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# Rapid Approach to 3,5-Disubstituted 1,4-Benzodiazepines via the Photo-Fries Rearrangement of Anilides

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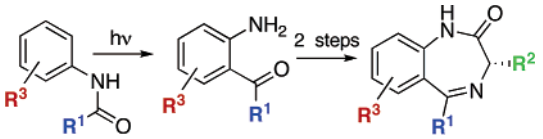


Different anilides derived from carboxylic acids and substituted anilines have been submitted to the photochemically induced Fries rearrangement giving the corresponding *o*-amino phenones under conditions that are compatible with the presence of acid-labile groups (such as N-Boc or TBDMSO) on $R^1$ and $R^3$. These compounds, not easily obtained in other ways, are useful building blocks for the preparation of benzocondensated heterocycles. After coupling with N-Boc amino acids and TFA-mediated deprotection, the products cyclized to the corresponding 3,5-disubstituted 1,4-benzodiazepin-2-ones, privileged structures predominantly active in the central nervous system. The same results were obtained by coupling with N-Cbz-protected α-amino acids followed by microwave assisted hydrogenolysis. When the Fries rearrangement was carried out on the anilide derived from N-Boc−Ala−OH and the further coupling done with N-Cbz−(OMe)Asp−OH, the formed benzodiazepines could be inserted in a peptide chain for the preparation of conformationally constrained peptidomimetics.

The formation of new core structures for the preparation of focalized libraries is becoming an important target in preparative combinatorial chemistry.[1] The scaffolds required must be cyclic, be present at a relatively low molecular weight, contain heteroatoms as H-bond acceptors, and possess two or more functionalizable positions for parallel decoration.[2] Druglike shapes are also particularly appreciated in scaffolds prepared for hit discovery.[3]

Benzodiazepines have been the first class of molecules recognized as privileged structures.[4] This term was in fact coined by Evans as a single molecular framework able to provide ligands for diverse receptors. This conclusion followed the observation that 1,4-benzodiazepin-2-ones were able to bind to cholecystokinin (CCK) and to several central nervous system receptors.[5] The benzodiazepine ring is contained in molecules that bind G-protein-coupled receptors and[6] in several drugs used for central nervous system diseases,[7] and it has found applications for the synthesis of peptidomimetics,[8] peptide antagonists,[9] inhibitors of DNA interactions,[10] antiviral or antimalarial compounds,[11] and many other potentially active molecules.[12] Despite the impressive diversity of benzodiazepines prepared to date, a great deal of work has been directed toward the synthesis of 1,4-benzodiazepin-2,5-diones,[13] presumably as a result of the relatively easy synthetic procedure available. The corresponding 1,4-benzodiazepin-2-ones have not been widely explored, and few examples deal with the 5- or 3-substituted ring.[14]

The classical approach to this system is based on the acylation of *o*-aminophenones with α-amino acids followed by ring

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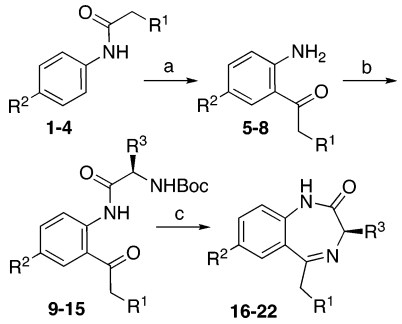
**SCHEME 1** [a]




[a] (a) MeCN, *hν* 254 nm, rt, 24 h. (b) DCC, DMAP, DMF, 12 h, rt. (c) TFA/$Et_3SiH$/$CH_2Cl_2$ 4 h, rt.

closure between N4 and C5.[8a,15] This method, developed and exploited especially by Elmann et al. in several combinatorial syntheses on the solid phase,[16] is limited by the low availability of *o*-aminophenones (or *o*-nitrophenones) with diversity on the aromatic ring and on the carbonyl. The preparation of these intermediates can be carried out via Friedel−Crafts acylation of anilines or multistep synthesis starting from nitrobenzenes.[12a]

Following our interest in the synthesis of peptidomimetics,[17] we explored the possibility to use the Fries rearrangement of amides derived from differently functionalized carboxylic acids to prepare *o*-aminophenones with diversity at the alkyl substituent and the aromatic ring. Although largely used for the preparation of substituted phenols starting from esters,[18] the Fries reaction on amides has been scarcely explored and the few examples reported are limited to simple acetanilides.[19] The reaction is generally carried out in the presence of corrosive Lewis acids that are not compatible with the presence in the molecule of several functional and protective groups. On the other hand, the photochemical version of the Fries rearrangement seemed to be a milder practicable route for the synthesis of differently functionalized phenones as compounds **5**−**8** in Scheme 1.

