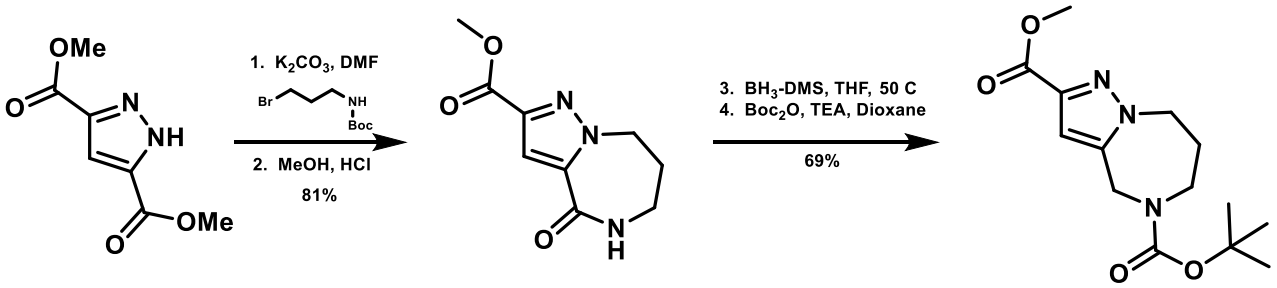
Synthesis and Chemistry of 5,6,7,8-Tetrahydro-4H-Pyrazolo[1,5-a] [1,4]Diazepine-2-Carboxylates.

Maya Natarajan[1], Anwar Hussain[1*], Jason S. Kingsbury[2] and Yu Kawamata[3]

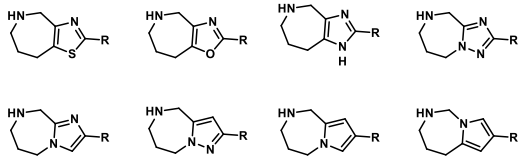
[1]Department of Chemistry, Socrates Biosciences Inc, 760 Calle Plano, Camarillo, CA 93012; [2]Department of Chemistry, California Lutheran University, Thousand Oaks, CA 93012; [3]Department of Chemistry, The Scripps Research Institute, Torrey Pines Road, La Jolla, CA 920301.



ABSTRACT: 5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a] diazepine carboxylates are valuable scaffolds for drug design and medicinal chemistry. In this paper we disclose a short scalable synthesis and chemical reactivity patterns of the pyrazolo-diazepine pharmacophore. Commercial and cheaply available Methyl pyrazole 3,5-dicarboxylate was alkylated with 3-bromo-N-Boc propyl amine and the resulting derivative underwent concomitant cyclization upon deprotection of the Boc protecting group to yield the pyrazolo-diazepine skeleton. Selective reduction of the lactam was accomplished cleanly using borane and the resulting amine was protected using a tert-butyloxycarbonyl protecting group. The free N-terminal of the diazepine underwent smooth Buchwald and Chan arylations among various standard chemistry applications examined on this pharmacophore.

Heterocycles play an incredibly important role in the drug design and discovery process. A wide array of heterocyclic scaffolds functionalized in myriad ways are readily available commercially in aid of lead optimization in drug discovery. They are used extensively to augment potency on target, improve selectivity off target, modify physical properties or improve metabolic stability and are ubiquitously represented in marketed drug molecules. Fused bicyclic saturated or unsaturated heterocycles represent another valuable subset in the armory of a medicinal chemist to utilize as a basic pharmacophore or a functional appendage in the discovery of new therapeutic entities. While the six-five fused heterocycles are widely known and studied in the field, the seven-five fused heterocycles are relatively novel. Figure 1 depicts a selection of seven-five fused bicyclic heterocycles based on hexahydroazepines and homopiperazines.

Figure 1. Representative hexahydroazepines and homopiperazine based 7,5 fused heterocycles.

