Tetrahedron Letters xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Divergent and facile Lewis acid-mediated synthesis of *N*-alkyl 2-aminomethylene-1,3-indanediones and 2-alkylamino-1,4-naphthoquinones

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ARTICLE INFO

Article history:
Received 8 December 2014
Revised 23 December 2014
Accepted 2 January 2015
Available online xxxx

Keywords:
2-Amino-1,4-naphthoquinone
Aminomethylene-1,3-indanedione
Antibacterial
Anticancer
Anti-inflammation

ABSTRACT

N-Alkyl 2-aminomethylene-1,3-indanediones and 2-alkylamino-1,4-naphthoquinones are known for their diverse and versatile bioactivities and applications. Traditionally, these two compounds were synthesized in separate routes using different materials. By employing Lewis acid, cycloaddition of alkyl azides and 1,4-naphthoquinone can provide these two classes of compound in one-pot fashion. Among the Lewis acids and conditions examined, TMSOTf under reflux offers the best overall yields. In addition, the purification of both classes of compounds can be easily achieved using flash column chromatography making this methodology feasible for scale-up synthesis of compounds with biological interests.

Molecules containing 1,4-naphthoquinone and 1,3-indanedione scaffolds have long been attracting great interest due to their diverse biological activities and applications.[1] For example, compounds bearing 2-alkyamino- or 2-arylamino-1,4-naphthoquinones scaffolds have been studied for their activity as antimycobacterial,[2] neuro-protective,[3] antiproliferative,[4] and antimalarial[5] agents (Fig. 1a). Aminomethylene-1,3-indanedione scaffolds can also been found in chemicals that exert various bioactivities, including anti-inflammation,[6] antibacteria,[6] inhibition of β-amyloid[7] and therapeutic for hypotension (Fig. 1b).[8]

In general, there are two main synthetic strategies for the synthesis of 2-amino-1,4-naphthoquinones: one approach involves the substitution of 2-halonaphthoquinones with amines (Scheme 1, methods A and B).[9] The second approach uses a conjugate addition of amines to 1,4-naphthoquinone followed with an oxidation catalyzed by molecular iodine under ultrasonic irradiation (Scheme 1, method C).[10] Method A requires the use of palladium whereas method B needs the use of excess amines (7 equiv) and the yields are modest (average yields around 40%). Method C appears to be the best protocol to synthesize 2-amino-1,4-naphthoquinones.

For the synthesis of *N*-alkyl 2-aminomethylene-1,3-indanediones, several reported syntheses employ 1,3-indanedione, **6**, and a specific reagent *N*,*N*-dimethylformamide dimethyl acetal, **7** as the starting compounds (Scheme 2, method A).[11a–c] In principal, different alkyl groups can be introduced. Another method involves the synthesis of 2-formyl-1,3-indanedione, **10** (Scheme 2, method B).[11d] A subsequent imine formation allowed the synthesis of *N*-alkyl 2-aminomethylene-1,3-indanediones. This method is superior in offering more diverse *N*-alkyl groups.

Overall, these syntheses of *N*-alkyl 2-aminomethylene-1,3-indanediones and 2-alkylamino-1,4-naphthoquinones require the use of different starting materials, reagents and approaches, and there is no concise method to produce both compounds concomitantly in an one-step fashion. In 2003, Aube and co-worker reported the synthesis of an enaminone, **12** from 2-cyclohexenone and benzyl azide under the catalysis of Lewis acid (Scheme 3).[12] Our group has also discovered that cycloaddition of 1,4-naphthoquinone and azides can lead to the formation of both 2-alkylamino-1,4-naphthoquinones **15** and *N*-alkyl 2-aminomethylene-1,3-indanediones **16** (Scheme 4).[13,14] However, these two compounds were often not observed in the employed conditions or isolated merely as the minor products. Inspired by these results and the pressing need for a simpler synthetic method, we decided to investigate in Lewis acid-mediated cycloaddition of 1,4-naphthoquinone and azides and tune the chemoselectivity to favor the synthesis of *N*-alkyl 2-aminomethylene-1,3-indanediones and 2-alkylamino-1,4-naphthoquinones.

