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Synthesis of PEG-Functionalized Amines Using Ruthenium-Catalyzed Hydrogen Borrowing

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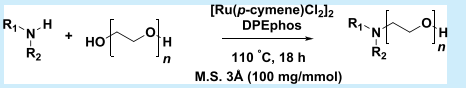
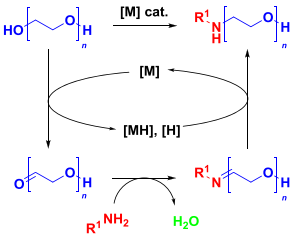
ABSTRACT: The polyethylene glycol (PEG) moiety has become increasingly important in medicinal chemistry. Herein, we describe the PEG functionalization of amines via hydrogen borrowing reductive amination. This was accomplished using the $[Ru(p\text{-cymene})Cl_2]_2$ catalyst and phosphorus-containing ligand dppf or DPE to yield a variety of PEGylated primary and secondary amine products. Furthermore, we illustrate the utility of this method with the synthesis of quetiapine (Seroquel) in 62% isolated yield.



Hydrogen borrowing has been shown in the literature to be a powerful approach for C−C, C−N, and C−O bond formation.[1] The basic concept of hydrogen borrowing involves a metal-catalyzed dehydrogenation of a primary or secondary alcohol into the corresponding aldehyde or ketone. The aldehyde or ketone forms an imine that is subsequently reduced by a previously abstracted hydride, thus "borrowing" the hydrogen (Scheme 1). This reaction can be catalyzed by both metals and metal oxides (Pd, Au, Ag, Ni, Cu, SiO_2, Al_2O_3, Ru, Ir, and Rh).[1−13]

Scheme 1. Hydrogen Borrowing Mechanism Applied to PEGs



Hydrogen borrowing processes can undergo one of two separate mechanistic pathways: the so-called "activation of reagent" or the "activation of intermediate".[14] Amine PEGylation belongs to the latter group, by which the nucleophilic species (PEG alcohol) is converted to an electrophilic species (PEG aldehyde).[15−17]

Recently, a plethora of alcohols and alcohol derivatives have been exploited as electrophilic sources for reductive amination.[18−23] One such alcohol is ethylene glycol, which has been shown in the literature to react with amines in this similar fashion to form linear chains as well as piperazine.[24] While ethylene glycol has shown up in hydrogen borrowing papers to the best of our knowledge, there are no reported examples of hydrogen borrowing reactions involving polyethylene glycol (PEG) as an electrophilic source.

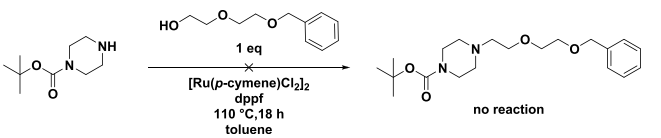
PEG linkers have found great utility in biotechnological and biopharmaceutical applications such as ADCs (antibody−drug conjugates), PDCs (peptide−drug conjugates), and DDSs (drug-delivery systems).[25−27] In medicinal chemistry, their relatively inert nature and enhanced hydrophilicity could help improve aqueous solubility among other preferred attributes.[28] This makes synthetic methods for the introduction of PEG linkers in medicinally relevant molecules very attractive.

Herein, we describe the hydrogen borrowing of PEG chains employing $[Ru(p\text{-cymene})Cl_2]_2$ transferred to amine nucleophiles. We tested a range of PEG lengths from diethylene glycol to octaethylene glycol.

Initial attempts at hydrogen borrowing using the standard conditions described by Williams failed to yield product (Scheme 2) due to difficulty with the oxidation step of the glycolic alcohol.[19] We believe this difficulty is likely due to the deactivating effect of the β-oxygen of the glycol chain.

Modification of Williams' protocol led to the discovery that using triethylene glycol **2** as the solvent (14 equiv) promoted the formation of PEGylated target **3**. From this initial result, a reaction screen was performed and led to conditions that achieved the best conversion of our desired PEGylated product **3** (Table 1). 4-(Naphthalen-2-yl)piperidine hydrochloric salt **1**

Scheme 2. Williams Conditions Using Monoprotected Glycol



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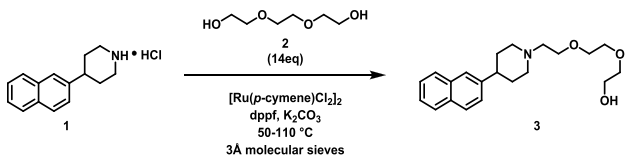
was used to efficiently evaluate the reaction due to the hydrophobicity and strong UV activity of the naphthyl moiety.

