1988**, *31*, 264.
(3) See introduction to Bock, M. G.; DiPardo, R. M.; Evans, B. E.; Rittle, K. E.; Whitter, W. L.; Veber, D. F.; Anderson, P. S., Freidinger, R. M. *J. Med. Chem.* **1989**, *32*, 13.
(4) For a compehensive review of the synthesis of 2-aminobenzophenones, see: Walsh, D. A. *Synthesis* **1980**, 677.
(5) Rieke, R. D.; Bales, S. E. *J. Am. Chem. Soc.* **1974**, *96*, 1775.
(6) Muchowski, J. M.; Venuti, M. C. *J. Org. Chem.* **1980**, *45*, 4798.
(7) Clark, R. H.; Wagner, E. C. *J. Org. Chem.* **1944**, *9*, 55.
(8) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
(9) Parham, W. E.; Bradsher, C. K. *Acc. Chem. Res.* **1982**, *15*, 300.

0022-3263/91/1956-3750$02.50/0

Table I. One-Pot Reaction of Aryl Bromides, Anthranilic Acid *N*-Methoxy-*N*-methylamide (9), and *n*-Butyllithium (Scheme III)

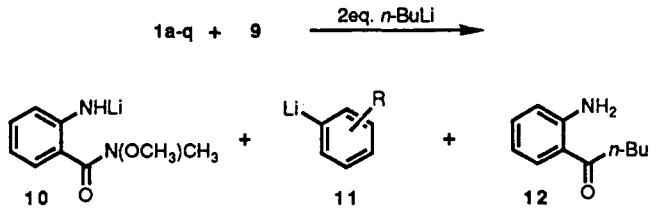


1a-q 4a-q

R[a]	temp, °C	yield, %
4a, *o*-OCH_2Ph	-78	68
4b, *m*-OCH_2Ph	-78	67
4c, *p*-OCH_2Ph	-78	70
4d, *o*-CH_2OSiPh_2-*t*-Bu	-78	47
4e, *m*-CH_2OSiPh_2-*t*-Bu	-78	50
4f, *p*-CH_2OSiPh_2-*t*-Bu	-78	50
4g, H	-78 and -100	70
4h, *o*-Me	-78	55
4i, *m*-Me	-78	70
4j, *p*-Me	-78	68
4k, *m*-Cl	-100	51
4l, *p*-Cl	-100	55
4m, *o*-F	-100	35
4n, *m*-CN	-100	34
4o, *p*-CN	-100	40
4p, *m*-CO_2-*t*-Bu	-100	52
4q, *p*-CO_2-*t*-Bu	-100	51

[a] Reaction of R = *o*-Cl, *o*-CN, *o*-CO_2-*t*-Bu, *o*- and *p*-NO_2, *p*-NH_2, *o*-OH, *o*-CH_2OH, and *p*-CH_2CO_2-*t*-Bu gave less than 5% of the desired product: see text for discussion.

Scheme IV



temperature has no marked effect on yield in the case where R = H (**4g**) and in general the reaction was carried out at −100 °C only in cases where previous research suggested that the lower temperature was necessary for selective halogen–metal exchange.[9] The effect of the alkyllithium used in the halogen–lithium exchange was examined for R = H (**4g**) and no improvement in yield is seen for *tert*-butyllithium versus *n*-butyllithium. If the aryllithium is preformed with 1 equiv of *n*-butyllithium and transferred into a solution of **9**, the yield is consistently lower than that in the one-pot procedure.

