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Nucleophilic Capture of the Imino-Quinone Methide Type Intermediates Generated from 2-Aminothiazol-5-yl Carbinols

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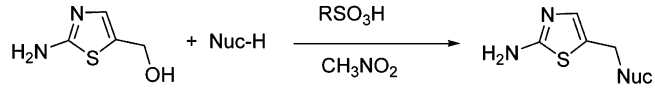
ABSTRACT



Generation of imino-quinone methide type intermediates from 2-aminothiazole-5-carbinols using alkylsulfonic acids in nitromethane followed by trapping with a wide range of nucleophiles effects C−C, C−O, C−N, C−S, and C−P bond formation.

Quinone methides (QM) have long been known to play key roles in the mechanism of action of many antitumor agents and natural products such as mitomycin C, adriamycin, and etoposide.[1] The potential toxicity of such intermediates is perhaps most well-known for the over-the-counter analgesic acetaminophen, which is metabolized in the liver to give an *N*-acyl-*p*-imino-quinone species that can covalently bind with proteins and nucleic acids.[2] Generation of QM species by bioreduction is utilized for release of drugs in the context of targeting.[3] Quinone methides also serve as useful intermediates in organic synthesis.[4] For example, in the field of anthracycline antibiotics, Angle reports the isolation of an *ortho*-quinone methide (*o*-QM) which undergoes addition reactions with amines, alcohols, thiols, and DNA bases.[5] Brown demonstrates that 5-hydroxyflavinoids are suitable substrates for acid-catalyzed solvolysis to an *o*-QM intermediate which is trapped by sodium benzenesulfinate to give a sulfone.[6] Furthermore, Borchardt describes the trimethylsilane reduction of an *o*-QM intermediate formed from 2-hydroxy benzyl alcohols in the presence of trifluoroacetic acid.[7] Gardner's work illustrates one of the first examples of C−C bond formation with an *o*-QM under basic conditions using sodium cyanide and diethyl malonate as the C-nucleophiles.[8] Macor reports the direct displacement of OH by amine and sulfonamide nucleophiles in hydroxymethylimidazoles.[9] Most recently, Martin reveals the trapping of carbocations stabilized by electron-rich aromatic rings with

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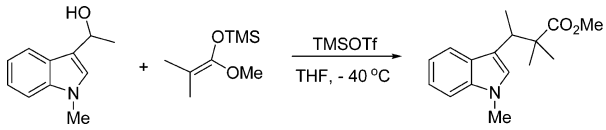
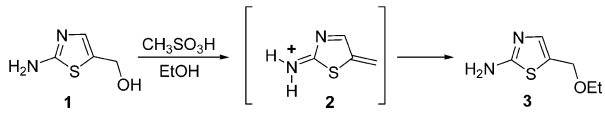
π-C-nucleophiles such as silyl ketene acetals.[10] Martin's work employs heterocyclic carbinol substrates such as indol-2-yl and indol-3-yl, as well as pyrrol-2-yl, furan-2-yl, and thiophen-2-yl carbinols which undergo Lewis acid catalyzed conversion to a heteroaryl-stabilized carbonium ion (Scheme 1).

Scheme 1. Martin Reaction of Indol-3-yl Carbinols[9]



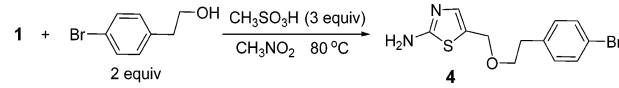
Herein, we now report a simple procedure for the generation and nucleophilic capture of imino-quinone methide type intermediates derived from 2-aminothiazole-5-carbinols that accommodates a wide variety of nucleophiles to effect C−C, C−O, C−N, C−S, and C−P bond formation. During the course of a medicinal chemistry program, we required a versatile route to a series of C-5-substituted 2-aminothiazole analogues. The most direct precursor in this context is 2-aminothiazol-5-yl carbinol (**1**). However, we were unsuccessful in attempts to utilize **1** under Mitsunobu conditions or by conversion to its mesylate or halogen derivatives. Perhaps, this is not surprising given that the 2-amino group in **1** is unprotected. However, we then reasoned that under acidic conditions solvolysis of **1** to its imino-quinone methide type (I-QM) intermediate **2** should take place: Indeed, **1** is converted quantitatively (by LCMS) to its ethyl ether **3** with 3 equiv of methanesulfonic acid (MSA) in ethanol solvent at 80 °C for 2 h (Scheme 2). Ether **3** is isolated by preparative HPLC in 80% yield.[11]