**TABLE 1. Compounds Prepared Following Scheme 1**

| aminophenones (yield, %) | amidophenones and benzodiazepines (yield, %) |
|---|---|
| $R^1 = -Ph$, $R^2 = OMe$ | $R^1 = -Ph$, $R^2 = OMe$, $R^3 = Me$ |
| **5** (56) | **9** (80), **16** (72) |
| $R^1 = -Ph$, $R^2 = H$ | $R^1 = -Ph$, $R^2 = H$, $R^3 = CH_2Ph$ |
| **6** (60) | **10** (74), **17** (57) |
| | $R^1 = -Ph$, $R^2 = H$, $R^3 = CHMe_2$ |
| | **11** (71), **18** (65) |
| $R^1 = -Ph$; $R^2 = OTBDMS$ | $R^1 = -Ph$, $R^2 = OTBDMS$, $R^3 = Me$ |
| **7** (55) | **12** (75) |
| | $R^1 = -Ph$, $R^2 = OH$, $R^3 = Me$ |
| | **19** (65) |
| $R^1 = -C_{11}H_{23}$, $R^2 = H$ | $R^1 = -C_{11}H_{23}$, $R^2 = H$, $R^3 = CHMe_2$ |
| **8** (61) | **13** (77), **20** (71) |
| | $R^1 = -C_{11}H_{23}$, $R^2 = H$, $R^3 = H$ |
| | **14** (80), **21** (75) |
| | $R^1 = -C_{11}H_{23}$, $R^2 = H$, $R^3 = (CH_2)_4NHCbz$ |
| | **15** (73), **22** (59) |

Using amide **1** ($R^1$ = Ph, $R^2$ = OMe, see Table 1) as the model compound, we explored different conditions for carrying out this reaction. First attempts were carried out using a medium-pressure Hg lamp in cyclohexane as the solvent. Although irradiated for long periods of time, compound **5** was formed in very little amounts. Thus, we tried to change the solvent, but using $CH_2Cl_2$ or $CHCl_3$, we observed degradation of the starting material. Better results were obtained with MeCN, although the reaction did not go to completion and some starting material was recovered. An additional improvement in the yields was obtained using a low-pressure Hg lamp at 254 nm working in quartz tubes. The best yields in **5** (56% of isolated product) were finally obtained using deoxygenated MeCN and irradiating for 24 h at room temperature. Following the same procedure, anilides **2**−**4** were transformed into *o*-aminophenones **6**−**8** in acceptable yields.[20]

For the exploration of the transformation into benzodiazepine, compound **6** was coupled with N-Boc−Ala−OH. This reaction was not very easy, as the $NH_2$ is relatively hindered and deactivated by the *ortho*-carbonyl group. Exclusively the use of DCC and DMAP as the coupling agents allowed the formation of amide **9** ($R^1$ = Ph, $R^2$ = OMe, $R^3$ = Me, see Table 1) in 72% yield after isolation by column chromatography.[21] Using this procedure, compounds **5**−**8** were coupled with different amino acids to give the corresponding products **10**−**15** in 70−80% yield. Deprotection of the Boc group with TFA/$Et_3SiH$ gave directly 2,5-disubstituted 1,4-benzodiazepin-4-ones **16**−**22** in yields ranging from 55 to 75%. During cyclization, the TBDMS protection was removed giving the phenolic benzodiazepine **19**.

As our goal was to introduce functional groups around the benzodiazepine ring for additional decoration, we decided to try the Fries rearrangement on anilide **23** derived from Cbz−Val−OH (Scheme 2). The Cbz group was chosen as orthogonal with Boc, as it should be maintained during the process of deprotection/cyclization. Unfortunately, the presence of the benzylic carbamate in the substrate prevented the photochemical

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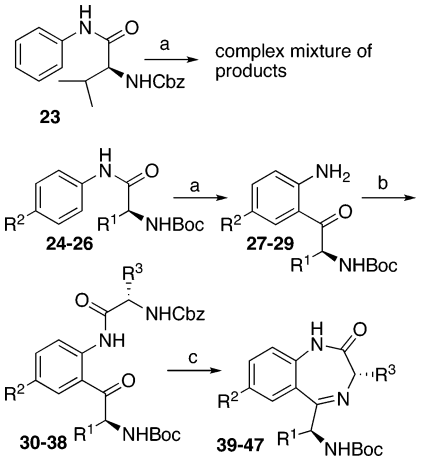
(20) Different amounts of the starting material were always observed at the end of the photo-Fries rearrangement. An increase of the reaction times gave degradation of the starting material without increasing the formation of the acetophenone. The yields reported (average 45−60%) are calculated without considering the recovery of the starting material that would push yields to an average of 65−80%.

