Gold(III)-Catalyzed 1,4-Nucleophilic Addition: Facile Approach to Prepare 2-Amino-1,4-naphthalenedione and 6-Amino-5,8-quinolinedione Derivatives

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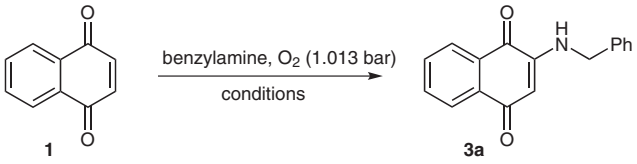
Abstract: An efficient approach is developed to prepare different 2-amino-1,4-naphthalenedione and 6-amino-5,8-quinolinedione derivatives regioselectively by Au(III)-catalyzed 1,4-nucleophilic addition and subsequent oxidation. A wide variety of primary, secondary, and aromatic amines, as well as allylamine and 2-butynylamine are well tolerated under the mild conditions to give products in moderate to good yields.

Key words: sodium tetrachloroaurate, 2-amino-1,4-naphthalenedione, 6-amino-5,8-quinolinedione

Considerable attention was given to the assembly of 2-amino-1,4-naphthalenedione and 6-amino-5,8-quinolinedione due to the presence of such structural frameworks in natural products and biologically important compounds.[1,2] Generally, the amino group was installed into the quinones by 1,4-nucleophilic addition or by nucleophilic substitution from the corresponding halo-substituted counterparts.[3] Although the former approach looks more attractive from a viewpoint of sustainable development, owing to the redox properties of quinones, the approach usually suffered from low conversion in conjunction with tedious purifications and the requirement of using excess quinones as oxidant. To overcome these problems, metal salts such as $Cu(OAc)_2$[4], $CeCl_3$,[5] and $Ni(OAc)_2$[6] as well as molecular I_2[7] were employed to catalyze the 1,4-nucleophilic addition of 1,4-naphthalenedione and 5,8-quinolinedione under air/O_2 atmosphere or ultrasound conditions. However, limitations still exist, and it is necessary to develop more efficient approaches.

In recent decade, gold(I) and gold(III) salts have emerged as versatile catalysts to carry out a variety of cycloisomerization reactions of substrates containing alkyne, alkene, and allene units. Such reactions were accompanied by the formation of different C–C, C–O, and C–N bonds.[8] In addition, Au(III) shows Lewis acid property in various chemical transformations. As one of the simplest gold(III) salts, $NaAuCl_4{\cdot}2H_2O$ can activate selectively the carbonyl group in some condensation and addition reactions. Arcadi[9] reported that $NaAuCl_4{\cdot}2H_2O$ could catalyze condensation of 1,3-diones involving β-ketoester and β-diketones with amines to form β-enaminoesters and β-enaminoketones. When 2-amino arylketones were used instead of amines, the Friedländer products obtained. $NaAuCl_4{\cdot}2H_2O$ could also catalyze conjugated addition of α,β-unsaturated ketones with indole and pyrrole.[10] Inspired by the above results, we envisaged that preparation of 2-amino-1,4-naphthalene-dione and 6-amino-5,8-quinolinedione derivatives directly from amines and 1,4-naphthalenedione (**1**) and 5,8-quinolinedione (**2**) by gold-catalyzed regioselective 1,4-nucleophilic addition and subsequent oxidation.



Scheme 1

Table 1 Different Conditions Screened

Entry	Reaction conditions[a]	Yield (%)
1	10 mol% $PtCl_2$, toluene, 100 °C, 2 h	46
2	5 mol% $AuPPh_3OTf$, $Cl_2(CH_2)_2$, 80 °C, 2 h	55
3	5 mol% $NaAuCl_4{\cdot}2H_2O$, MeCN, 80 °C, 2 h	69
4	5 mol% $NaAuCl_4{\cdot}2H_2O$, THF, 60 °C, 2 h	70
5	5 mol% $NaAuCl_4{\cdot}2H_2O$, EtOH, 80 °C, 1 h	74
6	1 mol% $NaAuCl_4{\cdot}2H_2O$, EtOH, 80 °C, 1 h	76
7[b]	1 mol% $NaAuCl_4{\cdot}2H_2O$, EtOH, 80 °C, 1 h	80
8[b]	10 mol% TFA, EtOH, 80 °C, 1 h	35

[a] The ratio of benzyamine/1,4-naphthalenedione is 1:1, unless mentioned.
[b] The ratio is 1.3:1.