The fact that this procedure works in 70% yield in several cases allows some interesting conclusions to be reached concerning the relative rates of potentially competing reactions.[10] As the *n*-butyllithium is added to a mixture of **1** and **9**, there are three possible sites of reaction that are consistent with the experimental results (Scheme IV): (1) deprotonation of the aniline nitrogen of **9** to give **10**; (2) halogen–lithium exchange to give **11**; (3) direct nucleophilic addition to **9** to form the corresponding butyrophenone (**12**). As long as the temperature of the reaction is maintained below −78 °C and the reaction is stirred efficiently, no appreciable **12** is formed[11] (based on TLC) and no alkylation with butyl bromide (produced from the halogen–metal exchange) is detected. The observation that only a trace of product is visible on TLC after addition of the first equivalent of *n*-butyllithium while addition of a second equivalent leads to a 70% conversion to the desired product (for **4c**) suggests that the first equivalent is consumed in deprotonating the aniline nitrogen of **9**. This conclusion is supported by the observation that when **9** alone is treated with 1 equiv of *n*-butyllithium at −78 °C and quenched it can be recovered in good yield. The second equivalent of *n*-butyllithium then serves to carry out the halogen–lithium exchange and once the two anions **10** and **11** are formed the major reaction pathway is nucleophilic addition of **11** to **10**. On the basis of this analysis, the deprotonation of **9** by the first equivalent of *n*-butyllithium serves to prevent quenching of the aryllithiums (**11**) by the acidic hydrogens of **9**. The fact that the yield is lower (35% versus 50% for **4f**), but not zero, when the reaction is carried out in two stages (initial formation of the aryllithium with 1 equiv of *n*-butyllithium followed by addition to **9**) demonstrates that nucleophilic addition of the aryllithiums to **9** can compete with deprotonation of **9** by aryllithiums.

The approach to 2-aminobenzophenones **4** presented here allows rapid and efficient preparation of some previously difficult to access compounds in conveniently protected forms (**4a–f,p,q**). Overall yields compare favorably to existing methods,[4] especially when the ease of preparation and availability of starting materials as well as simplicity of product isolation and purification are considered. The observation that in situ generation and trapping of aryllithiums by an *N*-methoxy-*N*-methylamide[8,11] can proceed in moderate to good yield should be of general utility and further applications are under investigation.[16]

Experimental Section

Starting materials were obtained from commercial suppliers and used without further purification. ^1H NMR spectra were acquired on a Varian 300-MHz spectrometer with TMS as an internal reference. Butyllithium was titrated once prior to use.[12] Compounds **4g–m** are known[4] and their melting points, ^1H NMR, and elemental analyses were consistent with their structure and the prior literature.

Aryl Bromides 1a–f,p,q. These compounds were prepared from commercially available aryl bromides by protection as the benzyl ether (**1a–c**),[13] *tert*-butyldiphenylsilyl ether (**1d–f**),[14] or *tert*-butyl ester (**1p,q**)[15] using standard methodology.

Anthranilic Acid *N*-Methoxy-*N*-methylamide (9).[7] To a solution of *N,O*-dimethylhydroxylamine hydrochloride (51.2 g, 0.53 mol) in 90% aqueous ethanol (200 mL) was added triethylamine (53 g, 0.53 mol), and, after 10 min of stirring at 25 °C, isatoic anhydride was added (37.0 g, 0.35 mol) in portions. The reaction was then heated at reflux for 1.5 h and poured onto an equal volume of ice and saturated sodium bicarbonate. The ethanol was then removed by rotary evaporation, the resulting aqueous mixture was extracted with ethyl acetate (3 × 150 mL),

(10) The rate of halogen–lithium exchange versus competing deprotonation reactions has been the source of some contention. For example, see: Narasimhan, N. S.; Sunder, N. M.; Ammanamanchi, R.; Bonde, B. D. *J. Am. Chem. Soc.* **1990**, *112*, 4431. Beak, P.; Musick, T. J.; Chen, C.-w. *J. Am. Chem. Soc.* **1988**, *110*, 3538. A review of the lithium–halogen interchange reaction has also appeared recently: Bailey, W. F.; Patricia, J. J. *J. Organomet. Chem.* **1988**, *352*, 1.

(11) An intramolecular Barbier reaction initiated by halogen–lithium exchange involving cyclization of an aryllithium onto a ketone has recently been reported: Kihara, M.; Kashimoto, M.; Kobayashi, Y.; Kobayashi, S. *Tetrahedron Lett.* **1990**, *31*, 5347. The success of the reaction presented in this work is also dependant upon the rate of halogen–lithium exchange being faster than nucleophilic addition of butyllithium to a carbonyl group.

