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Graphical Abstract

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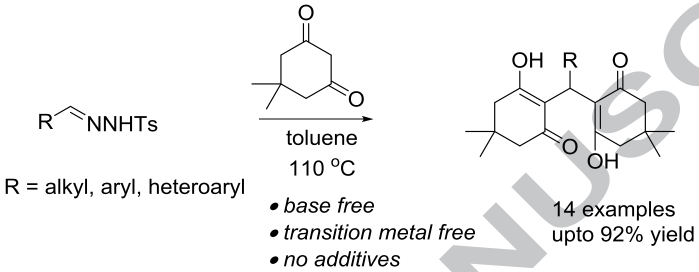

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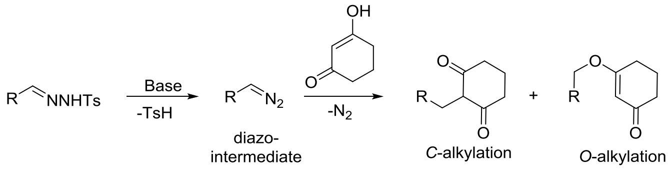
ABSTRACT

N-tosylhydrazones derived from a wide variety of aryl, alkyl and heteroaryl aldehydes undergo smooth coupling with 5,5-dimethylcyclohexane-1,3-dione under transition metal and base free conditions to generate tetraketo compounds in high yields. In presence of a base, the coupling reaction generates *β*-keto enol ether as the major product in a polar aprotic solvent. *N*-Tosylhydrazone can also be converted to xanthenedione in high yields in one-pot operation under mild acidic conditions.

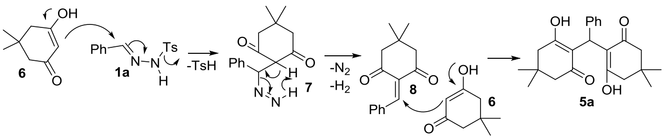
N-Tosylhydrazones have emerged as useful reagents for important organic transformations.[1] They are stable at room temperature and can be generated easily from carbonyl compounds. When treated with a base, *N*-tosylhydrazones generate diazo compounds via Bamford-Stevens reaction.[2] Cross-coupling of the diazo intermediates with carbon[3] and heteronucleophiles such as nitrogen,[4] oxygen[5] and sulphur[6] have been extensively studied by various research groups. Important examples of carbon nucleophiles include activated aryl group, alkyne and heteroaomatics. These coupling reactions often require a transition metal catalyst which generates metallocarbene complex responsible for effective cross-coupling reactions. In recent years, transition metal free cross-coupling reactions have gained significant importance.[7] Since the report of metal free coupling of *N*-tosylhydrazones with boronic acid[3b] and hydroxyl compounds[5] by Valdés and co-workers, the application of *N*-tosylhydrazones for various coupling reactions has improved significantly. In continuation with our on-going research interest in new synthetic applications of *N*-tosylhydrazones,[8] herein we report the coupling of a variety of *N*-tosylhydrazones with 5,5-dimethylcyclohexane-1,3-dione under transition metal free conditions.[9]



Scheme 1: Alkylation of 1,3-dicarbonyl compound with *N*-tosylhydrazone

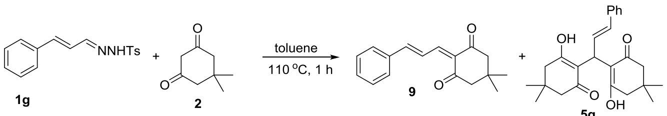
Our hypothesis of the coupling reaction is presented in Scheme 1. Coupling of the diazo intermediate with a 1,3-dicarbonyl compound would lead to new C-C or C-O bond formation. Our investigation started with *N*-tosylhydrazone **1a** derived from benzaldehyde. Compound **1a** was treated with dimedone in presence of a base in different solvents. As listed in Table 1, reaction in presence of 1.1 eq of K_2CO_3 in DMF generated *O*-alkylated product **3** in 28% yields along with the tetraketo compound **5a** (entry a, Table 1). The mono *C*-alkylated product **4** was not obtained under these conditions. Similar results were obtained when the reaction was carried out using Cs_2CO_3 as a base. Reactions in polar-aprotic solvents such as DMSO, DMPU, NMP, HMPA also resulted into low yield of *O*-alkylated product (entries c-f, Table 1). We were unable to find suitable conditions to generate the *O*-alkylated product in high yields.[10] When the reaction was carried out using 2.0 equivalent of dimedone in DMF, *O*-alkylated product was obtained in 45% yields along with 34% of the tetraketo compound **5a** and 14% yields of the mono *C*-alkylated product **4** (entry g, Table 1). In dioxane, the reaction resulted into 30% yields of *O*-alkylated product along with 48% yields of the tetraketo compound **5a** (entry h, Table 1). When the reaction was carried out in toluene, tetraketo compound was obtained in 82% yields along with trace amount of the *O*-alkylated product (entry i, Table 1). The reaction resulted into high yield of the tetraketo compound when carried out in presence of 0.5 equivalent of K_2CO_3 as a base. In absence of base, the reaction required 30 minutes for completion to give 90% yields of the tetraketo compound **5a** (entry k, Table 1).