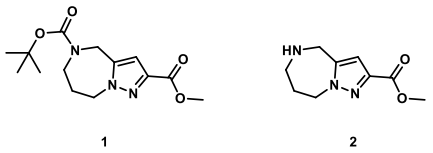


In conjunction with a program to design kinase inhibitors, we needed to make tetrahydropyrazolo diazepine 2-carboxylates and its derivatives. A survey of the literature indicated only one report on the synthesis of 2-carboxylated-tetrahydro-pyrazolo [1,4] diazepines[1]. A nosylated propargyl amine derivative **3** was first prepared from propargyl amine followed by alkylation of the sulfonamide by 1,3-bromo chloro propane. The resulting chloro derivative **4** was subjected to a high temperature cycloaddition by with ethyl diazoacetate at 180 C resulting in the formation of the pyrazolo-diazepine skeleton. The nosyl protecting group was removed using thiophenol under basic conditions to yield **6** (Scheme 1)[1]. For obvious reasons this synthesis is not readily adoptable on small scales due to the exotic starting materials and the large number of steps including a thermal cycloaddition using diazo acetate. The use of diazo acetate in a thermal cycloaddition at high temps is inherently dangerous. As such this synthesis is not practical and cannot be safely scaled up in significant quantities. Another reported synthesis of 2-Nitro tetrahydro pyrazolo [1,4] diazepines (Scheme 2)[2] starts with the not so readily available 2-nitro pyrazole-5-carboxylate **7**. Alkylation of the pyrazole with dibromo propane followed by reduction of the carboxylate to the corresponding primary alcohol using lithium borohydride and conversion of the resulting alcohol to its bromide using phosphorus tribromide in refluxing chloroform gave **10** which was set up to form a seven membered ring upon treatment with a suitable amine. In the literature precedent[2], methyl amine was used resulting in **11** a N-methyl pyrazolo-diazepine scaffold. It is conceivable that using benzyl amine would provide the analogous N-benzyl derivative, which could be deprotected to the corresponding diazepine after hydrogenolysis. The drawback of this synthesis arises from its use of exotic starting

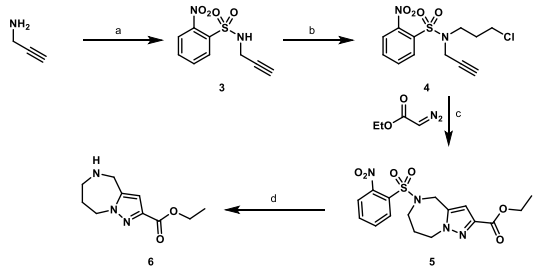
materials and multi-step transformation using harsh reaction conditions.

4-oxo pyrazolo diazepine carboxylates (**14**, Scheme-2) have been utilized as pharmacophore in drug candidates. Scientists at Merck[3] have reported a simple large scale synthesis of 4-oxo pyrazolo diazepine derivatives. We found it reasonable to take advantage of this synthesis of Oxo-pyrazolo-diazepines and use this intermediate as the starting material for the synthesis of pyrazolo diazepine 2-carboxylates provided a suitable reduction condition of the internal amide could be carried out while leaving the ester functionality intact. We postulated that this strategy would infact provide an easy entry into the pyrazolo diazepine 2-carboxylates.

Figure 2. 5,6,7,8-Tetrahydro Pyrazolo Diazapine 2-Carboxylates

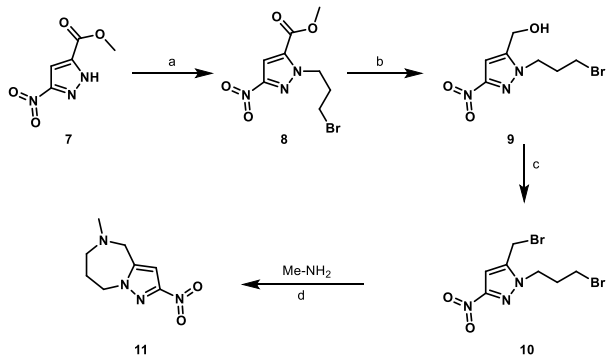


Scheme 1. Literature synthesis of 2-carboxylated-tetrahydro-pyrazolo [1,4] diazepines.



Reagents and conditions. a) K_2CO_3, NsCl, b) K_2CO_3, 1-Br-3-Cl-propane, c) ethyl diazoacetate, PhH, 140 ^oC, microwave, d) Thiophenol, cesium carbonate, acetonitrile.

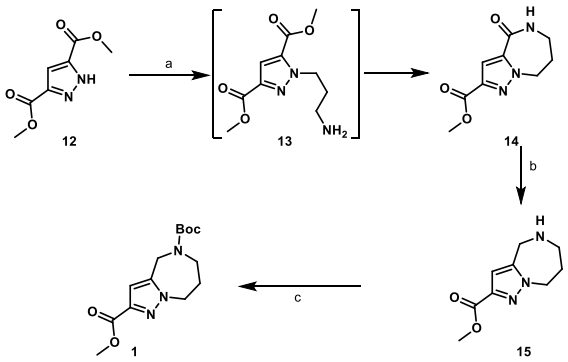
Scheme 2. Literature synthesis of 2-nitro-tetrahydropyrazolo[1,4] diazepines.