(12) Suffert, J. *J. Org. Chem.* **1989**, *54*, 509.

(13) Fletcher, H. G. *Methods Carbohydr. Chem.* **1963**, *II*, 166.

(14) Cunico, R. F., Bedell, L. *J. Org. Chem.* **1980**, *45*, 4797.

(15) Mathias, L. J. *Synthesis* **1979**, 561.

(16) **Note Added in Proof**: For a recent example of a metal-halogen exchange initiated intramolecular acylation via an *N*-methoxy-*N*-methylamide, see: Selnick, H. G.; Radzilowski, E. M.; Ponticello, G. S. *Tetrahedron Lett.* **1991**, *32*, 721.

and the combined extracts were washed with water and brine, dried over magnesium sulfate and activated charcoal, and concentrated to an orange oil. The oil was chromatographed on silica gel (1:1 diethyl ether/hexanes, then acetone) and distilled to give **9** as a pale yellow oil: yield 47.4 g (75%); bp 148–151 °C/0.35 mm; ^{1}H NMR ($CDCl_3$) δ 7.35 (d, 1 H, J = 8.1 Hz), 7.20 (t, 1 H, J = 8.1 Hz), 6.69 (m, 2 H), 4.65 (bs, 2 H), 3.61 (s, 3 H), 3.36 (s, 3 H). Anal. Calcd for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71; N. 15.55. Found: C, 59.72; H, 6.78; N, 15.47.

2′-(Benzyloxy)-2-aminobenzophenone (4a) (−78 °C procedure). To a mixture of **9** (2.00 g, 11.1 mmol) and **1a** (2.92 g, 11.1 mmol) in anhydrous tetrahydrofuran (65 mL) at −78 °C under nitrogen was added, with vigorous stirring, *n*-BuLi in hexanes (13.8 mL, 1.6 M, 22.2 mmol) at 0.6 mL/min. After 20 min, aqueous hydrochloric acid was added (1 N, 20 mL), the mixture was extracted with ethyl acetate (150 mL), and the ethyl acetate was washed with water and brine, dried over magnesium sulfate, and concentrated. Recrystallization from hexanes gave **4a** as yellow crystals: yield 2.29 g (68%); mp 108–109 °C; ^{1}H NMR ($CDCl_3$) δ 7.60–7.00 (m, 11 H), 6.70 (d, 1 H, J = 8.2 Hz), 6.53 (t, 1 H, J = 8.2 Hz), 6.33 (bs, 2 H), 5.06 (s, 2 H). Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.18; H, 5.65; N, 4.62. Found: C, 79.09; H, 5.64; N, 4.62.

3′-(Benzyloxy)-2-aminobenzophenone (4b). This compound was prepared in an identical fashion to **4a**: yield 67%; mp 106–107 °C; ^{1}H NMR ($CDCl_3$) δ 7.46–7.10 (m, 11 H), 6.73 (d, 1 H, J = 8.3 Hz), 6.57 (t, 1 H, J = 8.3 Hz), 6.08 (bs, 2 H), 5.05 (s, 2 H). Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.18; H, 5.65; N, 4.62. Found: C, 78,89; H, 5.70; N, 4.61.

4′-(Benzoyloxy)-2-aminobenzophenone (4c). This compound was prepared in an identical fashion to **4a**: yield 70%; mp 99–101 °C; ^{1}H NMR ($CDCl_3$) δ 7.69 (d, 2 H, J = 8.7 Hz), 7.38–7.25 (m, 7 H), 7.03 (d, 2 H, J = 8.7 Hz), 6.73 (d, 1 H, J = 8.3 Hz), 6.63 (t, 1 H, J = 8.3 Hz), 5.86 (bs, 2 H), 5.13 (s, 2 H). Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.18; H, 5.65; N, 4.62. Found: C, 79.12; H, 5.66; N, 4.54.