Table 1. Screening of Reaction Conditions[a]



entry	[Ru(*p*-cymene)Cl_2]$_2$ (mmol)	dppf (mmol)	K_2CO_3 (mmol)	temp (°C)	time (h)	conversion (%)[b]
1	0.02	0.05	2	110	16	68
2	0.02	0.05	–	110	16	93 (55)[c]
3	0.02	0.05	–	50	72	<1
4	0.02	0.05	–	110	16	28[d]
5	0.02	0.05	–	110	16	6[e]
6	–	0.025	–	110	16	<1[d]
7	0.01	–	–	110	16	<1[d]
8	–	–	–	110	16	–[d]

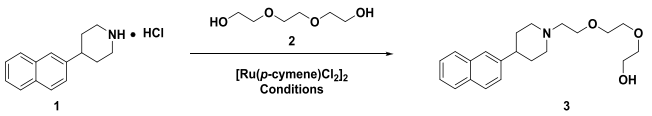
[a]General conditions: triethylene glycol **2** (14 mmol, 2 mL), [Ru(*p*-cymene)Cl_2]$_2$, dppf, and 3 Å molecular sieves (100 mg/mmol) were degassed and stirred at the respective temperature for 1 h. **1** (1 mmol) and base were added. [b]Conversions determined by LC-MS analysis. [c]Isolated yield. [d]No molecular sieves present in the reaction mixture. [e]With 1 mL of water.

The inexpensive [Ru(*p*-cymene)Cl_2]$_2$ catalyst system exhibited a good reductive amination efficiency as well as a low air sensitivity. The first attempt (entry 1) was performed in the presence of K_2CO_3 to accelerate the oxidation step, resulting in 68% conversion of our PEGylated target. However, removal of K_2CO_3 led to an increase in product conversion from 68% to 93% via LC-MS analysis and provided the desired PEGylated piperidine in 55% isolated yield (entry 2). We further evaluated the parameters of our protocol by decreasing the reaction temperature (entry 3), eliminating the use of molecular sieves (entry 4), and adding water (entry 5). Control reactions were also performed in the absence of catalyst, ligand, or both (entries 6–8). In each case, we observed a drastic decrease in the final conversion.

We next examined suitable co-solvents that would allow us to decrease the number of equivalents of glycol. We also investigated an additional ligand and various additives to evaluate their effect on product conversion (Table 2).

Decreasing the amount of triethylene glycol from 14 to 7 equiv and diluting the reaction mixture with various solvents resulted in poor conversion (entries 1–12, Table 2). The LC-MS yields ranged from no reaction to 37%; the best result was achieved with toluene, giving a final isolated yield of 31% (entry 1). Base additives appeared to be detrimental to product formation (entries 17–19). Additionally, the use of crown ethers appeared to have little or no positive effect on the reaction outcome (entries 13–16). However, we observed a significant improvement in conversion (98%) and isolated yield (66%) switching the ligand from dppf to DPEphos (entry 22), though using PEG as a solvent.

Table 2. Hydrogen Borrowing Protocol Optimization[a]



entry	[**1**] (mmol)	**2** (equiv)	solvent[b]	[Ru(*p*-cymene)Cl_2]$_2$ (mmol)	ligand dppf (mmol)	additive (equiv)	[**3**] (LC-MS %)
1	0.5	7	toluene	0.025	0.05	–	37 (31%)[d]
2	0.5	7	diglyme	0.025	0.05	–	16
3	0.2	7	diglyme	0.05	0.1	–	–
4	0.2	7	diglyme	0.1	0.2	–	–
5	0.5	7	dioxane	0.025	0.05	–	<1[e]
6	0.5	7	*tert*-butanol	0.025	0.05	–	38
7	0.5	7	*tert*-amyl alcohol	0.025	0.05	–	17
8	0.2	7	*tert*-amyl alcohol	0.05	0.1	–	–
9	0.5	7	NMPO	0.025	0.05	–	<1
10	0.5	7	AcOH	0.025	0.05	–	<1
11	0.4	7	CPME	0.025	0.05	–	<1
12	0.4	7	DCE	0.025	0.05	–	<1[e]
13	0.5	14	–	0.025	0.05	18-crown-6 (0.5)	98 (62%)[d]
14	0.5	7	*tert*-amyl alcohol	0.025	0.05	18-crown-6 (0.5)	4
15	0.5	7	diglyme	0.025	0.05	18-crown-6 (0.5)	30
16	0.4	14	–	0.025	0.05	15-crown-5 (0.5)	35
17	0.2	14	–	0.025	0.05	Cs_2CO_3 (2)	25
18	0.2	14	–	0.025	0.05	KOH (2)	<1
19	0.2	14	–	0.025	0.05	NaOH (2)	<1
20	0.4	14	–	0.05	0.1	–	17 (55%)
21	0.4	14	–	0.01	0.02	–	30
22	0.4	14	–	0.02	0.04[c]	–	99 (66%)[d]
23	0.2	7	diglyme	0.02	0.04[c]	–	–

[a]Reactions performed at 110 °C in the presence of activated 3 Å molecular sieves (100 mg/mmol) and checked with LC-MS after 16 h. Triethylene glycol, catalyst, and ligand were prestirred for 1 h at 110 °C before the addition of amine. The reaction mixture was degassed (three cycles of vacuum per nitrogen). [b]At 0.25 M. [c]DPEphos. [d]Isolated yield. [e]Reaction temperature of 90 °C.