Reagents and conditions. a) K_2CO_3, 1,3-dibromopropane b) $LiBH_4$, THF, 0 ^oC, c) PBr_3, $CHCl_3$, reflux d) Methyl amine, THF, RT

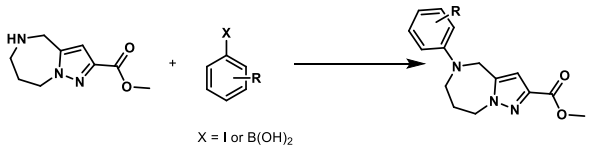
Pyrazole-3,5-dicarboxylic acids and their corresponding esters are readily available commercially. Alkylation of Methyl pyrazole 3,5-dicarboxylate with 3-Bromo propyl amine mediated using DBU in acetonitrile gave compound **14** in high yields. The key step of selective reduction was attempted using two conditions. Phenylsilane in presence of nickel chloride gave product **15** albeit with a modest yield of 30%. Reduction using borane-dimethyl sulfide complex in tetrahydrofuran at 50 C gave much superior conversion and the crude reaction was taken forward to the Boc derivative **1** using standard conditions. The Boc derivative **1** could be isolated in approximately 65% yield (3 steps from **12**). Capitalizing on the earlier work by the Merck group we were able to gain a practical and effective entry into pyrazolo [1,4] diazepine-2-carboxylate pharmacophore.

Scheme 3: New synthesis of 2-carboxylated tetrahydro pyrazolo [1,4] diazepines.



Reagents and conditions. a) 3-bromo propyl amine, DBU, ACN, THF 87% b) BMS, THF, 50 °C, and c) Boc_2O, TEA, Dioxane (68% over 2 steps).

Table 1. Buchwald and Chan arylation reactions on Tetrahydro-4H-pyrazolo [1,5-a] [1.4] diazepine 2-carboxylate



R	Yield (%)	
	Buckwald Coupling	Chan-Lam Coupling
-H	72%	68%
4-OMe	81%	59%
4-CF_3	80%	69%
2-Cl	59%	55%
4-*t*-Bu	79%	66%
3-Ph	78%	65%
4-Ph	78%	68%
3-Cl	69%	63%
3-COOMe	65%	60%

3-CN	62%	62%

Reagents and conditions. a) Buchwald: when X = I; $Pd(dba)_3$ (0.02), BINAP (0.03), Cs_2CO_3 (3 eq), Ar-I (1.1 eq) Toluene, 110 ^oC, 8h. b) Chan-Lam when X = $B(OH)_2$; $Cu(OAc)_2$ (0.2 eq), Ph-$B(OH)_2$ (1.6 eq), MeOH, RT, 12h.

With the synthesis of the 2-carboxylated tetrahydro pyrazolo [1,4] diazepines in hand, we decided to explore the utility of this scaffold towards installation of Aryl moiety on the diazepine N-atom. We have observed that both Buchwald arylations and Chan-Lam arylations proceeded with ease to yield the desired Arylated products. Buchwald coupling were carried out with Aryl iodides as coupling partners. It is conceivable that Aryl bromides would be similarly effective but that was not investigated at the time of preparation of this manuscript. Chan-Lam couplings were carried out by simply dissolving the starting diazepine in methanol followed by addition of the relevant boronic acid and copper (II) acetate. While the Chan-Lam couplings were easier to execute, the yields using the Chan-Lam arylations were consistently slightly lower than the corresponding Buchwald couplings. Nevertheless, this orthogonal arylation using Aryl boronic acids or Aryl iodides for N-arylation on the diazepines would be deemed useful.

ASSOCIATED CONTENT

AUTHOR INFORMATION

Corresponding Author

* Anwar.hussain@socratesbio.com, *Department of Chemistry, Socrates Biosciences Inc, 760 Calle Plano, Camarillo, CA 93012.*

Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript. AH, MN, JK, YK & PSB conceived the ideas illustrated in this manuscript. AH & MN carried out all the synthesis and characterization. AH wrote the manuscript with input from all co-authors.

ACKNOWLEDGMENT

MN would like to thank the scientific group at Socrates Biosciences for their guidance and scientific collaborations.