(21) Use of other coupling agents such as EDC, PyBOP, or DMTMM gave poor conversion into the required amides.

**SCHEME 2** [a]




[a] (a) MeCN, *hν* 254 nm, rt, 24 h. (b) Cbz-Gly-OH, DCC, DMAP, $CHCl_3$, rt, 12 h. (c) $HCOONH_4$, Pd/C, *i*-PrOH, MW, 6 min, 95 °C.

**TABLE 2. Compounds Prepared Following Scheme 2**

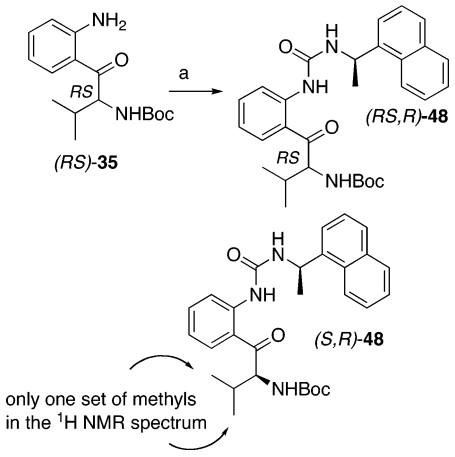
| aminophenones (yield, %) | amidophenones and benzodiazepines (yield, %) |
|---|---|
| $R^1 = -Me$, $R^2 = H$ | $R^1 = -Me$, $R^2 = H$, $R^3 = H$ |
| **27** (56) | **30** (71), **39** (74) |
| | $R^1 = -Me$, $R^2 = H$, $R^3 = -Me$ |
| | **31** (75), **40** (70) |
| | $R^1 = -Me$, $R^2 = H$, $R^3 = -CHMe_2$ |
| | **32** (74), **41** (65) |
| | $R^1 = -Me$, $R^2 = H$, $R^3 = -CH_2Ph$ |
| | **33** (80), **42** (68) |
| $R^1 = -CHMe_2$, $R^2 = H$ | $R^1 = -CHMe_2$, $R^2 = H$, $R^3 = H$ |
| **28** (61) | **34** (77), **43** (70) |
| | $R^1 = -CHMe_2$, $R^2 = H$, $R^3 = Me$ |
| | **35** (70), **44** (66) |
| | $R^1 = -CHMe_2$, $R^2 = H$, $R^3 = -CHMe_2$ |
| | **36** (69), **45** (58) |
| | $R^1 = -CHMe_2$, $R^2 = H$, $R^3 = -CH_2Ph$ |
| | **37** (69), **46** (71) |
| $R^1 = -Me$, $R^2 =$ OTBDMS | $R^1 = -Me$, $R^2 =$ OTBDMS, $R^3 = CH_2COOMe$ |
| **29** (52) | **38** (73), **47** (73) |

reaction from taking place with formation of several byproducts. Thus, we decided to carry out the rearrangement on anilide **24** derived from N-Boc−Ala−OH ($R^1$ = Me, $R^2$ = H, see Table 2) that gave **27** in acceptable yields under our standard conditions. This compound was then coupled with Cbz−Gly−OH with DCC/DMAP giving compound **30** ($R^1$ = Me, $R^2$ = $R^3$ = H, see Table 2) in 70% yield.

Benzodiazepines **39** were then obtained in 70% yield after treatment of **30** with ammonium formate in the presence of Pd-$(OH)_2$/C (20%) in *i*-PrOH[22] in a microwave monomode cavity (open vessel).[23] Following this general synthetic protocol, 1,4-benzodiazepines carrying different substituents in positions 3 and 5 and on the aromatic ring (**39**−**47**) were obtained in good yields as reported in Table 2.