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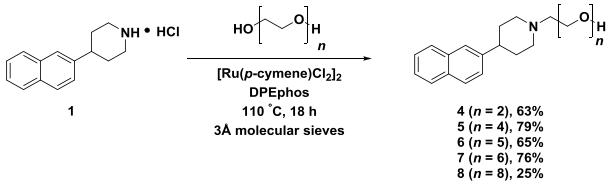
With optimized reactions conditions in hand, the PEGylation of 4-(naphthalen-2-yl)piperidine hydrochloride salt using different glycol chain lengths (Scheme 3) was examined. Good yields

Scheme 3. Piperidine PEGylation with Different Glycols[a]

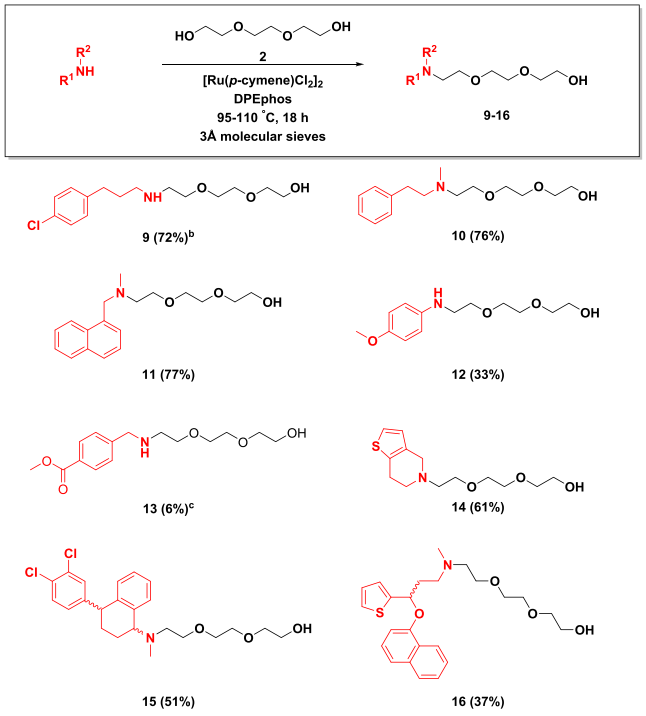


[a]PEG (5.6 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (0.02 mmol), DPEphos (0.04 mmol), and 3 Å molecular sieves (100 mg/mmol) were stirred for 1 h at 110 °C. **1** (0.4 mmol) was added, and the reaction mixture was stirred at 110 °C for 18 h.

were obtained for the PEGylations of the piperidine in most cases. However, the longest PEG ($n = 8$) example resulted in an only 25% isolated yield. The increase in the length of the PEG chain coincides with an enhanced hydrophilicity and water solubility of the final product, which presented workup and purification challenges.

We next evaluated a wider range of amines to more effectively assess the scope of the protocol (Scheme 4). Under optimized conditions, we were able to synthesize a large array of PEGylated amines.

Scheme 4. Amination of Triethylene Glycol[a]