Scheme 2. Solvolysis of 2-Aminothiazol-5-yl Carbinol



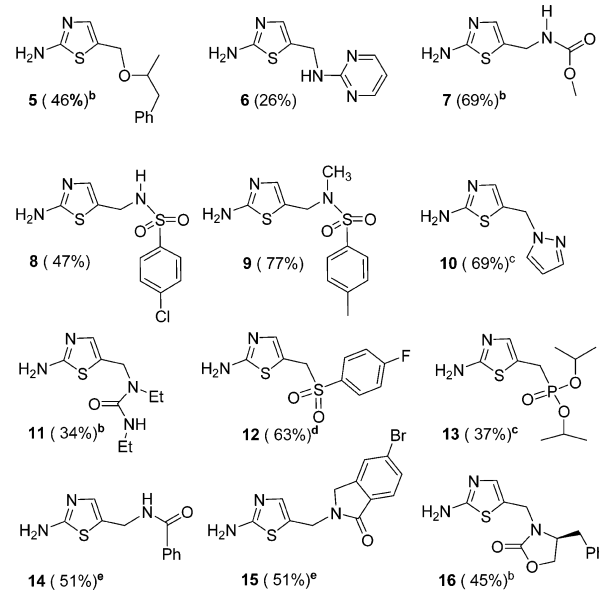
The formation of ether **3** implicates the generation and nucleophilic capture of I-QM intermediate **2**. However, the potential synthetic utility of **2** is limited by the use of the nucleophile, ethanol, as the solvent. Therefore, we explored the use of 2 equiv of an alcohol and 3 equiv of MSA using typical solvents without much success until nitromethane was employed. Under these conditions, **1** and 2-(4-bromophenyl)ethanol give ether **4** in 70% yield (Scheme 3).[12]

Scheme 3. Ether Formation from **1** under Acidic Conditions



The methanesulfonic acid/nitromethane conditions shown in Scheme 3 facilitate the use of a wide variety of nucleophiles. In addition to primary alcohols (i.e., **4**), secondary alcohols, anilines, sulfonamides, amides, lactams, carbamates, ureas, sulfinic acids, phosphites, and some NH-heterocycles also serve as suitable nucleophiles to capture intermediate **2**, as shown by the products **5**−**16** in Table 1. In some cases,

Table 1. Products from Solvolysis of **1** with Nucleophiles[a]



[a] All reactions are performed with 0.2−0.3 mmol of **1**, 2 equiv of nucleophile, and 3 equiv of MSA in nitromethane at 80 °C for 6−18 h unless otherwise noted. [b] With 3 equiv of MSA and 3 equiv of nucleophile. [c] With 3 equiv of MSA and 6 equiv of nucleophile. [d] With 3 equiv of sodium *p*-fluorobenzenesulfinate and 7 equiv of TfOH. [e] With 3 equiv of TfOH and 3 equiv of nucleophile.

trifluoromethanesulfonic acid (TfOH) gives better results than MSA. This may be due to the better solubility that TfOH affords in some cases and/or the presence of a basic atom in the nucleophile (vide infra). The successful use of amides and lactams is notable in that no O-alkylated products are observed: It is likely that the formation of such O-alkylated species is reversible under these reaction conditions.

