Expedient Synthesis of Mequitazine an Antihistaminic Drug by Palladium Catalyzed Allylic Alkylation of Sodium Phenothiazinate

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A short and straightforward synthesis of the antihistaminic drug mequitazine is reported, based on an efficient palladium catalyzed allylic alkylation of 1-aza-bicyclo[2.2.2]oct-2-en-3-ylmethyl acetate using sodium phenothiazinate in mild conditions.

Key words antihistaminic drug; allylic alkylation; mequitazine; phenothiazine

The synthesis of therapeutically important drugs remains a major focus of attention among organic chemists in the academic world as well as in pharmaceutical companies. Particularly appealing is the notion of using green, short and scalable mild processes that rely on atom economy transformations.[2—4)] Importantly, a large number of synthetic bioactive molecules possess the 3-substituted quinuclidine moiety that exhibits a broad pharmacological profile (Fig. 1).[5—10)]

Mequitazine **1**, is a potent H_1-receptors selective antihistaminic drug widely studied and used for allergic disorders such as hay fever and urticaria. This molecule is also one of the earliest second-generation antihistamines on the market, sold as the trade name Primalan®, which is beneficial in the symptomatic treatment of allergic rhinitis.[11)] Recent studies have demonstrated its potential use for the treatment of allergic conjunctivitis, and for its possible sedative properties.[12)] As a consequence the development of efficient synthesis of **1** is of prime importance for clinical evaluations, and more importantly for the elucidation of the mechanism of action with different biological targets and receptors. The existing strategies for the preparation of mequitazine **1**, most of which have been patented, rely mainly on the construction of the C9-N bond, either by alkylation or acylation of phenothiazine using appropriate 3-substituted quinuclidine electrophiles.[13—18)] However, these approaches are plagued by severe drawbacks such as, the rapid formation of large amount of the elimination product arising from 3-halomethyl-quinuclidine electrophiles, or the degradation of the sensitive 3-acyl-quinuclidine halide derivative. As part of our ongoing program on medicinal chemistry,[16)] we wish to describe a new strategic approach that circumvents these limitations in developing a reliable synthetic route for an expedient synthesis of rac-mequitazine. The key step of our approach is based on the palladium catalyzed allylic alkylation of sodium phenothiazinate. As shown in Chart 1, we first started with the preparation of the key allyl acetate **8**. The treatment of the known epoxide[19,20)] **5** with lithium diethylamide in ether under reflux conditions, resulted in a remarkably clean conversion to the corresponding allyl alcohol **6**.[21—23)] To the best of our knowledge, this selective epoxide rearrangement has never been reported earlier for bicyclo[2,2,2]heterocycles containing epoxides.[24—29)] While three type of products could be obtained, allyl alcohols, aldehyde and saturated alcohols, arising most likely by carbenoid insertion processes,[24—26)] the transformation was highly selective and afforded the desired crucial allyl alcohol **6** exclusively, in 96% of isolated yield (see Experimental).

Alternatively, we have also discovered that **6** could be efficiently generated *via* the Shapiro reaction,[30—32)] by the known trisylhydrazone **7** with excess *n*-BuLi followed by quenching the nucleophilic vinyllithium reagent with paraformaldehyde.[33)] After acetylation of the alcohol **6** under standard conditions affording the allylic acetate **8**,[34)] the critical allylic alkylation step was studied and optimized. Palladium-catalyzed allylic amination is a well-established method for the synthesis of allyl amines.[35—37)] However, few reports have mentioned the use of soft nucleophilic amines or the use of diaromatic amine such as **9**.[38—41)] Accordingly, our initial investigation began by screening the palladium cata-

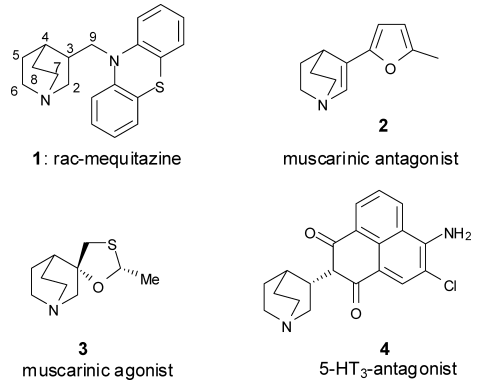
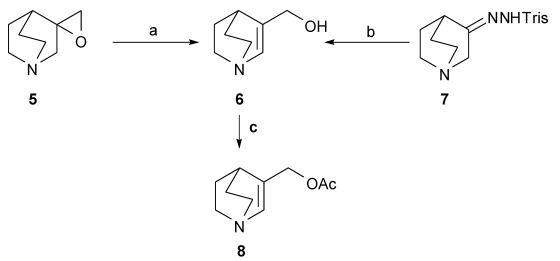


