Molecular Diversity, **5:** 1–5, 2000.
KLUWER/ESCOM

Regioselective alkylation at the N4 position of a 3-oxo-1,4-benzodiazepine on solid support

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Received 16 February 2000; Accepted 3 May 2000

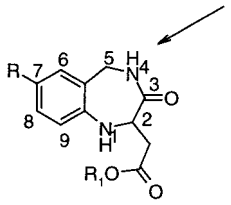
Key words: benzodiazepine, combinatorial array, diversity, Heck reaction, regioselective alkylation, Sasrin® resin

Summary

An efficient solid phase regioselective alkylation at the N4 position of a 3-oxo-1,4-benzodiazepine template exemplified by 4-H-2,3,4,5-tetrahydro-7-iodo-3-oxo-1H-1,4-benzodiazepine-2-acetate-polymer ester is described. Further chemical elaboration at position 7, utilizing a modified Heck reaction, allows the incorporation of amides from primary or secondary amines. The two diversity points at positions 4 and 7 were utilized to synthesize a 28-membered, combinatorial array on Sasrin® resin in moderate yields and > 80% purity. Having validated the chemistry on solid support, a combine and split approach to prepare a bead-bound combinatorial library is achievable utilizing similar experimental practices and procedures as in the array synthesis.

Our interest in developing a robust solid phase synthesis for alkylation of the N4 position of the 1,4-benzodiazepine core molecule (**1**) stemmed from an ongoing vitronectin receptor ($\alpha v\beta 3$) antagonist program. We identified several potent and selective vitronectin receptor ($\alpha v\beta 3$) antagonists through modification of the 7-amido R2 group (**2**) and a few modifications of the N4 substituent [1]. Analogs with modified 7-amido R2 groups were prepared, in solution phase, by coupling of the appropriate amine to the methyl-2,3,4,5-tetrahydro-7-carboxyl-4-substituted-3-oxo-1H-1,4-benzodiazepine-2-acetate ester [2].

Variation of the substituent at the N4 position revealed a trend in the structure-activity relationships that warranted further investigation. Since the route for the solution-phase synthesis requires a separate preparation of each N4-substituted-7-carboxyl-1,4-benzodiazepine-2-acetate, we considered immobilizing the core N4-unsubstituted 1,4-benzodiazepine-2-acetic acid template (**1**) on a polymer-supported



(1) R = I or Br; R1 = H
(2) R = CONHR2; R1 = Me

resin and carrying out the N4 alkylation step, then incorporating the 7-position substituent. As shown in Scheme 1, the core 4-H-2,3,4,5-tetrahydro-7-iodo-3-oxo-1H-1,4-benzodiazepine-2-acetic acid template (**1**), Scheme 2 [3], was immobilized on super-acid sensitive Sasrin® resin [4] using N,N′-dicyclohexylcarbodiimide (DCC) and 4-pyrrolidinopyridine [5]. We selected the Sasrin® resin for its facile cleavage with low acid concentration, since we found that the 1,4-benzodiazepine nucleus was unstable for prolonged acid exposure.[1] Anion formation was achieved using 2 equiv of n-butyl lithium or lithium hexamethyldisilazane (HMDS) at low temperature (–78 to –45 °C), followed by the addition of ex-