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(11) All yields is this paper refer to products purified by preparative reverse phase HPLC in 1 to 2 runs using a Phenomenex Luna 30 × 100 mm column with a linear gradient of solvent A (10% methanol/90% water with 0.1% TFA) and solvent B (90% methanol/10% water with 0.1% TFA) over 10 min with peak detection at 254 nM. Product fractions are then applied to a 1 g Waters Oasis MCX cation exchange cartridge using slight vacuum, washed with methanol, and then product is eluted off the cartridge with 15 mL of 2 M ammonia in methanol. Evaporation gives the pure product. It should be noted that this method is designed for rapid parallel synthesis, but there may be 10−30% material lost from this process as demonstrated by control runs.

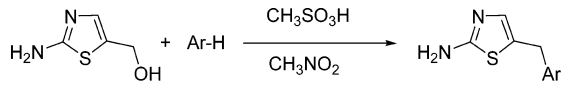
Aromatic and heteroaromatic rings also trap intermediate **2** to give products of C−C bond formation, as exemplified in Table 2. Anisole and various phenols predominantly undergo *para*-substitution.[13] In the case of 4-chlorophenol (entry 3), the yield is less than 25% with MSA, but a much improved result (77% yield) is obtained by the use of the stronger TfOH. Trapping of I-QM intermediate **2** by **1** and/or conversion to its labile nitromethane adduct can sometimes occur if the nucleophile is sufficiently less reactive.

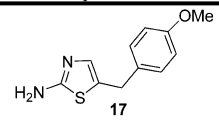
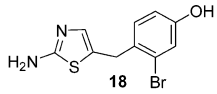
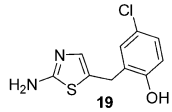
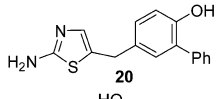
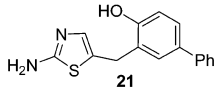
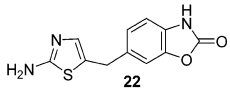
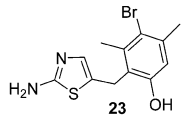
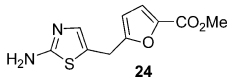
In the example of the reaction with 2-(isooxazol-5-yl)phenol (**25**), we discovered an interesting switch in the chemoselectivity of intermediate **2** dependent upon the ratio of acid to nucleophile used (Scheme 4). Reaction of **1** with 2 equiv of **25** and 3 equiv of trifluoromethanesulfonic acid at 80 °C for 5 h gives the expected product **26** via substitution *para* to the phenol, but in only 17% isolated yield. In an effort to improve this yield, the reaction was repeated using 5 equiv of trifluoromethanesulfonic acid and 9 equiv of phenol **25**. Under these conditions, compound **27**, the product of an N-alkylation-induced ring-opening reaction, is obtained in 42% yield. A possible mechanism for this result is shown in Scheme 4, wherein the I-QM intermediate **2** initially attacks the isoxazolyl nitrogen atom. Apparently, when there is more acid present than reagent **25**, this same nitrogen atom is sufficiently protonated such that intermediate **2** can attack *para* to the phenol to give **26**.

In addition to parent **1**, (2-(*p*-tolylamino)thiazol-5-yl)-carbinol (**28**) also serves as a suitable substrate for this acid-induced solvolysis chemistry. For example, **28** is prepared via S_NAr reaction of 2-chlorothiazol-5-yl carbinol and then is converted to representative products, as shown in Table 3. In the case of ether **34**, the use of additional acid (7 equiv) is required due to the neutralizing effect of the basic amino group.

