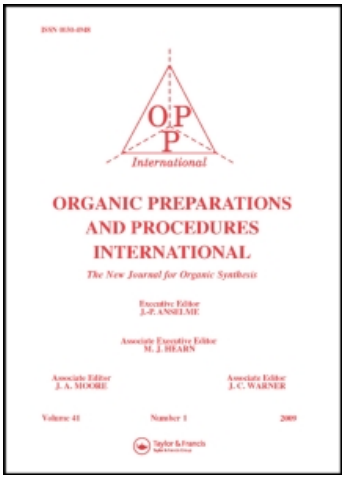



**Organic Preparations and Procedures International**
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

# A NEW SYNTHETIC METHOD FOR *ortho*-SUBSTITUTED BENZANILIDES

Alan R. Katritzky[a]; Wei-Qiang Fan[a]
[a] Department of Chemistry, University of Florida, Gainesville, FL

**To cite this Article** Katritzky, Alan R. and Fan, Wei-Qiang(1987) 'A NEW SYNTHETIC METHOD FOR *ortho*-SUBSTITUTED BENZANILIDES', Organic Preparations and Procedures International, 19: 4, 263 — 268
**To link to this Article: DOI:** 10.1080/00304948709356197
**URL:** http://dx.doi.org/10.1080/00304948709356197

ORGANIC PREPARATIONS AND PROCEDURES INT. 19(4-5), 263-268 (1987)

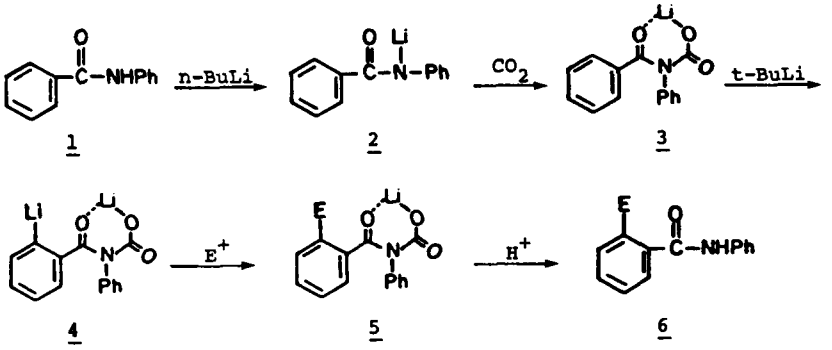
# A NEW SYNTHETIC METHOD FOR ortho-SUBSTITUTED BENZANILIDES†

Alan R. Katritzky* and Wei-Qiang Fan

Department of Chemistry, University of Florida
Gainesville, FL 32611



A number of alternative methods have been developed for the regiospecific synthesis of 1,2-disubstituted aromatic molecules. The sequence involving ortho-metallation, followed by reaction with an electrophile is now recognized as an efficient route for the regiospecific synthesis of a wide variety of 1,2-disubstituted aromatic compounds, including ortho-substituted aromatic amides. There are many contributions from the groups of Beak,[1] Snieckus,[2] Gschwend[3] and others to the directed lithiation of tertiary amides of aromatic acids and the resulting lithiated intermediates have been reacted successfully with a wide variety of electrophiles. However, the preparative ortho-lithiation and substitution of




1 2 3 4 5 6

secondary benzamides has received less attention. Hauser[4] reported the condensation with ketones and aldehydes at the ortho-position of benzanilide and N-methylbenzamide by means of excess n-butyllithium.

Recently, our novel one-pot synthetic sequence using carbon dioxide

as an easily removed protecting group[5] has been applied to the conversion of N-alkylanilines into ortho-substituted N-alkylanilines.[5c] We have now successfully extended this methodology to lithiation followed by carbon-carbon bond formation at the ortho-position of benzanilide. The novel one-pot synthetic sequence 1 to 6 that we have used for the regiospecific ortho-functionalization of benzanilide is shown in scheme. The sequence is composed of four operations:

(i) Protection via conversion of benzanilide 1 into the corresponding N-lithium carboxylate 3 by the treatment with n-butyllithium in tetrahydrofuran and 5% (v/v) HMPA (1 to 2), followed by quenching with carbon dioxide (2 to 3).

(ii) Lithiation of this N-lithium carboxylate 3 to give 4 was accomplished by reaction with 1.2 equivalents of t-butyllithium in tetrahydrofuran at ca -20°C.

(iii) Carbon-carbon bond formation to intermediate 5 by the reaction of 4 with the corresponding electrophile at -70°C and then allowing the reaction mixture temperature to rise to 25°C over a few hours.