Fig. 1. Structure of Relevant 3-Substituted Quinuclidine Compound



a: *n*-BuLi, 2.5 eq., Et_2NH, 2.5 eq., Et_2O, reflux, 67 h, 96%
b: *n*-BuLi, 3 eq., THF -78°C (2h), 0°C (30 min.), then CH_2O, rt 3h, 91%
c: Ac_2O, CH_2Cl_2, 0°C to rt, 3h, 84%

Chart 1. Preparation of Key Allyl Alcohol **6**

This paper is dedicated to Dr. Charles Mioskowski.

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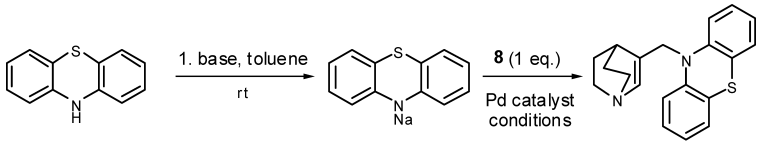
Table 1. Optimization of the Palladium Allylic Alkylation of Phenothiazine[a)]



9 10 11

Entry[a)]	Base	Alkylation solvent with **8**	Conditions	Pd catalyst	Yield[b)] (%)
1	—	THF	rt, 16 h	$Pd(PPh_3)_4$	0
2	$NaNH_2$	THF	rt, 16 h	$Pd(PPh_3)_4$	14
3	$NaNH_2$	THF	80 °C, 16 h	$Pd(PPh_3)_4$[c)]	33
4	$NaNH_2$	DMF	80 °C, 48 h	[1,1′-Bis(dppf)]$PdCl_2CH_2Cl_2$[c)]	<3[d)]
5	$NaNH_2$	DMF	80 °C, 48 h	$PdCl_2CH_3CN$[c,e)]	<3[d)]
6	$NaNH_2$	THF	110 °C, 48 h	$Pd(PPh_3)_4$	43
7	$NaNH_2$	THF	110 °C, 48 h	$Pd_2(dba)_3PPh_3$	45
8[f)]	NaH	THF	rt, 1 h 30	$Pd(PPh_3)_4$	74
9[f)]	NaH	DMF	rt, 1 h 30	$Pd(PPh_3)_4$	36
10[f)]	NaH	CH_2Cl_2	rt, 1 h 30	$Pd(PPh_3)_4$	40
11[f)]	NaH	DMSO	rt, 1 h 30	$Pd(PPh_3)_4$	28
12[f)]	NaH	THF/HMPT	rt, 1 h 30	$Pd(PPh_3)_4$	60
13[h)]	NaH	THF	rt, 1 h 30	$Pd(PPh_3)_4$	92

a) Unless otherwise stated, the reactions were performed by generating first the sodium phenothiazinate **10** (1 eq) in toluene with the indicated base. To this solution is then added *via* canula, a solution containing 1 eq of **8** premixed with the Pd catalyst (10 mol%). *b*) Isolated yield after column chromatography on silica gel. *c*) 20 mol% of Pd catalyst was used. *d*) Determined based on the analysis of the ^{1}H-NMR of the crude reaction mixture. *e*) 20 mol% of dppf (1,1′-bis(diphenylphosphino)ferrocene) ligand was added to the palladium catalyst. *f*) 2 eq of **9** was used and initially formed in THF, DMF, DCM, DMSO or THF/HMPT, the solvent of the reaction (see entries 8 to 12). *g*) 1 : 1 mixture (v/v). *h*) 3 eq of **9** was used.

lyst to evaluate their ability to promote efficiently, the allylic substitution of **8** with phenotiazine **9**. First, it appears that in the absence of base, at room temperature and in the presence of $Pd(PPh_3)_4$ as catalyst, the reaction failed to furnish the desired product **11** due to the presumed low nucleophilicity of the diaromatic amine **9** (Table 1, entry 1).