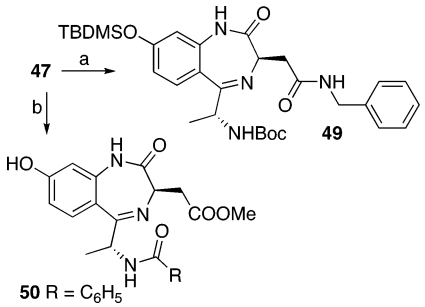
To verify that racemization did not occur on the photo-Fries rearrangement product, the anilide derived from racemic Boc−Val−OH was submitted to the rearrangement. The corresponding racemic compound (*R*,*S*)-**35** was reacted with (*R*)-1-naphtylethylisocyanate to give product (*R*,*S*,*R*)-**48** (Scheme 3). The $^1$H NMR spectrum (400 MHz) of (*R*,*S*,*R*)-**48** showed an appreciable difference in the resonance of the methyl groups derived from Valine. When compound (*S*,*R*)-**48** was prepared starting from **35** (derived from L-Val), only one set of methyls appeared in the spectrum showing that racemization occurred at least in less than 5%.[24]

**SCHEME 3** [a]




[a] (*R*)-1-Naphtylethylisocyanate, Py, rt, 12 h (86%).

**SCHEME 4** [a]




[a] (a) $PhCH_2NH_2$, $AlMe_3$ in toluene, reflux, 36 h. (b) (i) TFA/$Et_3SiH$, DCM, rt, 2 h; (ii) PhCOCl, $CHCl_3$, Py, rt, 12 h.

Moreover, in the case of compounds **40**−**42** and **44**−**47**, a single diastereoisomer was obtained showing that no racemization occurred even during the cyclization step.

Compound **47** was particularly interesting as it has three different functional groups that can be selectively functionalized, as reported in Scheme 4. The carboxymethyl group in position 3 of compound **47** could be directly transformed into the amide **49** in the presence of benzyl amine and $AlMe_3$.

On the other hand, treatment of **47** with TFA/$Et_3SiH$ removed the OTBDMS and the Boc group, and the primary amine was selectively acylated with benzoyl chloride to give compound **50.** In conclusion, we have developed a simple and rapid method for the synthesis of 3,5-substituted 1,4-benzodiazepin-2-ones. The method allows the regiocontrolled formation of the diaz-

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(23) This reaction was carried out inside a Discover monomode MW system from CEM. During the preparation of products **39** and **43**, the formation of 10% of the corresponding 1,4-benzodiazepan-2-one was observed.

(24) When aminophenone **27** (as an oil), kept in a glass flask at room temperature for a long time (1 month), was used in the coupling with alanine to give amidophenone **31**, we noticed the formation of a mixture of diastereoisomers (approximately 3:1), suggesting that **27** racemizes on standing.

epine ring with respect to a substituent on the aromatic ring and the formation of enantiomerically pure benzodiazepine starting from a naturally occurring amino acid. Moreover, compounds such as **47** in Scheme 4 can be considered as a conformationally constrained cyclic dipeptide in a form suitable for insertion in a peptidic strand and for the preparation of new peptidomimetics.

## Experimental Section

**(*S*)-2-(*tert*-Butoxycarboylamino)-1-(2′-aminophenyl)-propan-1-one, 27. General Procedure.** A solution of compound **24** (0.40 g, 1.51 mmol) in MeCN (150 mL degassed with two cycles of freezing-vacuum treatment) was irradiated under magnetic stirring with a Hg lamp at 254 nm (distance of the sample from the lamp is 1 cm) for 48 h with care to maintain the internal temperature of the solution below 25 °C. After removal of the solvent under reduced pressure, the residue was purified by flash chromatography, eluting with 9:1 petroleum ether/EtOAc to give 0.224 g (56%) of compound **1** as an oil. $^1$H NMR (200 MHz, 27 °C, $CDCl_3$): $\delta$ 1.34 (d, $J$ = 6.9 Hz, 3H), 1.41 (s, 9H), 5.22−5.30 (m, 1H), 5.61−5.66 (m, 1H), 6.31 (bs, 2H), 6.54−6.63(m, 2H), 7.20 (t, $J$ = 8.2 Hz, 1H), 7.65 (d, $J$ = 8.2 Hz, 1H). $^{13}$C NMR (200 MHz, 27 °C, $CDCl_3$): $\delta$ 20.31, 28.13, 50.39, 79.21, 114.49, 115.62, 117.26, 130.56, 134.61, 151.16, 154.69, 200.53. ESI-MS: 287 (M + Na). Anal. Calcd for $C_{14}H_{20}N_2O_3$: C, 63.62; H, 7.63; N, 10.60. Found: C, 63.46; H, 7.53; N, 10.72.