(iv) Deprotection and work-up by the slow addition of aqueous 2N hydrochloric acid to the reaction mixture at 0°C converted 5 into 6, which was collected and recrystallized.

The results shown in Table 1 demonstrate that a wide range of electrophiles may be employed: alkyl halides (both iodides and bromides) react readily to give o-alkylbenzanilides, aldehydes afford the expected secondary alcohol derivatives, isocyanates as electrophiles give phthalic acid diamides, esters and carbon dioxide give respectively o-acyl and o-carboxyl derivatives, and deuteration also takes place at the ortho-position. The reaction of intermediate 4 with benzophenone, gives the lactone 8 by cyclization of the benzanilide intermediate 7. The yields ranged from 73 to 91%.

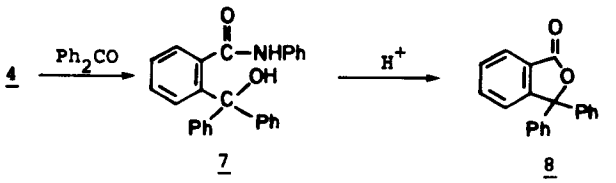



TABLE 1. Preparation of ortho-Substituted Benzanilides

| Entry | Electrophile | ortho-substituent | Yield[a] (%) | mp. (°C) | lit. mp. (°C) |
|---|---|---|---|---|---|
| 1 | $D_2O$ | D | 91(100)[f] | 161-163 | 162-164 |
| 2 | MeI | Me | 76 | 121-123[b] | 125[6] |
| 3 | EtI | Et | 90 | 138-140[b] | 141-142.5[7] |
| 4 | n-BuBr | n-Bu | 73 | 72-73[b] | ------ |
| 5 | $Ph_2CO$ | lactone(8) | 74 | 116-118[c] | 116.116.5[8] |
| 6 | p-$MeC_6H_4CHO$ | $CH(OH)C_6H_4Me$-p | 82 | 145-147[d] | ------ |
| 7 | p-$MeOC_6H_4CHO$ | $CH(OH)C_6H_4OMe$-p | 78 | 150-151[d] | 147-148[4b] |
| 8 | t-BuNCO | CONHtBu | 76 | 244-246[e] | ------ |
| 9 | PhNCO | CONHPh | 80 | 230-232[d] | 230-231[9] |
| 10 | $CO_2$ | $CO_2H$ | 80 | 160-162[e] | 155-158[10] |
| 11 | p-$MeC_6H_4CO_2Et$ | $COC_6H_4Me$-p | 78 | 208-210[d] | ------ |

a) Isolated yield in all cases. b) Recrystallized from $CHCl_3$-hexane.
c) Recrystallized from ether-hexane. d) Recrystallized from ethanol.
e) Recrystallized from ethanol-$CHCl_3$. f) 100% Deuterated.

In summary, our one-pot synthetic sequence for the ortho-functionalization of benzanilide offers advantages over other existing methods in that the protecting group can be introduced and removed very easily, the procedure is simple, a wide range of electrophiles can be used, and the yields are high. The method should be applicable to other secondary anilides. In particular, unlike the dilithiation method,[5] there is no danger of the electrophile reacting at the nitrogen atom.

## EXPERIMENTAL SECTION

$^1H$ NMR spectra were taken with a Varian EM 360L, $^{13}C$ NMR spectra were recorded on a JEOL JNM FX 100 spectrometer. Infrared spectra were obtained on a Perkin-Elmer 283B spectrophotometer. Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. Elemental analyses were carried out under the supervision of Dr. R. King of this department. n-Butyllithium and t-butyllithium (Aldrich) were used without further purification. Tetrahydrofuran was dried by refluxing with calcium hydride and used directly after distillation under dry argon. Carbon dioxide (Matheson) was used after drying by passage through anhydrous calcium sulfate. Processes (i)-(iii) were carried out under a dry argon atmosphere.

Preparation of ortho-Substituted Benzanilides.- A solution of benzanilide (0.01 mole, 1.97 g in 28.5 ml THF and 1.5 ml HMPA) in a Schlenk type reactor under an argon atmosphere was cooled to -70°C and n-butyllithium (4.0 ml of 2.5 M n-hexane solution) was slowly added dropwise. The resulting solution was kept at -70°C for a few minutes, and the temperature then allowed to rise to 25°C. Carbon dioxide gas was passed through the solution for 5 min. The solvent was removed under reduced pressure to give the lithium benzanilide-N-carboxylate. The atmosphere was replaced with argon and THF (30 ml) was added. Then, the solution was cooled to ca -70°C and t-butyllithium (6.5 ml of 1.7 M n-pentane solution) was added slowly. The cooling bath was changed to ice-salt, and the solution was kept at -20°C for 30 min. The whole was then cooled to -70°C and the electrophile (0.01 mole) in 5 ml THF was added. The reaction mixture was allowed to return to 25°C and stirred at that temperature for a few hours. The solvent was removed and aqueous hydrochloric acid (2N) was added at 0°C. The resulting precipitate was collected, and recrystallized from a suitable solvent to give the pure ortho-substituted benzanilide (see Table 1).