To find out the scope of the base free coupling of *N*-tosylhydrazones with 1,3-diketones for the synthesis of tetraketo compounds, we tested several *N*-tosylhydrazones derived from aliphatic, aromatic, heteroaromatic and *α,β*-unsaturated aldehydes and the results are presented in Table 2. Aromatic aldehyde derived substrates provided high yields of the tetraketo compounds. Substrates containing electron withdrawing groups in the benzene ring provided tetraketo compounds in high yields in short reaction time. *N*-Tosylhydrazone derived from 4-hydroxy benzaldehyde provided corresponding tetraketo compound **5d** in 84% yields. The reaction required 4 hours for completion. However, no coupling was observed with *N*-tosylhydrazone derived from *o*-hydroxybenzaldehyde. On the other hand, *N*-tosylhydrazone derived from 2,4-dimethoxybenzaldehyde underwent smooth coupling with dimedone and the corresponding tetraketo compound **5f** was obtained in 80% yields. *N*-Tosylhydrazone derived from cinnamaldehyde produced trace amount of product **5g**. Knoevenagel adduct **9** was isolated in 76% yields after column chromatography. Condensation of *N*-tosylhydrazone derived from *α*-naphthaldehyde with dimedone was slow and required 4 hours for completion to give 84% yield of the corresponding tetraketo compound **5h**. *N*-tosylhydrazones derived from heteroaryl aldehydes also underwent smooth coupling with dimedone to generate the corresponding tetraketo compounds in high yields. Substrate derived from *N*-Boc 5-bromo indole-3- carboxaldehyde generated the corresponding tetraketo compound **5i** in 82% yields. Reactions of thiophene-2-carboxaldehyde and furfuryl-2-carboxaldehyde derived substrates were complete within 30 minutes and generated the corresponding tetraketo compounds **5j** and **5k** in 84% and 80% yields respectively. Reaction of *N*-tosylhydrazone derived from pyridine 3-carboxaldehyde required 2 hours for completion to generate tetraketo compound **5l** in 83% yields. Substrate derived from cyclohexane carboxaldehyde underwent smooth coupling with dimedone generating tetraketo compound **5m** in 85% yields. Besides dimedone, we also tested a few 1,3-dicarbonyl compounds for the base free coupling reaction with *N*-tosylhydrazone **1a**. Cyclohexane 1,3-dione underwent smooth coupling with *N*-toshylhydrazone **1a** to generate tetraketo compound **5n** in 86% yields. However, Acetyl acetone failed to generate measurable amount of product even after heating for 12 hours. Dibenzoylmethane and ethyl acetoacetate also failed to undergo effective coupling with *N*-tosylhydrazone **1a** possibly due to stabilization of the enol forms by intramolecular H-bonding.



Scheme 2: Mechanism of tetraketones synthesis

The plausible mechanism of base free coupling of *N*-tosylhydrazone with dimedone is depicted in Scheme 2. Nucleophilic addition of dimedone to the *N*-tosylhydrazone **1a** leads to the intermediate **7** which would decompose intramolecularly to generate the Knoevenagel adduct **8**. In case of *N*-tosylhydrazone **1g** derived from cinnamaldehyde, the highly conjugated Knoevenagel adduct **9** could be isolated in good yields (Scheme 3). The Knoevenagel adduct **8** reacts with a second molecule of dimedone to generate the tetraketo compound **5a**. Except cinnamaldehyde derived *N*-tosylhydrazone, we did not observe the Knoevenagel adduct intermediate in the coupling reactions.