Interestingly, the use of sodium phenothiazinate **10**, generated first with sodium amide at room temperature gave, albeit in modest yield (14%), the expected coupled compound **11** (entry 2). Increasing the temperature to 80 °C with increased $Pd(PPh_3)_4$ catalyst (20 mol%) allowed to improve consistently the yield to 33% (entry 3). The substitution of $Pd(PPh_3)_4$ catalyst by commercial [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complexed with dichloromethane or $PdCl_2(CH_3CN)$, with the same loading (20 mol%), and prolonged reaction time (48 h) at 80 °C, was unsatisfactory since only minute amount (<3%) of **11** was detected by analysis of the ^{1}H-NMR of the crude reaction mixture (entries 4, 5). Gratifyingly, when the reaction was performed at higher (110 °C) for a prolonged reaction time 48 h, and in the presence of 10 mol% of $Pd(PPh_3)_4$ or $Pd_2(dba)_3$, 2,3-dehydromequitazine **11** was isolated in acceptable 43% and 45% of yield, respectively (entries 6, 7). At this point of our study, it was postulated that the *in situ* generated ammonia, due to the use of $NaNH_2$ as base, could poison and deactivate the palladium catalyst and/or might also react with the electrophilic allyl acetate **8** during the reaction. As a consequence, to further obtain the optimal conditions, a variety of variables including the choice of base, solvent, temperature, reaction time, and stoechiometry of the reactants were systematically explored.[42)] A survey of various solvents revealed that THF, combined with the use of sodium hydride as base, gave the product with better reactivities and shorter reaction time at room temperature. This improved result and conditions were reached when 2 eq of sodium phenothiazinate **10** was reacted with 1 eq of the allylic acetate **8** in the presence of 10 mol% of $Pd(PPh_3)_4$ (entry 8, 74%). In the same conditions, other solvent systems such as DMF, DCM, DMSO or the use of THF/hexamethylphosphoramide (HMPT) combination were less effective, and the isolated yield of **11** was always decreased (entries 9—12). Finally, the use of excess nucleophile **10** (3 eq) gave the desired product **11** in an excellent isolated yield of 92% (entry 13). The hydrogenation of **11** realized in MeOH under an atmosphere of hydrogen (1 atm), and in the presence of 20 mol% (w/w) of Pd/C delivered quantitatively and cleanly the targeted racmequitazine **1**, that matched with reported analytical data,[15)] in 54% of overall yield over 5 steps.

In summary, this contribution provides a convenient and expedient synthesis of racemic mequitazine **1** in high overall yield. Besides this achievement, the optimized approach based on the palladium catalyzed allylic alkylation offers a new general alternative for the incorporation of the 3-quinuclidine moiety, in complex molecular scaffolds. The development of this methodology for other saturated *N*-, *S*- and *O*-heterocycles with various nucleophiles is currently under investigation. Further studies devoted to the asymmetric hydrogenation of **11** are underway in our laboratories and will also be reported in due course.

Experimental

Typical Procedures for the Preparation of Allylic Alcohol 6 a) Epoxide Rearrangement: To an anhydrous Et_2O solution (5 ml) of diethylamine (200 μl, 1.96 mmol, 2.5 eq) at 0 °C, and under an atmosphere of Argon, is added dropwise *n*-butyllithium (1.2 ml, 1.96 mmol, 2.5 eq). The resulting mixture is stirred for 10 min, and an anhydrous Et_2O solution (1 ml) of the epoxide **5** (109 mg, 0.79 mmol, 1 eq) is added at 0 °C. The reaction medium is then stirred under reflux for 67 h. The mixture is then cooled to room temperature, quenched with an aqueous solution of K_2CO_3 (10%, 5 ml) and extracted trice with dichloromethane (3×6 ml). The combined organic phases were dried over Na_2SO_4, concentrated under vacuum to yield 101 mg the allylic alcohol **7** as a yellow oil (purity >95%, based on ^{1}H-NMR analysis)

that can be used for acetylation without any further purification step.