2-Deuteriobenzanilide $^1H$ NMR ($DMSO-d_6$): $\delta$ 7.0-7.6 (m, 6H, Ar-H), 7.65-8.10 (3H, Ar-H), 9.65 (br s, 1H, CONH).

2-Methylbenzanilide $^1H$ NMR ($CDCl_3$): $\delta$ 2.25 (s, 3H, $CH_3$), 6.95-7.85 (m, 9H, Ar-H), 8.18 (brs, 1H CONH); $^{13}C$ NMR: $\delta$ 168.4 (C=O), 138.0, 136.2, 135.9, 130.8, 129.8, 128.7, 126.6, 125.5, 124.2, 120.0, 19.6 ($CH_3$).

2-Ethylbenzanilide $^1H$ NMR ($CDCl_3$): $\delta$ 1.23 (t, 3H, $CH_2$ $\underline{CH_3}$), 2.79 (q, 2H, $\underline{CH_2}CH_3$), 7.0-8.1 (m, 10H, Ar-H and CONH); $^{13}C$ NMR: $\delta$ 168.4 (C=O), 142.4, 138.0, 130.2, 129.5, 128.5, 126.6, 125.7, 124.4, 120.0, 26.3 ($CH_2$), 15.8 ($CH_3$).

2-n-Butylbenzanilide $^1H$ NMR ($CDCl_3$): $\delta$ 0.88 (t, 3H, $CH_3$), 1.1-1.9 (m, 4H, $CH_2\underline{CH_2}\underline{CH_2}CH_3$), 2.80 (t, $\underline{CH_2}CH_2CH_2CH_3$), 7.0-7.8 (m, 9H, Ar-H), 8.12 (s,

1H, CONH); $^{13}C$ NMR: $\delta$ 168.4, 140.8, 138.0, 136.2, 129.8, 128.7, 126.6, 125.5, 124.2, 120.0, 33.5 (Ar-$\underline{C}H_2$), 32.6 ($\underline{C}H_2CH_2CH_3$), 22.4 ($\underline{C}H_2CH_3$), 13.8 ($CH_3$).

Anal. Calcd for $C_{17}H_{19}NO$: C, 80.63; H, 7.51; N, 5.53
Found: C, 80.91; H, 7.68; N, 5.25

3,3-Diphenylphthalide(8) $^1H$ NMR ($CDCl_3$): $\delta$ 7.1-8.3 (m, Ar-H); $^{13}C$ NMR: $\delta$ 169.5 (C=O), 151.8, 140.1, 134.0, 129.2, 128.4, 126.9, 125.8, 125,3, 124.0, 111.6, 91.5 ($\underline{C}Ph_2$).

2-(α-Hydroxy-4-methylbenzyl)benzanilide $^1H$ NMR (DMSO-$d_6$): $\delta$ 2.32 (s, 3H, $CH_3$), 5.80 (d, 1H, OH), 6.19 (d, 1H, C<u>H</u>OH), 7.0-7.9 (m, 13H, Ar-H), 10.20 (s, 1H, CONH); $^{13}C$ NMR: $\delta$ 167.9 (C=O), 143.8, 142.3, 139.0, 135.7, 129.8, 128.5, 127.1, 126.4, 123.7, 119.9, 106.7, 70.0 ($\underline{C}$HOH), 20.7 ($CH_3$); IR ($CHBr_3$): 3400, 1660 (C=O), 1600, 1540 $cm^{-1}$.

Anal. Calcd for $C_{21}H_{19}NO_2$: C, 79.50; H, 5.99; N, 4.42
Found: C, 79.32; H, 6.25; N, 4.32

2-(α-Hydroxy-4-methoxybenzyl)benzanilide $^1H$ NMR ($CDCl_3$): $\delta$ 3.87 (s, 4H, $OCH_3$ and OH), 6.47 (s, 1H, C<u>H</u>OH), 6.88-8.20 (m, 14H, Ar-H and CONH; $^{13}C$ NMR: $\delta$ 170.4 (C=O), 160.2, 149.6, 136.2, 134.1, 129.9, 128.6, 128.0, 127.6, 126.2, 125.6, 125.2, 122.8, 120.4, 114.1, 82.6 ($\underline{C}$HOH), 55.1 ($OCH_3$).