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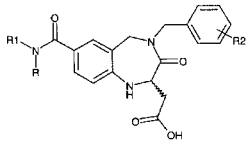
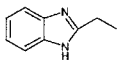
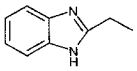
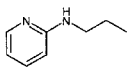
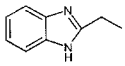
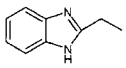
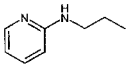
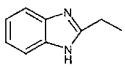
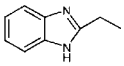
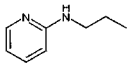
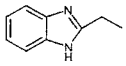
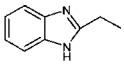
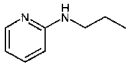
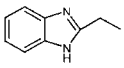
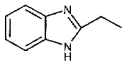
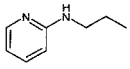
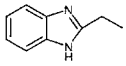
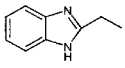
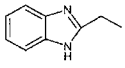
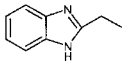
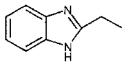
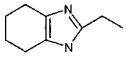
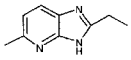
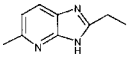
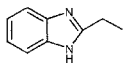
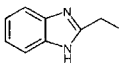
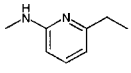
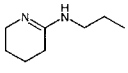
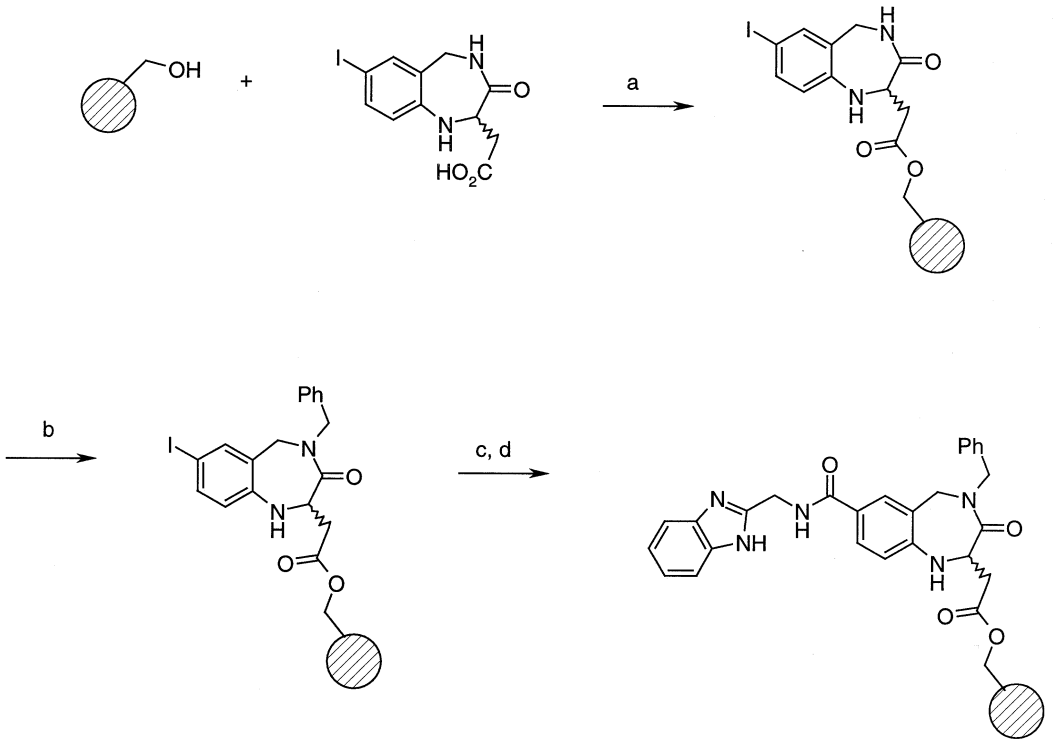
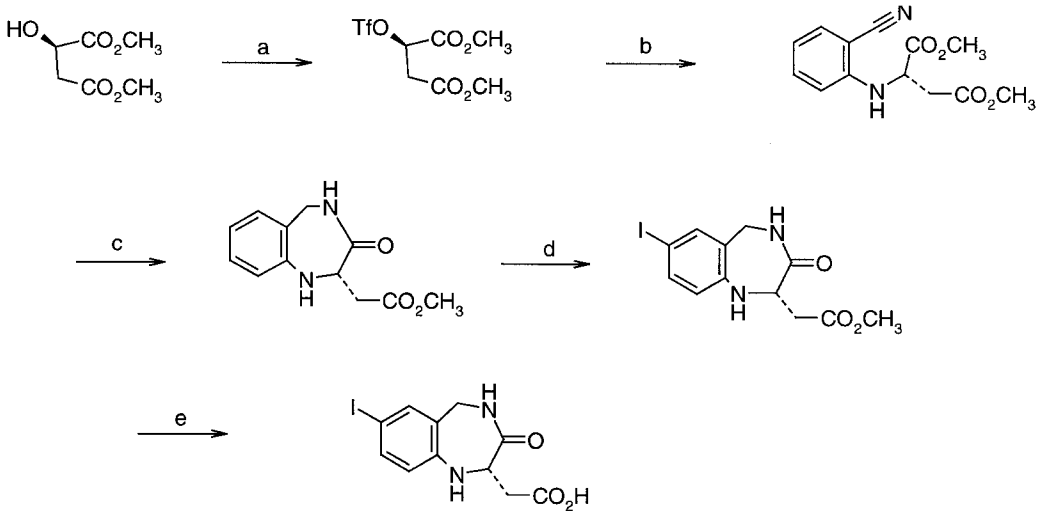
Table 1. 4-Substituted 2,3,4,5-tetrahydro-7-substituted (methylamino) carbonyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid analogs[4]



No	R1	R	R2	No	R1	R	R2
1		H	H	2		CH_3	H
3		H	H	4		H	$2,4,6,(CH_3)_3$
5		CH_3	$2,4,6,(CH_3)_3$	6		H	$2,4,6,(CH_3)_3$
7		H	4-CF_3	8		CH_3	4-CF_3
9		H	4-CF_3	10		H	2- CH_3
11		CH_3	2- CH_3	12		H	2- CH_3
13		H	4-NO_2	14		CH_3	4-NO_2
15		H	4-NO_2	16		CH_3	3-CN
17		CH_3	4-OCH_3	18		CH_3	4-OCF_3
19		CH_3	4-t-Bu	20		CH_3	2,3,4-F
21		cycl.	H	22		CH_3	H
23		H	H	24		CH_3	H
25		CH_3	2- OCH_3-4-NO_2	26		CH_3	3-CF_3
27		CH_3	H	28		H	H



Scheme 1. (a) Sasrin® resin, DCC, 4-pyrrolidinopyridine (15 mole %), DMF, RT, 18 h; (b) 2 equiv n-BuLi, anhydrous distilled THF at –78 °C, 90 min, 15 equiv BnBr in DMF at –78 °C to RT, 18 h; (c) 2-(aminomethyl) benzimidazole, Hunig's base, bis-(triphenylphosphine) palladium Il chloride (0.2 equiv), carbon monoxide balloon, NMP at 110 °C, 3 h; (d) 2% trifluoroacetic acid in dichloromethane.