We selected octyl azide (**13a**) as the model compound to react with 1,4-naphthoquinone, and screened commonly used Lewis acids and conditions to optimize the production of compounds **15a** and **16a**. Among the conditions we examined, we were

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http://dx.doi.org/10.1016/j.tetlet.2015.01.014
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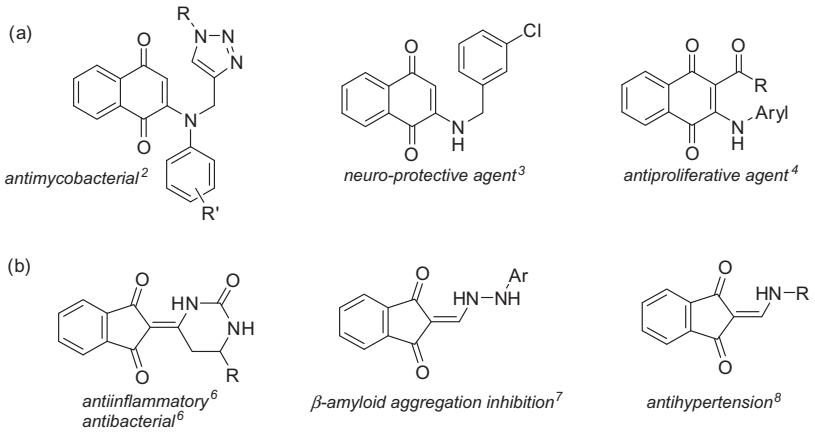
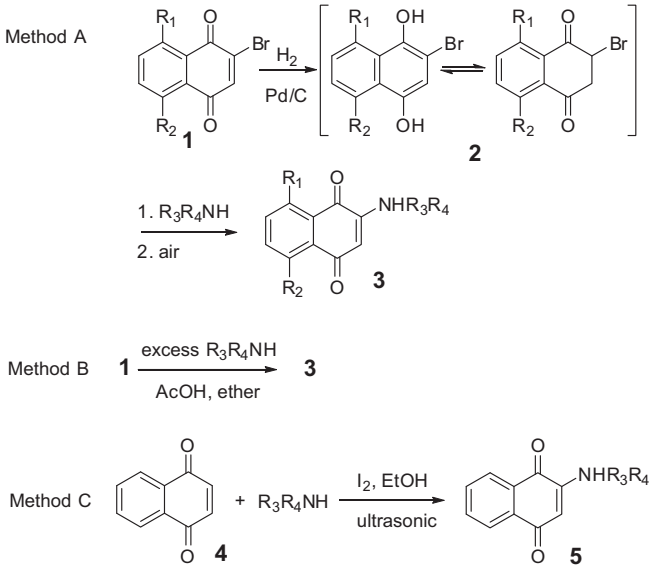
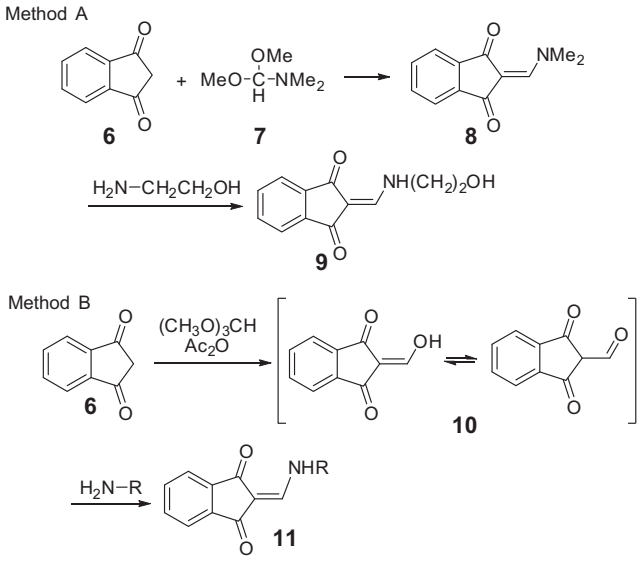


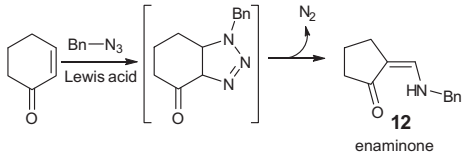
Figure 1. Examples of molecules containing 2-alkyamino 1,4-naphthoquinone and aminomethylene-1,3-indanedione scaffolds.



Scheme 1. Previous synthetic strategies for the synthesis of 2-amino-1,4-naphthoquinones.



Scheme 2. Examples for the synthesis of 2-aminomethylene-1,3-indanediones.