Scheme 3: Coupling of N-tosyl hydrazone **1g** with dimedone

The structure of compound **5a** has been confirmed by single crystal X-ray studies (Figure 1). The ‘Y’ shaped three dimensional structure of compound **5a** is stabilized by intramolecular H-bonding between O-atom of carbonyl group and H-atom of enolic hydroxyl group.[11]

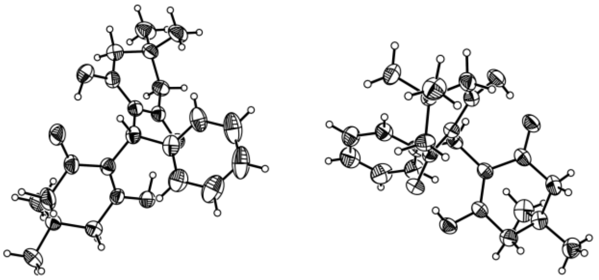


Figure 1: ORTEP diagram of compound **5a**

The tetraketo compounds are useful intermediate for heterocycle synthesis. Under mild acidic conditions, tetraketones undergo intramolecular condensation to generate xanthendiones.[12] The base free clean condensation of N-tosylhydrazone with dimedone encouraged us to carry out one-pot synthesis of xanthendione. Thus, addition of 0.10 equivalent of *p*-toluenesulfonic acid to the reaction mixture of *N*-tosylhydrazone **1a** and dimedone resulted into xanthendione **10a** in 82% yields (Table 3). Similarly, *N*-tosylhydrazone generated from 1-naphthaldehyde and pyridine-3-carboxyladehyde also produced the corresponding xanthenediones **10b** and **10c** in high yields under one-pot operation. *p*-Toluenesulfonic acid must be added after complete conversion of *N*-tosylhydrazone to tetraketone for obtaining high yields of xanthendione.

In summary, transition metal and base free coupling of *N*-tosylhydrazones with 5,5-dimethylcyclohexane-1,3-dione generates synthetically important tetraketones in high yields.[13] Reactivity studies of *N*-tosylhydrazones derived from aromatic aldehydes exhibit that the coupling reaction tolerates a methoxy groups but fails with a hydroxyl group at the ortho position. *N*-tosylhydrazone generated from *α,β*-unsaturated aldehyde provides Knoevenagel adduct under the base free conditions. The mild reaction conditions enabled the synthesis of tetraketone having *N*-Boc indole moiety in high yields. *N*-tosylhydrazone can also be converted to xanthendiones in one-pot operation under mild acidic conditions in high yields. Initial results suggest that synthesis of *β*-keto enol ether is possible under transition metal free coupling of *N*-tosylhydrazone with dimedone.

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Supplimentary data

Supplementary data is available for the manuscript

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9. a) Knoevenagel condensation of 2,4-petanedione with *N*-tosylhydrazones using stoichiometric amount of $CuCl_2$ was reported, see: Attanasi O, Filippone P, Mei A. *Synth Commun*. 1983;13:1203; b) Intramolecular cyclization of dicarbonyl compounds via *N*-tosylhydrazone has been reported, see: Zhu C, Qiu L, Xu G, Li J, Sun J. *Chem Eur J*. 2015;21:12871

10. K_2CO_3 mediated coupling of dimedone with *N*-tosylhydrazone generated from cyclohexanone in DMF at 110 °C also resulted

into *O*-alkylated dimedone in 23% yields (see supporting information).

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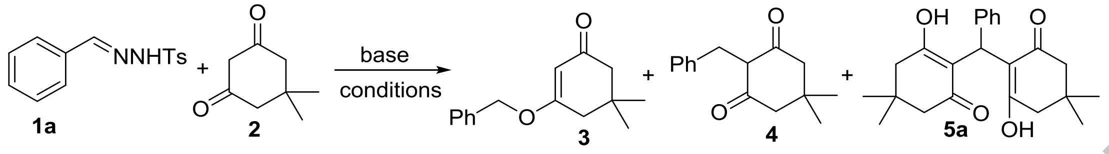
13. *Experimental procedure for the synthesis of tetraketone*: A mixture of *N*-tosylhydrazone **1a** (200 mg, 0.73 mmol), dimedone (214 mg, 1.53 mmol) in toluene (3.0 mL) was stirred at 110 ^{o}C for 30 min. The reaction mixture was then cooled to rt and diluted with ethyl acetate (25 mL). The organic layer was washed with 5% AcOH solution (aq) (1 x 10 mL), brine (1 x 10 mL), dried over Na2SO4 solution and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography using 10% ethyl acetate in hexanes as eluent to obtain tetraketo compound **5a** (242 mg, 90%) as a white solid (Please see the supplementary information for spectral data).