We then decided to explore chemoselectivity differences between the various nucleophiles accommodated by this chemistry. Primary amides react preferentially to secondary amides as shown by a competition experiment with **28** and 3 equiv each of benzamide, *N*-methylbenzamide, and TfOH;

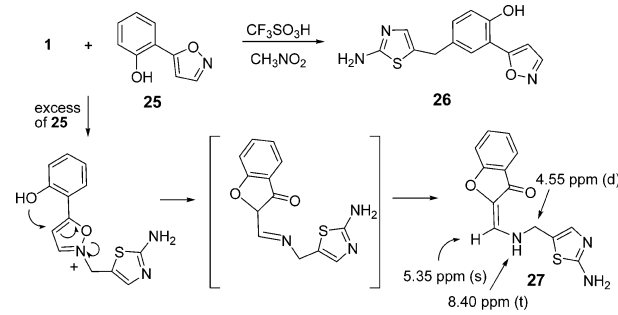
Table 2. C−C Bond Formation with Aromatic Nucleophiles[a]



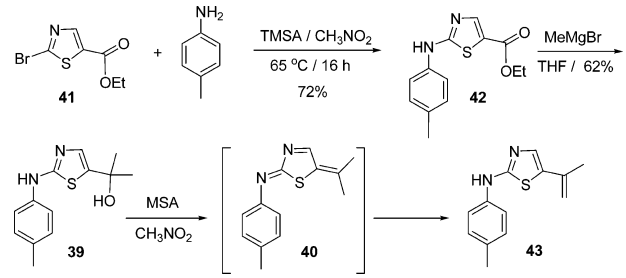
entry	product	yield
1	 **17**	61
2	 **18**	49
3[b]	 **19**	77
4	 **20**	80
5	 **21**	59
6[b]	 **22**	72
7[b]	 **23**	37
8	 **24**	43

[a] All reactions are performed with 0.2−0.3 mmol of **1**, 2 equiv of ArH, and 3 equiv of MSA in nitromethane at 80 °C for 6−12 h unless otherwise noted. [b] With 4 equiv of TfOH and 3 equiv of nucleophile at 80 °C for 5 h.

Scheme 4. N-Alkylation-Induced Ring-Opening Reaction with **1**



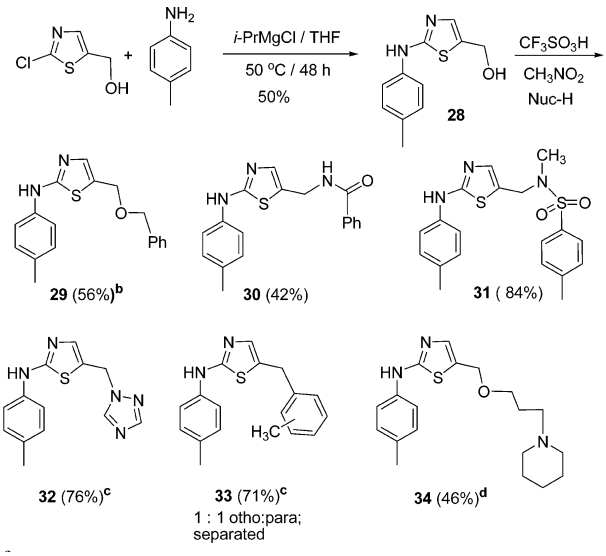
Scheme 5. Attempted Trapping of I-QM Species **40**



(12) Representative procedure follows: A mixture of **1** (25.0 mg, 0.19 mmol) and 4-chlorophenol (78 mg, 0.60 mmol) in nitromethane (3 mL) is sonicated briefly, then treated with neat TfOH (69 μlit, 0.78 mmol). The resulting solution is heated at 80 °C for 5 h, cooled to −20 C, and quenched with a cold solution of 7 M NH_3 in MeOH. The solvent is evaporated, the residue dissolved in MeOH (1.8 mL) and purified in one run by preparative HPLC as described in ref 11 to give 35.5 mg of **19** (77%): ^{1}H NMR (DMSO-d_6) δ 9.79 (s, 1H), 7.08−7.05 (m, 2H), 6.81 (d, 1H, J = 9.1 Hz), 6.68 (s, 1 H), 6.66 (br s, 2H), 3.79 (s, 2H); HRMS calcd for $C_{10}H_{10}ON_2ClS$ 241.0197 (M + H^+), obs 241.0197.

