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Synthesis of a library of 2-aryl-2*H*-tetrazole-5-carboxamides for photoaffinity labeling of aminergic G-protein coupled receptors

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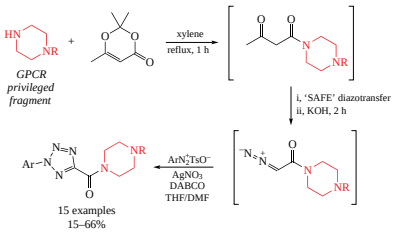
A four-step approach to 2-aryl-2*H*-tetrazole-5-carboxamides bearing GPCR-focused *N*-substituted piperazine residues involves 'SAFE' diazotransfer onto 1-(piperazin-1-yl)butane-1,3-diones followed by [3+2] cycloaddition of arenediazonium cations at the intermediate α-diazo acetamides. The compounds prepared are intended for photoaffinity labeling of aminergic G-protein coupled receptors.



Keywords: α-diazo acetamides, [3+2] cycloaddition, silver(I) catalysis, tetrazoles, GPCR privileged ligands, photoaffinity labeling.

In the current drug discovery paradigm, reliable linking of the observed pharmacological response to an interaction of the therapeutic agent with a specific protein target in the organism is a must from both scientific and regulatory prospective.[1] First described in the 1970s,[2] photoaffinity labels are the powerful tools for 'freezing' such ligand–protein interactions through covalent cross-linking, and have a broad utility in medicinal chemistry and drug discovery.[3] The earlier approaches to photoactivated protein labeling were fairly non-specific, working through non-specific C−H/X−H bond insertion reactions with the protein of interest by the highly reactive photo-generated intermediate.[4] However, more recently, ligand-directed photoaffinity labeling emerged[5] which allowed not only for identification but also for mapping of the binding sites of various small molecule biotargets.[6]

A range of photoactivated reactive functionalities have been employed in the design of photoaffinity labels including the earliest examples of phenyl azide,[7] diazirine[8] and benzophenone[9] groups. Recently, it was hypothesized that an appropriately functionalized photo-reactive tetrazole[10] could serve as a highly selective, electrophilic photoaffinity label for *in situ* target capture.[11] This led to the introduction of 2-aryl-5-carboxy-tetrazole (ACT) as a new photoaffinity label for drug target identification.[12] The main principle behind the photolabeling event is the generation of the reactive carboxy-nitrile imine (CNI) intermediate on irradiation of the tetrazole linked to the small molecule drug ligand. The reactive CNI intermediate was shown to interact with the nearby (aspartate and/or glutamate) carboxylate residues. The initial acyloxy hydrazone adduct is further transformed into more stable *N*,*N*′-diacyl hydrazine adduct which could be reliably detected by mass-spectrometry (Figure 1).[12]

Recently, we described a silver-catalyzed [3+2] cycloaddition between α-diazo carbonyl[13] or α-diazo sulfonyl[14] compounds and arenediazonium tosylates, which gave rise to 2,5-disubstituted tetrazoles. We reasoned that if the diazo partners for this

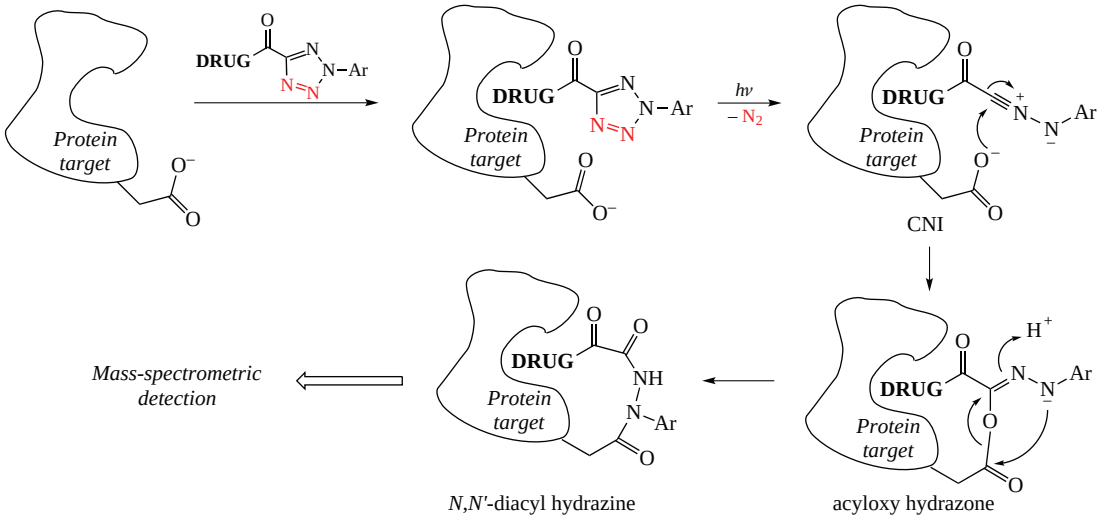


Figure 1 Mechanism of photoactivation of ACT for ligand-directed protein photoaffinity labeling.