b) Shapiro Reaction: The trisylhydrazone **7** (10.3 g, 25.3 mmol, 1 eq) is first dissolved in anhydrous THF (50 ml) and the resulting homogeneous solution is cooled to −78 °C. *n*-Butyllithium (47.5 ml, 76 mmol, 3 eq) is then added dropwise over a period of 30 min. The red solution is then stirred for 2 h at −78 °C, and cooled to 0 °C. Nitrogen evolution takes place over a period of 15 min, while the reaction mixture turns from orange to yellow. Solid paraformaldehyde (2.28 g, 76 mmol, 3 eq) is then added at 0 °C and the reaction medium is stirred at room temperature for 3 h. During this period of time, the mixture turns to clear yellow color. The reaction is then quenched with an aqueous solution of K_2CO_3 (10%, 40 ml) and extracted with Et_2O (3×50 ml). The combined organic phases were dried over Na_2SO_4, filtered and evaporated to dryness. The crude is then purified by flash chromatography on silica (eluting with: CH_2Cl_2 : MeOH : NEt_3, 9 : 1 : 0.1, v/v/v) to yield **6** as a yellow oil (6.4 g, 91%).

Rf=0.1 (CH_2Cl_2 : MeOH, 9 : 1, v/v); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 6.15 (s, 1H), 4.08 (s, 2H), 2.78—2.87 (m, 2H), 2.42—2.54 (m, 3H), 1.50—1.60 (m, 2H), 1.30—1.50 (m, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 148.8, 133.6, 61.0, 49.2, 27.8, 27.5; IR (KBr) cm^{-1}: 3387, 2949, 2873, 1651, 1456, 1306, 1129, 1056, 1017, 765, 669; HR-MS (*m*/*z*): Calcd for $C_8H_{13}NO$: 139.0997, Found: 139.0994.

Typical Procedure for the Synthesis of 11 a) Preparation of sodium phenothiazinate **10**: To a stirred THF (8 ml) solution of phenothiazine **9** (150 mg, 0.75 mmol, 3 eq) and under an atmosphere of Argon, NaH (60% in oil, 33 mg, 0.83 mmol, 3.3 eq) is added portion wise. The reaction mixture is stirred for 25 min while the medium becomes dark green.

b) In an another flame dried flask under an Argon atmosphere, containing THF (2 ml) and the allylic acetate **7** (45.3 mg, 0.25 mmol, 1 eq), the palladium catalyst $Pd(PPh_3)_4$ is added (29 mg, 0.025 mmol, 10 mol%). The resulting red mixture is stirred for 10—15 min at room temperature and then transfered, *via* a canula to the flask containing the sodium phenothiazinate **10**. After 3 h at room temperature, the reaction is quenched with a saturated aqueous solution of K_2CO_3 (6 ml) and extracted with CH_2Cl_2. The resulting organic phases were dried with Na_2SO_4, and concentrated under vacuum. The crude green oil is then purified by flash chromatography on silica (eluting with: CH_2Cl_2 : MeOH : NEt_3, 96 : 4 : 0.5, v/v/v) to afford a slightly yellow solid (74 mg, 92%).

Rf=0.1 (CH_2Cl_2 : MeOH, 9 : 1, v/v); mp 149 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.06—7.15 (m, 4H), 6.90 (td, ^3J=7.4 Hz, ^4J=1 Hz, 2H), 6.82 (d, ^3J=8.0 Hz, 2H), 6.52 (s, 1H), 4.58 (s, 2H), 2.84—3.00 (m, 2H), 2.77 (s, 1H), 2.40—2.60 (m, 2H), 1.50—1.65 (m, 2H), 1.10—1.34 (m, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 144.9, 143.1, 138.4, 127.2, 127.1, 125.0, 122.8, 115.9, 49.5, 49.2, 28.0, 27.8; IR (KBr) cm^{-1}: 2943, 2867, 1593, 1571, 1463, 1365, 1319, 1286, 1255, 1219, 1127, 1038, 751; HR-MS (*m*/*z*): Calcd for $C_{20}H_{20}N_2S$: 320.1348, Found: 320.1452.

Typical Procedure for the Preparation of 1 by Hydrogenation of 11 A methanolic solution (2 ml) of **11** (35 mg, 0.11 mmol) containing 3.5 mg (10%, w/w) was first degassed at room temperature using a standard water pump. The flask atmosphere was then kept under an atmosphere of H_2 (1 atm) by charging a balloon containing hydrogen on the top of the flask. The reaction mixture is stirred at room temperature for 24 h. After total conversion of the starting material, the catalyst was filtered off, and the solvent was evaporated to dryness. The crude slurry was purified by column chromatography on neutral alumina eluting with ethyl acetate yielding 32 mg (91%) of analytically pure *rac*-mequitazine 1.

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