(13) Very small amounts of *ortho*-substitution products are also likely formed but are not isolated.

Table 3. Preparation and Reaction of (2-(*p*-Tolylamino)thiazol-5-yl)carbinol with Nucleophiles[a]

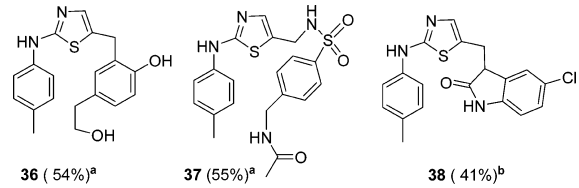


[a] All reactions are performed with 0.3 mmol of **28**, 2 equiv of nucleophile, and 3 equiv of TfOH at 80 °C for 6−18 h in nitromethane unless otherwise noted. [b] With 3 equiv of MSA and 3 equiv of benzyl alcohol. [c] With 3 equiv of TfOH and 5 equiv of nucleophile. [d] With 7 equiv of TfOH and 3 equiv of amino-alcohol.

A 4:1 mixture favoring amide product **30** over the corresponding *N*-methyl amide is isolated in 69% combined yield. The products shown in Table 4 are examples wherein carbinol **28** is combined with nucleophiles bearing more than one potential site of reaction. Whereas alcohols containing an aromatic ring give ethers vis-à-vis electrophilic attack on the aromatic ring (compounds **4**, **5**, **29**, vide supra), the chemoselectivity is completely switched when the aromatic ring contains a strong electron-donating group. Thus, phenol alcohol **36** is formed exclusively in the reaction of **28** with 4-(2-hydroxyethyl)phenol. The reaction of the sulfonamide group in the presence of an amide is preferred (compound **37**), and C−C bond formation takes place at C-3 when 5-chlorooxindole is used as the nucleophile (compound **38**).

In an endeavor to increase the stability of imino-quinone methide (I-QM) **2**, we envisioned tertiary alcohol **39** as precursor to the corresponding I-QM **40** (Scheme 5).

Table 4. Chemoselectivity of **28** with Bifunctional Nucleophiles



[a] With 0.3−0.4 mmol of **28**, 3 equiv of nucleophile, and 3 equiv of TfOH at 80 °C in nitromethane for 2−3 h. [b] With 0.4 mmol of **28**, 3 equiv of MSA, and 5 equiv of 5-chlorooxindole at 80 °C for 3 h.

Interestingly, these same nitromethane/TfOH conditions serve as an excellent method for an otherwise difficult S_NAr reaction of *p*-toluidine with 2-bromothiazole ester **41** to assemble the requisite 2-aminothiazole ester **42** in 72% yield.[14] Treating **39** with 3 equiv of MSA in nitromethane in the presence of 4-chlorophenol at rt for 30 min gives only the olefin **43** in 69% yield.[11] Further heating the reaction at 80−100 °C for 16−20 h does not lead to any incorporation of the phenol as nucleophile, vis-à-vis **19**. It is likely that the initially generated intermediate I-QM **40** rapidly tautomerizes to the isomeric olefin **43**, therefore precluding its nucleophilic capture. Further exploration of other heterocyclic systems suitable for the generation and nucleophilic capture of related I-QM intermediates would provide an opportunity for expansion of the scope of the chemistry described herein.

Acknowledgment. We thank Dr. Yingzi Wang of our DAS group for NMR support.

Supporting Information Available: Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) The use of acid catalysis for weakly basic amines in S_NAr reactions is known. For example, the combination of trifluoroacetic acid in trifluoroethanol facilitates S_NAr displacement of fluorine and chlorine from pyrimidine and purine substrates with weakly basic substituted anilines. See: Whitfield, H. J.; Griffin, R. J.; Hardcastle, I. R.; Henderson, A.; Meneyrol, J.; Mesguiche, V.; Sayle, K. L.; Golding, B. T. *J. Chem. Soc., Chem. Commun.* **2003**, 2802.