Table 1: Optimization of conditions for coupling of *N*-tosylhydrazone with dimedone

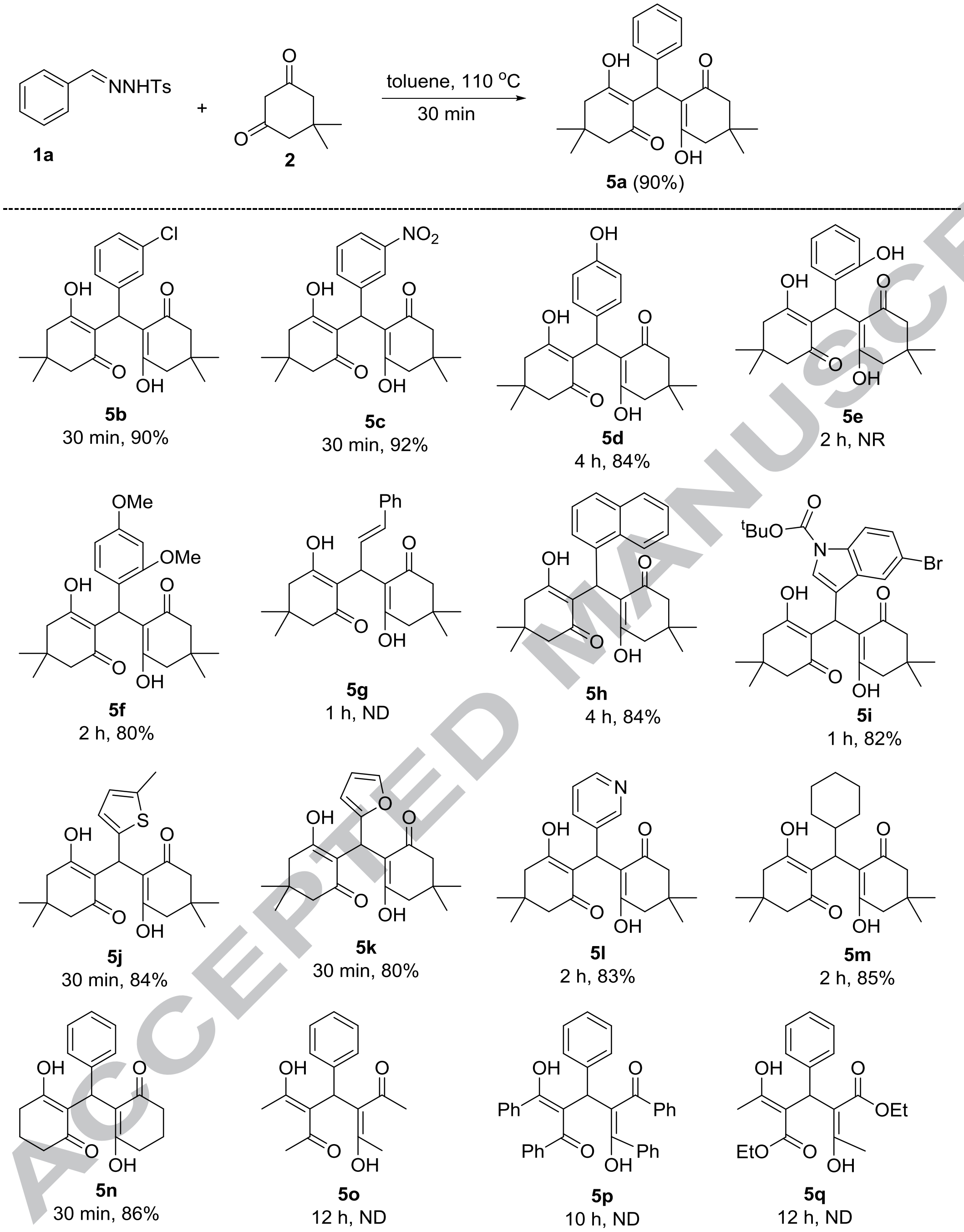


Entry	Dimedone (eq)	Base	(eq)	Conditions	Yield (%)[a]		
					3	**4**	**5a**
a	1.0	K_2CO_3	(1.1)	DMF, 110 ^oC, 30 min	28	-	15
b	1.0	Cs_2CO_3	(1.1)	DMF, 110 ^oC, 30 min	30	-	18
c	1.0	K_2CO_3	(1.1)	DMSO, 110 ^oC, 45 min	26	-	20
d	1.0	K_2CO_3	(1.1)	DMPU, 110 ^oC, 30 min	25	-	16
e	1.0	K_2CO_3	(1.1)	NMP, 110 ^oC, 45 min	27		15
f	1.0	K_2CO_3	(1.1)	HMPA, 110 ^oC, 30 min	26		20
g	2.0	K_2CO_3	(1.1)	DMF, 110 ^oC, 30 min	45	14	34
h	2.0	K_2CO_3	(1.1)	Dioxane, 110 ^oC, 30 min	30	10	48
i	2.0	K_2CO_3	(1.1)	Toluene, 110 ^oC, 15 min	trace	-	82
j	2.0	K_2CO_3	(0.5)	Toluene, 110 ^oC, 15 min	-	-	85
k	2.1	-	-	Toluene, 110 ^oC, 15 min	-	-	90[b]

[a] All reactions were carried out using 1.0 eq of *N*-tosylhydrazone in appropriate solvent (0.5M)

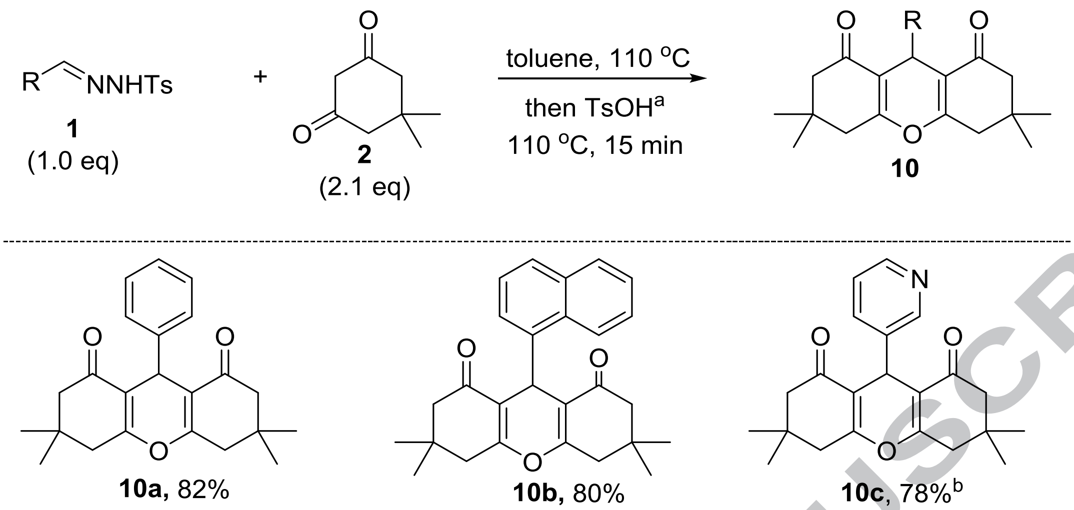
[b] reaction was carried out in absence of K_2CO_3

Table 2: Synthesis of tetraketones from *N*-tosylhydrazones[a]



[a] All reactions were carried out using 1.0 eq of *N*-tosylhydrazone, 2.1 eq of dicarbonyl compound in toluene (0.4 M) at 110 °C; NR = no reaction; ND = yield not determined

Table 3: One-pot synthesis of xanthenedione from *N*-tosylhydrazone



10a, 82%

10b, 80%

10c, 78%[b]

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[a] TsOH was added after complete conversion of *N*-tosylhydrazone to tetraketone;

[b] 1.1 eq of TsOH was used and product isolated after neutralization with aq. $NaHCO_3$

.

Highlights:

1. Transition metal and base free coupling
2. Tetraketones synthesis under mild conditions in high yields
3. Wide substrate scope.
4. Base mediated reactions generate C-O coupling as major product.
5. One-pot synthesis of xanthenedione under mild acidic conditions.