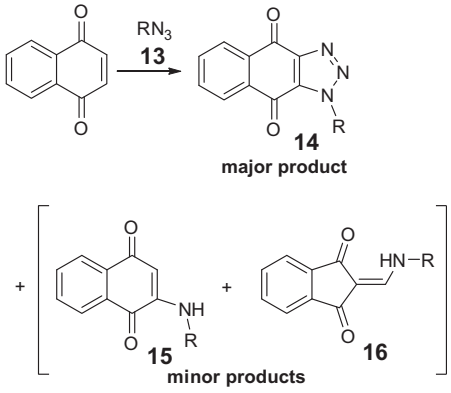


Scheme 3. Lewis acid-mediated ring contraction reactions.

delighted to discover that both of the compounds **15a** and **16a** can be obtained at room temperature as the dominant products (Table 1). Compounds **15a** and **16a** have very different polarities and, thus, can be readily separated via flash column chromatography. Among the Lewis acids examined, TMSOTf provided the best combined yields of compounds **15a** and **16a** while $FeCl_3$ and $ZnCl_2$ offered no products (Table 1, entries 2, 6, and 7). Without the presence of Lewis Acid, there were no products isolated as well (Table 1, entry1). In all cases and various conditions we examined, it is not possible to tune the selectivity in favoring specifically compounds **15a** or **16a** although compounds **16a** were the major products in all cases. Interestingly, no cycloaddition products, **14a** were ever observed in the presence of Lewis Acid. Finally, by increasing reaction temperature to reflux (40 °C, the bp of CH_2Cl_2) and using two equivalents of TMSOTf, we have improved the combined yields of compounds **15a** and **16a** to 94% (Table 1, entry 9), which will be used as the optimized condition for further studies.

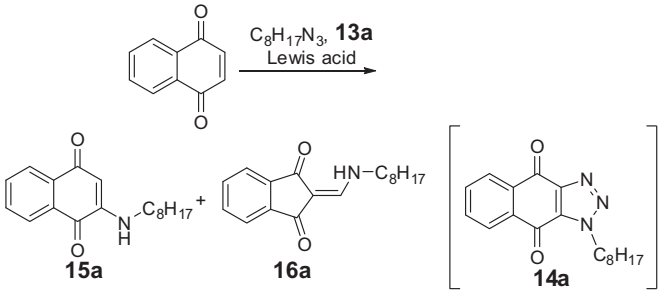
The role of Lewis acid is believed to facilitate the degradation of triazoline intermediate following the cycloaddition in a mechanism similar to the one proposed previously (Scheme 5).[12,15] In the presence of Lewis acid (TMSOTf), the most nucleophilic nitrogen atom, N-3 is prone to react with the Lewis acid giving **17**. The intermediate **17** undergoes ring contraction, rearrangement, and fragmentation, and leads to the formation of **16** (Scheme 5, route A). In a different route, deprotonation and fragmentation of **17** can provide **15** (Scheme 5, route B). The intramolecular ring-contraction of **17** can occur alone whereas the deprotonation of **17** needs to involve a base, which may explain higher yields for **16** over **15** in all the examined cases.

Following the identification of optimal condition, we decided to examine more alkyl azides (**13b–k**) of different alkyl chain length and functional groups (Table 2). All the tested alkyl azides offered expected 2-alkylamino-1,4-naphthoquinones (**15b–k**) and *N*-alkyl



Scheme 4. Cycloaddition of 1,4-naphthoquinone and azides.

Table 1
Optimisation studies[a]

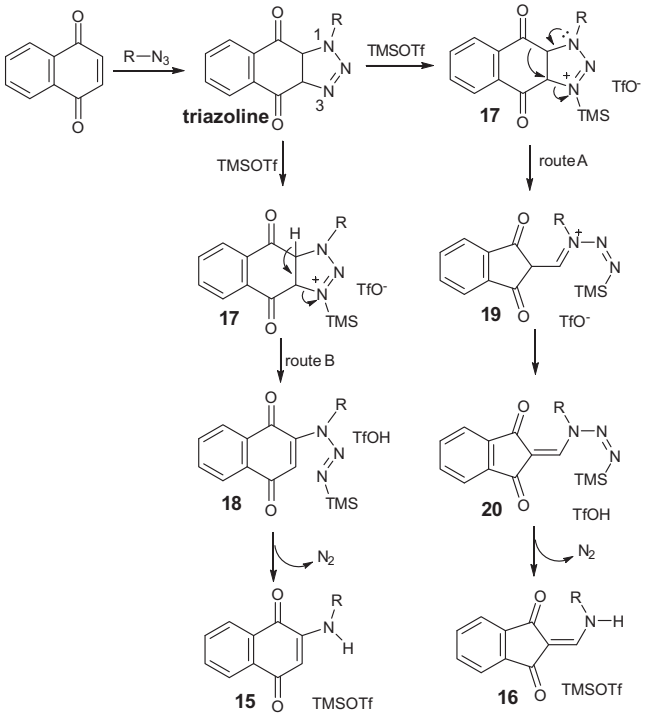


Entry	Lewis acid (equiv)	Temp	Yield of **15a**[14] (%)[a]	Yield of **16a**[a] (%)
1	None	rt	0	0
2	TMSOTf (1)	rt	24	45
3	$BF_3{\cdot}Et_2O$ (1)	rt	12	31
4	$AlCl_3$ (1)	rt	14	33
5	$SnCl_4$ (1)	rt	9	29
6	$FeCl_3$ (1)	rt	0	0
7	$ZnCl_2$ (1)	rt	0	0
8	TMSOTf (1)	Reflux	28	49
9	TMSOTf (2)	Reflux	35	59

[a] The two products with different polarities could be easily separated by flash chromatography. For entry 2, the yield is the isolated yield. For the rest, the yield is estimated based on the integration of ^{1}H NMR.