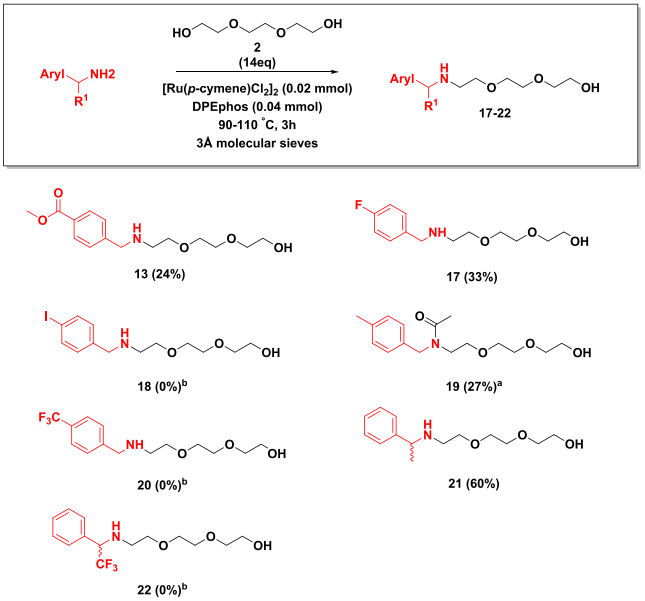


[a]PEG (5.6 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (0.02 mmol), DPEphos (0.04 mmol), and 3 Å molecular sieves (100 mg/mmol) were stirred for 1 h at 110 °C. Amine (0.4 mmol) was added, and the reaction mixture was stirred at 110 °C for 18 h. [b]Primary amines need a temperature of 95 °C due to the high reactivity and the formation of the di-PEGylated adduct. [c]Yields of 60% recovered starting material and 34% di-PEGylated adduct.

Compounds **9** and **10** were isolated in good yield (72% and 76%, respectively). Secondary benzylic amine **11** (77%) and the electron-rich aniline **12** (33%) were also obtained. The low yield of aniline can be explained by its poor nucleophilicity. Benzylamine **13** resulted in an only 6% yield, with recovered starting material (60%) and di-PEGylated adduct (34%) being the major components. Compound **14**, utilizing the important antibacterial building block 4,5,6,7-tetrahydrothieno[3,2-*c*]-pyridine, was obtained in 61% yield.[29] This provides an interesting alternative scaffold for the synthesis of such bioactive compounds. This protocol was also shown to synthesize PEGylated versions of commercial drug substances such as sertraline (Zoloft) **15** (51%), an antidepressant of the selective serotonin reuptake inhibitor (SSRI) class, and duloxetine (Cymbalta) **16** (37%), used for the major depressive disorder treatment.[30,31]

Benzylamines seemed to give a di-PEGylated product similar to primary amine **9**. We decided to employ a similar strategy of decreasing the temperature but also decreasing the time (Scheme 5). Even with these modifications, both electron-rich

Scheme 5. PEGylation of Benzylamines



[a]The product was acetylated to ease isolation. Acetylation conditions: Ac_2O (3 equiv), TEA (2 equiv), DCM (1 mL), 0.3 h, rt. [b]Only starting material recovered.

and electron-poor benzylamines showed a low conversion and a relatively low isolated yield. The yield of compound **13** was improved from 6% to 24%. Benzylamines **17** and **19** were isolated in yields of 33% and 27%, respectively, with **19** requiring a transformation to an acetyl derivative after PEGylation to ease chromatographic isolation. Syntheses of *p*-iodobenzylamine **18** and *p*-trifluoromethylbenzylamine **20** were also attempted but resulted in recovery of only starting material. α-Methyl analogue **21** gave an improved 60% yield. Reaction of α-trifluoromethyl benzylamine **22** led to only recovered starting material. Considering competitive dimerization of the amine and the difficulty of isolation, the primary benzylamines proved to be a challenging substrate for the PEGylation. However, α-methyl substrates were compatible with the PEGylation conditions, affording satisfactory yields of the product.

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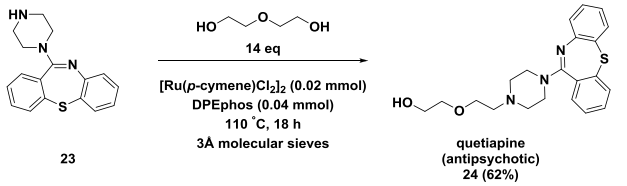
We applied our optimized hydrogen borrowing conditions to the synthesis of quetiapine (Seroquel), an antipsychotic for the treatment of schizophrenia, bipolar disorder, and major depressive disorder.[32] Starting from 11-(piperazin-1-yl)-dibenzo[*b*,*f*][1,4]thiazepine **23**, we were able to synthesize quetiapine **24** directly in 62% isolated yield (Scheme 6). This synthesis demonstrates an alternative preparation for this bioactive compound in a yield comparable to those of published routes.[33]

Scheme 6. Seroquel Synthesis



In conclusion, we have shown the first direct PEGylation of amines exploiting hydrogen borrowing with aliphatic and benzylic amines, as well as electron-rich anilines, utilizing the $[Ru(p\text{-cymene})Cl_2]_2$/DPEphos catalytic system. PEG alcohols reacted efficiently with primary and secondary aliphatic amines, piperidine, and piperazine, affording PEGylated products in good yields. We observed good yields exploring the scope of the glycol chain length using 4-(naphthalen-2-yl)piperidine hydrochloride as the starting material. A limitation to this method was found with benzylic PEG amines, as these substrates resulted in poor yields, except for α-methylbenzylamine. Lastly, we demonstrated the pharmaceutical application of this method with the synthesis of the antipsychotic quetiapine, affording the final target in 62% isolated yield.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01965.

Experimental procedures and characterization and spectral data for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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