REFERENCES

1. a) Blackburn, Christopher; Chin, Janice; Gigstad, Kenneth M.; Xu, He, United States, US20110251184 A1 2011-10-13; b). Lin, Hong; Luengo, Juan; Johnson, Neil; Hospital, Audrey, World Intellectual Property Organization, WO2023154766 A1 2023-08-17
2. a) Garnier, Jean-Marc Daniel; Brzozowski, Martin; Feutrill, John Thomas; Lessene, Guillaume Laurent; Gardner, Christopher; Czabotar, Peter Edward; Cowan, Angus; Davies, Katherine; Sharma, Pooja; Schuster-Klein, Carole Annie; Poitevin, Christophe, World Intellectual Property Organization, WO2021253095 A1 2021-12-23; b) Brzozowski, Martin; Garnier, Jean-Marc Daniel; Gardner, Christopher; Lessene, Guillaume Laurent; Kersten, Wilco, World Intellectual Property Organization, WO2023115149 A1 2023-06-29
3. a) Jimenez-Somarribas, Alberto; Mao, Shuli; Yoon, Jeong-Joong; Weisshaar, Marco; Cox, Robert M.; Marengo, Jose R.; Mitchell, Deborah G.; Morehouse, Zachary P.; Yan, Dan; Solis, Ivan; Liotta, Dennis C. ; Natchus, Michael G.; Plemper, Richard K., Journal of Medicinal Chemistry (2017), 60(6), 2305-2325; b) Peng, Hairuo; Xin, Zhili; Zhang, Lei; Sun, Lihong; Kumaravel, Gnanasambandam; Taveras, Art, World Intellectual Property Organization, WO2014152725 A1 2014-09-25
4. a) Surase, Yogesh B.; Samby, Kirandeep; Amale, Sagar R.; Sood, Ruchi; Purnapatre, Kedar P.; Pareek, Pawan K.; Das, Biswajit; Nanda, Kamna; Kumar, Subodh; Verma, Ashwani K., "Identification and synthesis of novel inhibitors of mycobacterium ATP synthase." *Bioorganic & Medicinal Chemistry Letters* 27.15 (2017): 3454-3459.; b) Cvetovich, Raymond J.; Pipik, Brenda; Hartner, Frederick W.; Grabowski, Edward J. J., "Rapid synthesis of tetrahydro-4H-pyrazolo [1, 5-a] diazepine-2-carboxylate." *Tetrahedron letters* 44.31 (2003): 5867-5870.
5. a) Fors, Brett P., and Stephen L. Buchwald. "A multiligand based Pd catalyst for C− N cross-coupling reactions." *Journal of the American Chemical Society* 132.45 (2010): 15914-15917.; b) Fors, B. P., and S. L. Buchwald. "A Multiligand-Based Palladium Catalyst for CN Cross-Coupling Reactions." *Synfacts* 2011.02 (2011): 0199-0199.
6. a) Chan, Dominic; Monaco, Kevin; Li, Renhua; Bonne, Damien; Clark, Charles; Lam, Patrick (2003). "Copper Promoted C-N and C-O Bond Cross-coupling with Phenyl and Pyridylboronates". Tetrahedron Lett. 44: 3863–3865. b) Antilla, Jon C., and Stephen L. Buchwald. "Copper-catalyzed coupling of arylboronic acids and amines." *Organic Letters* 3.13 (2001): 2077-2079.; c) Quach, Tan D., and Robert A. Batey. "Ligand-and base-free copper (II)-catalyzed C− N bond formation: cross-coupling reactions of organoboron compounds with aliphatic amines and anilines." *Organic letters* 5.23 (2003): 4397-4400.
7. Procedure for synthesis of **1**. Compound 12 (18 g, 97.8 mmoles) was dissolved in a mixture of 27 mL of acetonitrile and 156 mL of tetrahydrofuran. To the reaction mixture was added Diazabicycloundecane (73 mL, 489 mmoles, 5 eq) followed by cooling the reaction mixture to zero degrees and slow addition of 3-bromo propyl amine hydrogen bromide salt (42.8 g, 195 mmoles, 2 eq). The reaction mixture was stirred for 18 h at room temperature. The reaction mixture was cooled to 10 ^oC followed by addition of 200 mL of

ethyl acetate and 200 mL of phosphoric acid . The organic layers was separated and washed with brine and dried over sodium sulfate and concentrated to give **14** (18 g, 87%). **14** (5 g, 24 mmoles) was dissolved in 90 mL of anhydrous tetrahydrofuran. The reaction mixture was cooled to 0 ºC followed by slow addition of borane-dimethyl sulfide (47.8 mmoles, 2.0 eq) . After stirring at 0 ºC for 15 minutes, the reaction mixture was heated to 70 ºC for 3 hours. After heating the reaction was cooled back to room temperature followed by dropwise addition of 4N hydrochloric acid in dioxane (20 mL). The reaction was stirred for 30 minutes and the resulting white precipitate was filtered and dried to yield 5 g of **15**. This white precipitate was dissolved in 90 mL of dichloromethane, followed by addition of triethyl amine (15 mL, 108 mmoles) followed by addition of $(Boc)_2O$ (5.6 g, 26 mmoles) . The reaction was stirred for 1 hour at room temperature . After stirring the reaction mixture was diluted with 90 mL of dichloromethane, washed with saturated bicarbonate solution, brine, dried over sodium sulfate and concentrated to a residue which was purified by column chromatography to yield 4.8 g of **1**.