2′-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-2-aminobenzophenone (4d). This compound was prepared in an identical fashion to **4a** and isolated by silica gel chromatography (sgc: hexanes/ethyl acetate); yield 47% as a viscous yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.63–7.22 (m, 16 H), 6.67 (d, 1 H, J = 8.1 Hz), 6.49 (t, 1 H, J = 8.1 Hz), 6.27 (bs, 2 H), 4.78 (s, 2 H), 0.95 (s, 9 H). An analytical sample was obtained by Kugelrohr distillation; bp ~210 °C/0.02 mm. Anal. Calcd for $C_{30}H_{31}NO_2Si$: C, 77.38; H, 6.71; N, 3.01. Found: C, 77.20; H, 6.74; N, 2.95.

3′-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-2-aminobenzophenone (4e). This compound was prepared and isolated in an identical fashion to **4d**: yield 50% as a viscous yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.69 (d, 4 H, J = 7.2 Hz), 7.60–7.23 (m, 12 H), 6.74 (d, 1 H, J = 8.1 Hz), 6.49 (t, 1 H, J = 8.1 Hz), 6.08 (bs, 2 H), 4.81 (s, 2 H), 1.09 (s, 9 H). An analytical sample was obtained by Kugelrohr distillation; bp ~210 °C/0.02 mm. Anal. Calcd for $C_{30}H_{31}NO_2Si$: C, 77.38; H, 6.71; N, 3.01. Found: C, 77.44; H, 6.73; N, 3.00.

4′-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-2-aminobenzophenone (4f). This compound was prepared and isolated in an identical fashion to **4d**: yield 50% as a viscous yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.71 (d, 4 H, J = 7.2 Hz), 7.63 (d, 2 H, J = 8.0 Hz), 7.49–7.23 (m, 10 H), 6.75 (d, 1 H, J = 8.1 Hz), 6.63 (t, 1 H, J = 8.1 Hz), 6.05 (bs, 2 H), 4.82 (s, 2 H), 1.10 (s, 9 H). An analytical sample was obtained by Kugelrohr distillation; bp ~210 °C/0.02 mm; crystallized on standing; mp 106–108 °C. Anal. Calcd for $C_{30}H_{31}NO_2Si$: C, 77.38; H, 6.71; N, 3.01. Found: C, 77.28; H, 6.74; N, 3.00.

3′-Cyano-2-aminobenzophenone (4n) (−100 °C procedure). To a mixture of **9** (2.00 g, 11.1 mmol) and **1n** (2.02 g, 11.1 mmol) in anhydrous tetrahydrofuran (65 mL) at −100 °C under nitrogen was added, with vigorous stirring, *n*-BuLi in hexanes (13.8 mL, 1.6 M, 22.2 mmol) at 0.6 mL/min. After the addition was complete the reaction was allowed to warm to −70 °C (internal temperature), aqueous hydrochloric acid was added (1 N, 20 mL), the mixture extracted with ethyl acetate (150 mL), and the ethyl acetate was washed with water and brine, dried over magnesium sulfate, and concentrated. Purification by sgc (hexanes/ethyl acetate) and recrystallization from hexanes gave **4n** as yellow crystals: yield 0.84 g (34%); mp 114–115 °C; ^{1}H NMR ($CDCl_3$) δ 7.94–7.77 (m, 3 H), 7.59 (t, 1 H, J = 8.0 Hz), 7.36–7.29 (m, 2 H), 6.75 (d, 1 H, J = 8.2 Hz), 6.63 (t, 1 H, J = 8.2 Hz), 6.19 (bs, 2 H). Anal. Calcd for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.60. Found: C, 75.57; H, 4.56; N, 12.53.

4′-Cyano-2-aminobenzophenone (4o). This compound was prepared in an identical fashion to **4n**: yield 40%; mp 157–159 °C; ^{1}H NMR ($CDCl_3$) δ 7.77 (d, 1 H, J = 7.5 Hz), 7.70 (d, 1 H, J = 7.5 Hz), 7.37–7.28 (m, 2 H), 6.76 (d, 1 H, J = 8.2 Hz), 6.61 (t, 1 H, J = 8.2 Hz), 6.24 (bs, 2 H). Anal. Calcd for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.60. Found: C, 75.39; H, 4.59; N, 12.51.