We chose benzylamine and 1,4-naphthalenedione as a model system and began the studies by optimizing the conditions (Scheme 1, Table 1).[11] The reaction was initially performed in toluene at 100 °C by using 10 mol% $PtCl_2$ as the catalyst. The expected product was obtained in 46% yield after 2 hours (entry 1). When the gold(I) species $AuPPh_3OTf$ was employed, the yield increased to 55% (entry 2). While the catalyst was switched to $NaAuCl_4{\cdot}2H_2O$, different solvents including MeCN, THF, and EtOH were screened. Among them, ethanol

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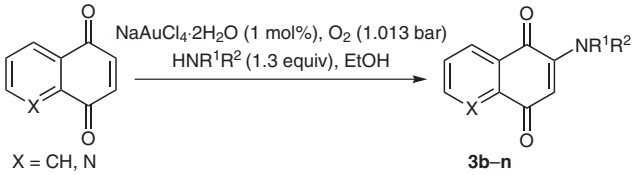
gave the best yield (entries 3–5). Attempt to reduce the amount of $NaAuCl_4 \cdot 2H_2O$ from 5 mol% to 1 mol% resulted in almost little change of the yield (entry 6). Using 1.3 equivalents of benzylamine led to a moderate increase in the yield (entry 7). In addition, when TFA was used instead of gold catalysts, the efficiency became inferior (entry 8).



Scheme 2

Using the optimized conditions,[12] the scope of the Au(III)-catalyzed sequential 1,4-nucleophilic addition and oxidation of 1,4-naphthalenedione was screened (Scheme 2, Table 2). Primary amines containing an indole unit or possessing a chiral center could undergo the reaction with 1,4-naphthalenedione smoothly, and the yields of the adducts were 65% and 75%, respectively (entries 1, 2). Allylamine and 2-butynylamine gave the adducts in 85% and 70% yield, which illustrated that the double bond and triple bond were tolerated under the reaction conditions (entries 3, 4). Besides primary amines, secondary amines also worked well (entry 5). However, aromatic amines reacted differently according to the substituents on the benzene ring (entries 6–8). For the substrates with electron-donating group (OMe), the yield was high (up to 88%), while substrates with electron-withdrawing group (CO_2Et) gave a lower yield. After screened various amines, we changed the 1,4-naphthalenedione to 5,8-quinolinedione and investigated the regioselectivity of the reaction. When 5,8-quinolinedione was used, in principle there are two alternative pathways which can lead to the formation of isomeric mixtures. However, in our catalytic system, 6-amino-substituted 5,8-quinolinedione was achieved without any 7-amino adduct detected. Primary and secondary amines as well as aromatic amines underwent regioselectively cascade 1,4-nucleophilic addition and oxidation at room temperature in a yield ranging from 60– 70% (entries 9–13).

Table 2 $NaAuCl_4 \cdot 2H_2O$-Catalyzed 1,4-Nucleophilic Addition–Oxidation of 1,4-Naphthalenedione and 5,8-Quinolinedione