Scheme 2. (a) Triflic anhydride $(TfO)_2$/pyridine CH_2Cl_2 at 0 °C (95%); (b) 2-aminobenzonitrile, 2,6-di-tert-butylpyridine in $CHCl_3$/Hex mix for 3 days, flash silica (EtOAc/Hex) (62%); (c) H_2 balloon, Ra Ni, Et_3N, MeOH for 2 days, flash silica (74%), chiral HPLC analysis revealed ~30% of the R-enantiomer; (d) iodomonochloride/pyridine complex (from ICI and pyridine in CH_2Cl_2 at 5 °C for 20 min) in 1:1 CH_2Cl_2/MeOH at RT for 40 min (quant.); (e) 1 N NaOH (1.5 equiv) in 1:1 THF/MeOH, then neutralization (75%).

cess electrophile. Most of the electrophiles used were derivatives of benzyl bromide that provide a range of steric, electron-donating and electron-withdrawing properties.[2] The resin-bound N4-alkylated template was then reacted with a primary or a secondary amine using palladium (0) catalyzed carboamidation under modified Heck reaction conditions [6, 7]. The amines selected were of interest to the ongoing program. The progress of the reactions on solid support was followed by magic angle spinning ^{1}H NMR (MAS-NMR). Members of the array were cleaved from the resin using a low concentration (1–2%) of trifluoroacetic acid in dichloromethane solution. Upon cleavage from the resin, all members of the array, shown in Table 1, were characterized using ^{1}H NMR, HPLC and mass spectral analysis. In each case, a single component was obtained in > 80% purity, allowing for biological screening of the crude products without any further purification[3].

Intriguingly, the results that were confirmed by NMR indicated that a regioselective alkylation at N4 over Nl took place[4]. The regioselectivity observed can be attributed to the more acidic nature (lower pk_a value) of the N4 proton (amide) relative to the proton at N1 (aniline) [8]. In addition, we observed no reaction between the organolithium reagents and the aromatic halogen to give a halogen/lithium exchange, nor did these reagents react with the ester to prematurely cleave the compound from the resin.

In conclusion, we have developed an efficient solid-phase procedure to regioselectively alkylate at the N4 position of a 1,4-benzodiazepine that was utilized to produce a 28-membered array. The procedure is amenable for production of larger arrays and a bead-bound combinatorial library utilizing similar experimental practices and procedures as described herein.

Acknowledgements

We thank the departments of analytical chemistry and physical and structural chemistry for their supports in solution ^{1}H NMR, elemental and mass spectral analysis.

Notes

1. We found that prolonged acid exposure of the 1,4-benzodiazepine molecule resulted in diazepine ring opening and loss of the 2-carboxyl as a result of oxidative decarboxylation side products.
2. Other alkyl halide, such as methyl iodide was used successfully during the development of the procedure.
3. Alkylation of the N4 position gave 60–80% isolated yield based on weight gain of the resin of the N4 alkylated product; the carboamidation step afforded 30–50% yield of isolated product after cleavage and triturating with diethyl ether. All isolated products were characterized using ^{1}H NMR, HPLC and mass spectral analysis to indicate a single component, each with > 80% purity.
4. The regioselectivity for the N4 benzylation over N1 was confirmed during the development of the procedure by ^{1}H NMR using proton correlated spectroscopy (COSY) and ^{13}C NMR using heteronuclear multiple bond correlation (HMBC) for proton–carbon 2–3 bonds coupling correlation and heteronuclear multiple quantum coherence (HMQC) for direct proton–carbon coupling correlation. ^{1}H NMR of these compounds typified by entry 2 using a 36O MHz Bruker AMX3 60 spectrometer maintained at 300 K in DMSO-d_6/TFA: δ 7.8 (m, 2H), 7.55 (m, 2H), 7.19 (s, 5H), 7.17 (m, 1H), 7.1 (d, 1H), 6.58 (d, 1H), 5.48 (d, 1H), 5.15 (m, 1H), 5.0 (s, 2H), 4.75 (d, 1H), 4.4 (d, 1H), 3.85 (d, 1H), 3.10 (s, 3H), 2.85 (dd, 1H), 2.6 (dd, 1H). In developing a model reaction, the stoichiometry of the n-BuLi was varied from 1.1 to 6 equiv and only one regioisomer was observed.

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