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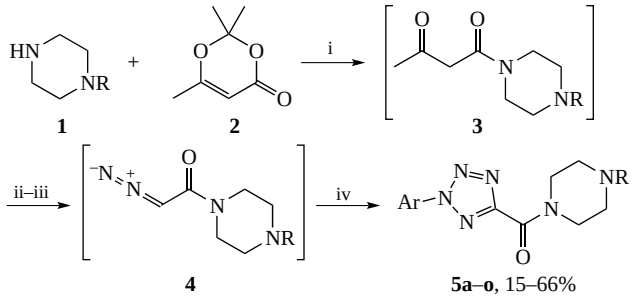
cycloaddition process were α-diazoacetamides containing, as the amide residues, moieties endowed with affinity to certain proteins, this would open an entry to a library of 2-aryl-2*H*-tetrazole-5-carboxamides as candidate tools for photoaffinity labeling of those biological targets. In light of our current interest to modulators of aminergic G-protein coupled receptors (specifically, trace amine-associated receptors[15,16]), in this work we focused on diversely *N*-substituted piperazine carboxamides. Such piperazine motifs are the well-established privileged motifs for GPCR ligand design.[17–19] Herein, we report on a practical realization of this strategy (Scheme 1).

The entire four-step synthetic sequence towards the target 2-aryl-2*H*-tetrazole-5-carboxamides **5a**–**o** included only one purification operation. Condensation of *N*-substituted piperazines **1** with Meldrum's acid **2** afforded 1-(piperazin-1-yl)butane-1,3-diones **3**. The latter were sufficiently C–H acidic to allow for the direct Regitz diazotransfer[20] under the recently developed 'sulfonyl-azide-free' ('SAFE') conditions which implies *in situ* generation of water-soluble 3-carboxybenzenesulfonyl azide (as a potassium salt) in aqueous acetonitrile and allows one to avoid handling of potentially hazardous sulfonyl azide diazotransfer reagents.[21,22] Following the treatment of the initial diazotransfer product with alkali (causing de-acetylation), α-diazoacetamide **4** ready for the silver-catalyzed [3+2] cycloaddition with arenediazonium salts was obtained. The latter reaction was conducted with arenediazonium tosylates $ArN_2^+TsO^-$ (prepared as described previously[13,14]) using $AgNO_3$ (10 mol%) as the catalyst. Following chromatographic purification, target *N*-substituted (2-aryl-2*H*-tetrazol-5-yl)(piperazin-1-yl)-methanones **5a**–**o** were obtained in moderate to good overall yields in four steps (see Scheme 1).



a Ar = 4-$MeOC_6H_4$, R = Bn, 54%
b Ar = 4-FC_6H_4, R = Bn, 34%
c Ar = 4-$F_3CC_6H_4$, R = Bn, 28%
d Ar = Ph, R = 4-$ClC_6H_4CH_2$, 24%
e Ar = 4-$MeOC_6H_4$, R = 4-$ClC_6H_4CH_2$, 34%
f Ar = 3,4-$(OCH_2CH_2O)C_6H_3$, R = 4-$ClC_6H_4CH_2$, 58%
g Ar = 4-(1-Ad)C_6H_4, R = 4-$ClC_6H_4CH_2$, 15%
h Ar = Ph, R = 4-$FC_6H_4CH_2$, 48%
i Ar = 4-$F_3CC_6H_4$, R = 4-$FC_6H_4CH_2$, 32%
j Ar = Ph, R = 2-$FC_6H_4CH_2$, 34%
k Ar = 4-$MeOC_6H_4$, R = 2-$FC_6H_4CH_2$, 38%
l Ar = Ph, R = 2-$MeOC_6H_4$, 58%
m Ar = 4-$MeOC_6H_4$, R = 2-$MeOC_6H_4$, 66%
n Ar = Ph, R = 3-$ClC_6H_4CH_2CH_2$, 58%
o Ar = 4-$MeOC_6H_4$, R = 3-$ClC_6H_4CH_2CH_2$, 15%

Scheme 1 *Reagents and conditions*: i, xylene, reflux, 1 h; ii, 3-$ClSO_2C_6H_4CO_2H$, NaN_3, K_2CO_3, MeCN (aq.), room temperature, 2 h; iii, KOH, MeCN (aq.), room temperature, 3 h; iv, $ArN_2^+TsO^-$, $AgNO_3$, DABCO, THF/DMF (10 : 1), room temperature, 18 h.

In conclusion, a streamlined approach to 2-aryl-2*H*-tetrazole-5-carboxamides bearing GPCR-focused *N*-substituted piperazine residues has been developed from simple and readily available precursors using the toolbox of diazo chemistry. The newly synthesized tetrazoles will be tested as photoactivated probes for the photoaffinity labeling of aminergic G-protein coupled receptors and the results will be reported in due course.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.09.011.

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