N-tert-Butyl-N'-phenylphthalic Diamide $^1H$ NMR ($CDCl_3$/DMSO-$d_6$): $\delta$ 1.37 (s, 9H, $CMe_3$), 7.15-7.95 (m, 10H, Ar-H), 10.40 (brs, 2H, CONH); $^{13}C$ NMR: $\delta$ 166.3, 165.5, 137.7, 135.5, 134.5, 133.6, 126.9, 126.0, 125.4, 121.8, 117.8, 49.4 ($\underline{C}Me_3$), 26.8 ($CH_3$); IR ($CHBr_3$): 3250 (CONH), 1660 (C=O), 1625 (C=O), 1595, 1500 $cm^{-1}$.

Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.87; H, 6.76; N, 9.46
Found: C, 72.47; H, 6.98; N, 9.27

N,N'-Diphenylphthalic Diamide $^1H$ NMR (DMSO-$d_6$): $\delta$ 6.9-7.9 (m, 14H, Ar-H), 10.3 (s, 2H, CONH); $^{13}C$ NMR: $\delta$ 166.9, 139.4, 136.7, 134.7, 129.7, 128.8, 128.5, 123.4.

Phthalic Acid Monoanilide $^1H$ NMR (DMSO-$d_6$): $\delta$ 6.75-7.95 (m, 9H, Ar-H), 10.25 (s, 1H, $CO_2H$), 12.9 (brs, 1H, CONH).

2-(p-Methylbenzoyl)benzanilide $^1H$ NMR ($CDCl_3$/DMSO-$d_6$): $\delta$ 2.32 (s, 3H, $CH_3$), 6.90-8.10 (m, 14H, Ar-H, CONH); $^{13}C$ NMR: $\delta$ 166.3 (CONH), 149.5, 147.1, 136.8, 136.4, 132.5, 129.7, 128.5, 127.8, 126.7, 125.6, 125.2, 122.2, 92.2, 20.5 ($CH_3$).

Anal. Calcd for $C_{21}H_{17}NO$: C, 80.00; H, 5.40; N, 4.44
Found: C, 80.25; H, 5.27; N, 4.61

## REFERENCES

† Part. 6. Carbon Dioxide as a Reagent for the Protection of Nucleophilic Centers and the Simultaneous Activation of Electrophilic Attack. For Part 5, see A. R. Katritzky and K. Akutagawa, J. Am. Chem. Soc., 108, 6808 (1986).

1. a) P. Beak and V. Snieckus, Acc. Chem. Res., 15, 306 (1982).
   b) P. Beak and R. A. Brown, J. Org. Chem., 42, 1823 (1977).

2. a) M. Watanabe, M. Sahara, S. Furukawa, R. Billedeau and V. Snieckus, Tetrahedron Lett., 1647 (1982).
   b) M. P. Sibi, M. A. J. Miah, and V. Snieckus, J. Org. Chem., 49, 737 (1984).
   c) M. Watanabe, M. Sahara, M. Kubo, S. Furukawa, R. J. Billedeau and V. Snieckus, ibid., 49, 742 (1984).

3. L. Barsky, H. W. Gschwend, J. McKenna, and H. R. Rodriguez, ibid., 41, 3651 (1976).

4. a) C. L. Mao, I. T. Barnish and C. R. Hauser, J. Heterocycl. Chem., 6, 475 (1969).
   b) C. F. Beam, C. A. Park, D. C. Reames, S. A. Miller and C. R. Hauser, J. Chem. Eng. Data, 23, 183 (1978).

5. a) A. R. Katritzky and K. Akutagawa, Tetrahedron Lett., 5935 (1985).
   b) A. R. Katritzky and K. Akutagawa, Tetrahedron, 42, 2571 (1986).
   c) A. R. Katritzky, W.-Q. Fan and K. Akutagawa, ibid., 42, 4027 (1986).
   d) A. R. Katritzky, W.-Q. Fan and K. Akutagawa, Submitted to Synthesis.

6. L. G. Makarova and A. N. Nesmeyanov, Otdel. Khim. Nauk., 1019 (1954), C. A., 50, 241b (1956).

7. P. A. S. Smith and E. P. Antoniades, Tetrahedron, 9, 210 (1960).

8. F. N. Janes and C. R. Hauser, J. Org. Chem., 27, 3364 (1962).

9. R. D. Reynolds and C. L. Anderson, ibid., 28, 3223 (1963).

10. C. U. Frederick, ibid., 26, 2998 (1961).

(Received October 14, 1986; in revised form January 26, 1987)