3′-(*tert*-Butoxycarbonyl)-2-aminobenzophenone (4p). This compound was prepared in an identical fashion to **4n** and isolated as an oil: yield 52%; ^{1}H NMR ($CDCl_3$) δ 8.23 (t, 1 H, J = 1.9 Hz), 8.14 (dt, 1 H, J = 7.8, 1.9 Hz), 7.76 (dt, 1 H, J = 7.8, 1.9 Hz), 7.51 (t, 1 H, J = 7.8 Hz), 7.39 (d, 1 H, J = 7.4 Hz), 7.31 (m, 1 H), 6.75 (d, 1 H, J = 7.8 Hz), 6.61 (t, 1 H, J = 7.8 Hz), 6.15 (bs, 2 H), 1.60 (s, 9 H). An analytical sample was obtained by Kugelrohr distillation; bp ~250 °C/0.02 mm; crystallized on standing; mp 129–130 °C. Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.60; H, 6.47; N, 4.69.

4′-(*tert*-Butoxycarbonyl)-2-aminobenzophenone (4q). This compound was prepared in an identical fashion to **4p**: yield 51%; ^{1}H NMR ($CDCl_3$) δ 8.07 (d, 2 H, J = 8.4 Hz), 7.64 (d, 2 H, J = 8.4 Hz), 7.39–7.26 (m, 2 H), 6.74 (d, 1 H, J = 8.3 Hz), 6.58 (t, 1 H, J = 8.3 Hz), 6.19 (bs, 2 H), 1.62 (s, 9 H). An analytical sample was obtained by Kugelrohr distillation; bp ~250 °C/0.02 mm. Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.74; H, 6.47; N, 4.68.

A New Chemical Method for Synthesizing and Recycling Acyl Coenzyme A Thioesters

Tianmei Ouyang and David R. Walt*

Max Tishler Laboratory for Organic Chemistry, Department of Chemistry, Tufts University, Medford, Massachusetts 02155

Received August 13, 1990 (Revised Manuscript Received January 28, 1991)

Introduction

Coenzyme A functions as an acyl carrier in the biosynthetic pathways of most organisms. It participates in stereoselective carbon–carbon bond formation and is potentially useful for synthesizing complex organic molecules. Coenzyme A thioesters (acyl-CoA) serve as substrates for a wide variety of enzyme-catalyzed reactions including both fatty acid and polyketide biosynthesis.[1]

A variety of procedures have been described for preparing CoA thioesters of fatty acids. Those employed most frequently involve selective acylation of the CoA-thiol with acylating agents including acid anhydrides,[2] acyl chlorides,[3] a mixed anhydride of ethyl hydrogen carbonate,[4] and *N*-hydroxysuccinimide esters of fatty acids.[5] However all of these reagents are relatively nonspecific; they may react not only with the sulfhydryl group, but also with other functional groups present in CoA. Furthermore all of the methods employ organic solvents.

Enzymatic systems, on the other hand, have the advantage of working in aqueous buffers. The most commonly used enzyme for acyl-CoA synthesis is acyl-CoA synthetase (ACS). The disadvantage of this method is that the yields are low (50%) and products are contaminated with lipids present in the enzyme preparation[6,7] unless

(1) Herbert, R. B. *Biosynthesis of Secondary Metabolites*; Chapman & Hall: London, 1981; pp 28–44.
(2) Simon, E. J.; Shemin, D. *J. Am. Chem. Soc.* **1953**, *75*, 2520.
(3) Seubert, W. *Biochem. Prep.* **1960**, *7*, 80.
(4) Goldman, P.; Vagelos, P. R. *J. Biol. Chem.* **1961**, *236*, 2620.
(5) Al-Arif, A.; Blecher, M. *J. Lipid Res.* **1969**, *10*, 355.
(6) Kornberg, A.; Pricer, W. E. *J. Biol. Chem.* **1953**, *204*, 329–343.

0022-3263/91/1956-3752$02.50/0