**Amide 31. General Procedure.** To a solution of compound **27** (0.40 mg, 1.5 mmol) in dry $CHCl_3$ was added CbzAlaOH (0.370 mg, 1.65 mmol), DMAP (0.05 g, 0.4 mmol), and DCC (0.370 mg, 1.8 mmol). The mixture was stirred overnight at room temperature. After filtration and removal of solvent under reduced pressure, the residue was purified by flash chromatography, eluting with petroleum ether/EtOAc from 9:1 to 5:1 to afford compound **31** (0.50 mg, 70%) as an oil. $^1$H NMR (200 MHz, 27 °C, $CDCl_3$): $\delta$ 1.31 (d, $J$ = 6 Hz, 3H), 1.43 (s, 9H), 1.47 (d, $J$ = 7.3 Hz, 3H), 4.30−4.50 (m, 1H), 5.12 (s, 2H), 5.20−5.35 (m, 1H), 5.40−5.52 (m, 1H), 5.12−5.32 (m, 1H), 7.11 (t, $J$ = 7.9 Hz, 1H), 7.23−7.43 (m, 5H), 7.49 (t, $J$ = 7.0 Hz, 1H), 7.87 (d, $J$ = 7.7 Hz, 1H), 8.66 (d, $J$ = 8.3 Hz, 1H), 11.72 (bs, 1H). $^{13}$C NMR (200 MHz, 27 °C, $CDCl_3$): $\delta$ 18.52, 19.75, 28.22, 51.40, 52.08, 66.94, 79.87, 119.89, 122.94, 124.12, 127.80, 128.32, 128.67, 130.42, 135.19, 136.00, 140.60, 155.02, 155.81, 171.75, 203.45. ESI-MS: 492 (M + Na). Anal. Calcd for $C_{25}H_{31}N_3O_6$: C, 63.95; H, 6.65; N, 8.95. Found: C, 64.34; H, 6.70; N, 8.94.

**5-(1-*tert*-Butoxycarbonylamino-1-ethyl)-3-methyl-2,3-dihydro-1*H*-benzo[*e*]$^{1,4}$diazepin-2-one, 40. General Procedure.** To a solution of compound **31** (0. 240 g, 0.5 mmol) in *i*-PrOH was added $HCOONH_4$ (130 mg, 2 mmol) and $Pd(OH)_2$/C (20%) (0.06 g). The mixture was irradiated under microwaves (MW) in the cavity of a CEM Discover system (open vessel, power 100 W, max internal temp 150 °C). The reaction was monitored by TLC until disappearance of compound **31** (approximately four cycles of 3 min each). After filtration of the catalyst on Celite (*Warning, Pd on Carbon may be pyroforic after exposure to hydrogen*), the residue was concentrated and purified by flash chromatography, eluting with 3:1 petroleum ether/EtOAc to give compound **40** (0.093 g, 70%) as an oil. $^1$H NMR (200 MHz, 27 °C, $CDCl_3$): $\delta$ 1.04 (d, $J$ = 6.7 Hz, 3H), 1.45 (s, 9H), 1.60 (d, $J$ = 6.5 Hz, 3H), 3.59 (q, $J$ = 6.5 Hz, 1H), 4.91 (t, $J$ = 6.7 Hz, 1H), 6.00−6.08 (m, 1H), 7.13 (d, $J$ = 8.0 Hz, 1H), 7.20 (t, $J$ = 7.6 Hz, 1H), 7.46 (t, $J$ = 7.1 Hz, 1H), 7.67 (d, $J$ = 7.6 Hz, 1H), 9.33 (bs, 1H). $^{13}$C NMR (200 MHz, 27 °C, $CDCl_3$): $\delta$ 16.53, 20.41, 28.39, 50.64, 57.47, 79.21, 121.07, 124.16, 126.24, 127.74, 131.61, 137.63, 155.34, 170.04, 172.96. ESI-MS: 356 (M + K), 340 (M + Na), 318 (M + H). Anal. Calcd for $C_{17}H_{23}N_3O_3$: C, 64.33; H, 7.30; N, 13.24. Found: C, 64.86; H, 7.19; N, 13.29.

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**Supporting Information Available:** Experimental procedures and complete characterization of compounds **5**−**8**, **16**−**22**, **28**, **29**, and **39**−**50**. This material is available free of charge via the Internet at http://pubs.acs.org.

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