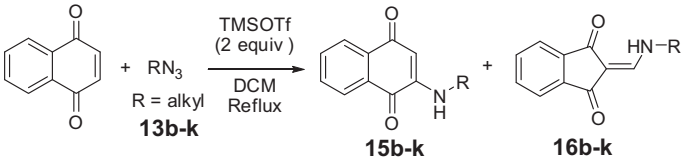
2-aminomethylene-1,3-indanediones (**16b–k**) with combined yields ranging from 70% to 98%. The separation of these two products can all be readily achieved due to the drastic polarity differences of these two products. In addition, all 2-alkyamino-1, 4-naphthoquinones, **15b–k**, show a very distinct reddish color visible on TLC plates that further facilitate the purification process.

In conclusion, we have reported a divergent and facile synthesis of two heterocyclic adducts from cycloaddition of 1,4-naphthoquinone and alkyl azides, *N*-substituted 2-amino-1,4-naphthoquinones, and *N*-substituted 2-aminomethylene-1,3-indanediones. Both classes of compounds have been known to exert therapeutic bioactivities. In the presence of TMSOTf, both classes of compounds with the variation of the *N*-alkyl groups can be obtained in a one-step fashion with excellent combined yields. The developed method employs cost-effective alkyl azides and 1,4-naphthoquinone as the starting materials. In addition, the purification of both classes of compounds can be easily achieved using flash column chromatography making this methodology feasible for scale-up synthesis of lead compounds with biological interests.



Scheme 5. Proposed mechanism of Lewis acid-mediated cycloaddition.

Table 2
Preparation of *N*-alkylated 2-aminomethylene-1,3-indanediones



Entry	Alkyl azide	Yield of **15** (%)	Yield of **16** (%)
1	$C_{16}H_{33}N_3$, **13b**	**15b**[16] (27)	**16b** (57)
2	$C_{12}H_{25}N_3$, **13c**	**15c**[14] (26)	**16c** (46)
3	$C_{11}H_{23}N_3$, **13d**	**15d** (29)	**16d** (51)
4	$C_{10}H_{21}N_3$, **13e**	**15e**[14] (24)	**16e** (53)
5	$C_9H_{19}N_3$, **13f**	**15f**[14] (32)	**16f** (51)
6	$C_6H_{13}N_3$, **13g**	**15g**[14] (34)	**16g** (52)
7	$C_5H_{11}N_3$, **13h**	**15h**[14] (32)	**16h**[17] (55)
8	$CH_3OC(O)CH_2N_3$, **13i**	**15i**[17] (25)	**16i** (48)
9	$CH_3(OCH_2CH_2)_4N_3$, **13j**	**15j** (34)	**16j** (64)
10	Benzyl azide, **13k**	**15k**[3b] (28)	**16k**[13] (58)

General procedure for Lewis acid-mediated cycloaddition of 1,4-naphthoquinone and azides

0.5 g 1,4-naphthoquinone, 1.5 equiv of alkyl azide, and 2 equiv of TMSOTf were dissolved into 20 mL methylene dichloride in a 50 mL round bottom flask. The reaction mixture was refluxed for overnight. The reaction can be monitored by TLC (eluted with Hexane/EtOAc = 3/1). 2-Alkylamino-1,4-naphthoquinones have R_f values around 0.5 whereas *N*-alkylated 2-aminomethylene-1,3-indanediones naphthoquinones have R_f values around 0.2. After completion of the reaction, the reaction mixture was quenched by adding aqueous $NaHCO_3$ and extracted with DCM. The combined organic layers were washed with water, brine, and dried over anhydrous Na_2SO_4. The residue obtained after the evaporation of solvent was subjected to flash chromatography. Gradient

column chromatography (Hexane/EtOAc = 100/0 to 80/20) afforded the *N*-alkylated 2-aminomethylene-1,3-indanediones as yellowish powder, and 2-alkylamino-1,4-naphoquinones could also be separated as reddish powder.

Acknowledgment

We acknowledge the support from Department of Chemistry and Biochemistry, Utah State University.

Supplementary data

Supplementary data (^{1}H, ^{13}C, and related spectra of the synthesized compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.01.014.

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