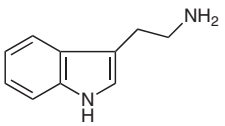
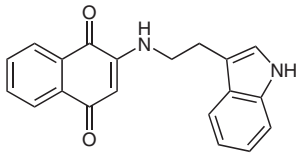
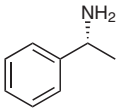
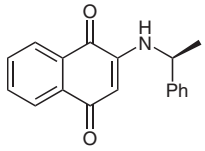
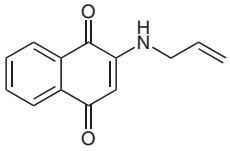
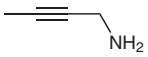
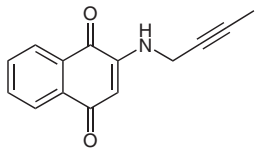
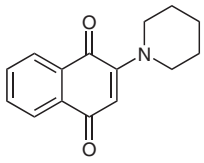
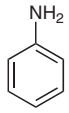
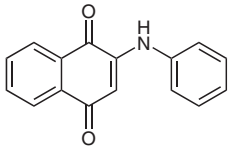
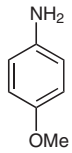
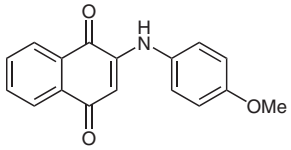
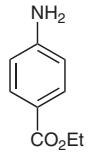
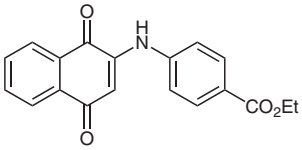
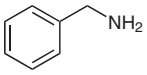
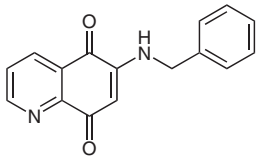
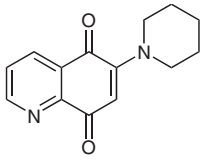
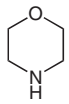
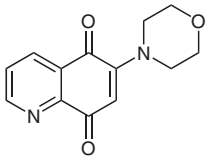
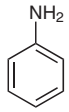
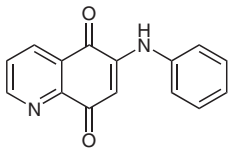
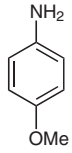
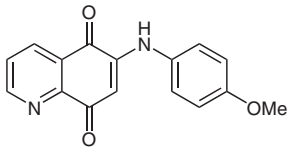
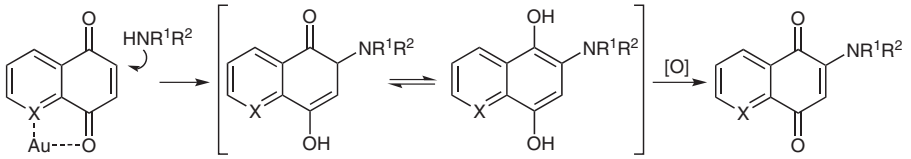
Entry	Amine	Product	Conditions	Yield (%)
1		 **3b**	80 °C, 1 h	65
2		 **3c**	80 °C, 2 h	75
3		 **3d**	50 °C, 2 h	85
4		 **3e**	80 °C, 2 h	70
5		 **3f**	80 °C, 1 h	58

Table 2 $NaAuCl_4 \cdot 2H_2O$-Catalyzed 1,4-Nucleophilic Addition–Oxidation of 1,4-Naphthalenedione and 5,8-Quinolinedione (continued)

Entry	Amine	Product	Conditions	Yield (%)
6		 **3g**	80 °C, 4 h	63
7		 **3h**	80 °C, 3 h	88
8		 **3i**	80 °C, 4 h	50
9		 **3j**	25 °C, 1 h	62
10		 **3k**	25 °C, 1 h	60
11		 **3l**	25 °C, 1 h	64
12		 **3m**	25 °C, 1 h	60
13		 **3n**	25 °C, 2 h	70

The proposed mechanism for the formation of 2-amino-1,4-naphthalenediones and 6-amino-5,8-quinolinediones from different amines with 1,4-naphthalenedione and 5,8-quinolinedione consists of 1,4-uncleophilic addition followed by oxidation (Scheme 3). Activation of carbonyl group of the quinones by Au(III) facilitated the nucleophilic addition step. For 5,8-quinolinedione, the coordination of Au(III) with the nitrogen and 8-carbonyl group determines the regioselectivity and outcome of the reac-



Scheme 3

tion. Under atmospheric oxygen, the adduct amino-hydroquinones can be oxidized to quinones.[13]

To summarize, an efficient approach is developed to prepare different 2-amino-1,4-naphthalenedione and 6-amino-5,8-quinolinedione derivatives regioselectively by Au(III)-catalyzed 1,4-nucleophilic addition and subsequent oxidation. Amines such as allyl and propargyl amines which are well tolerated under the conditions gave moderate to good yields as well as different substituted primary, secondary, and aromatic amines. Further exploration of this approach is in progress.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(12) **General Procedures for the Preparation of 2-Amino-1,4-naphthalenediones (3a–i) and 6-Amino-5,8-quinolinediones (3j–n)**
1,4-Naphthalenedione (1.0 mmol) or 5,8-quinolinedione (1.0 mmol) and $NaAuCl_4 \cdot 2H_2O$ (0.01 mmol) were dissolved in EtOH (2.0 mL) under oxygen atmosphere. Then the amine (1.3 mmol) was added to the above solution by syringe. The formed solution was heated at 80 °C or run at r.t. for a certain time (monitored by TLC). After cooling, the mixture was poured into H_2O (20 mL), and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extract was dried by anhyd $MgSO_4$, and the solvent was removed by distillation. The crude products obtained were purified by flash chromatography to give 2-amino-1,4-naphthalenediones and 6-amino-5,8-quinolinediones.

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