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Efficient synthesis of *N*-nosyl-protected 3-azabicyclo[4.3.0] nonen-8-one by an aniline- and nitrobenzene-mediated Pauson–Khand cyclization

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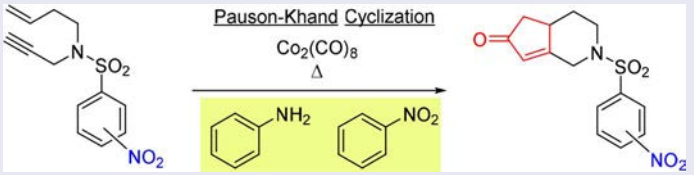
ABSTRACT

The intramolecular Pauson–Khand cyclization in the presence of both aniline and nitrobenzene was used to improve the construction of *N*-nitrobenzenesulfonyl-protected 3-azabicyclo[4.3.0]nonane skeletons. We found that aniline enhanced the cyclization and that nitrobenzene prevents the concurrent reduction in this process. This combination of mediators allows for the efficient synthesis of bioactive azabicyclic nonane-type alkaloids and the use of milder deprotection conditions in the synthetic route.

GRAPHICAL ABSTRACT



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KEYWORDS
Aromatic amine; aza-bicyclononane; nitrobenzenesulfonyl protecting group; Pauson–Khand reaction

Introduction

3-Azabicyclo[4.3.0]nonane, or cyclopenta[*c*]piperidine, is a common structural motif in bioactive alkaloids, such as nakadomarin A (**1**),[1] incarvillateine (**2**),[2] skytanthine (**3**),[3] and tecomanine (**4**)[4] (Figure 1).

The Pauson–Khand reaction (PKR) is a key step in the synthesis of these alkaloids,[5] providing a reliable single-step method of assembling the cyclopentenone from an alkene, an alkyne, and carbon monoxide through a cobalt–carbonyl complex (Scheme 1).[6] For example, the intramolecular PKR allows effective construction of the bicyclic skeleton of **6** from the corresponding enyne-arylsulfonamide precursor **5**. The *p*-toluenesulfonyl (Ts) nitrogen-protecting group is commonly used because of its chemical stability and ease of handling. However, the removal of Ts group requires the use of harsh reaction conditions, which are often problematic.[7] Thus, we used the nitrobenzenesulfonyl (nosyl, Ns)

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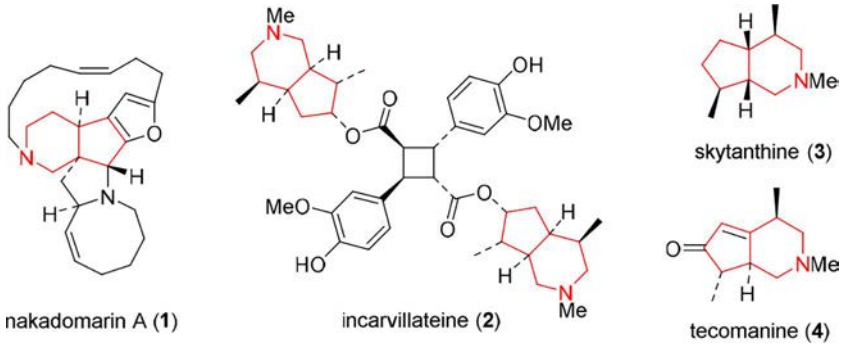


Figure 1. Bioactive alkaloids containing 3-azabicyclo[4.3.0]nonane skeletons.

group,[8] which is more easily removed through a Meisenheimer complex than Ts in the PKR.[5c]

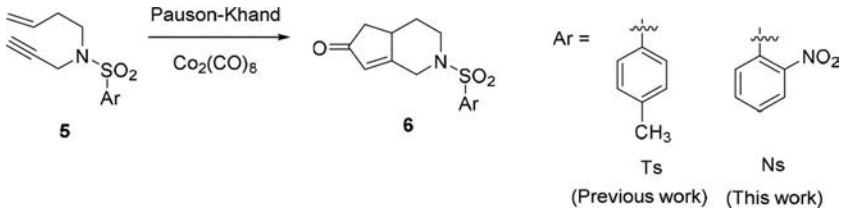
We encountered low conversion yields in our attempts to use the PKR to synthesize **8** from the Ns-protected enyne-precursor **7** (Scheme 2) as well as generation of the undesired aminoarene **9**.[5c] In contrast, the enyne-aminoarene **10** could be converted to **9** in 56% yield under the same reaction conditions. These results indicate that the substituents on the aromatic ring affected the PKR process.

In 1997, the Sugihara and Yamaguchi group reported that amine additives, in particular cyclohexylamine, enhance the PKR and proposed a mechanism involving the labilization of a cobalt–carbonyl complex.[9] However, the effect of intramolecular aromatic amines on the PKR is unknown. In this communication, we report the results of our investigation of PKR in the presence of aromatic amino- and nitro-functional groups to improve the yield of the important compound, *N*-Ns 3-azabicyclo[4.3.0]nonen-8-one (**8**).

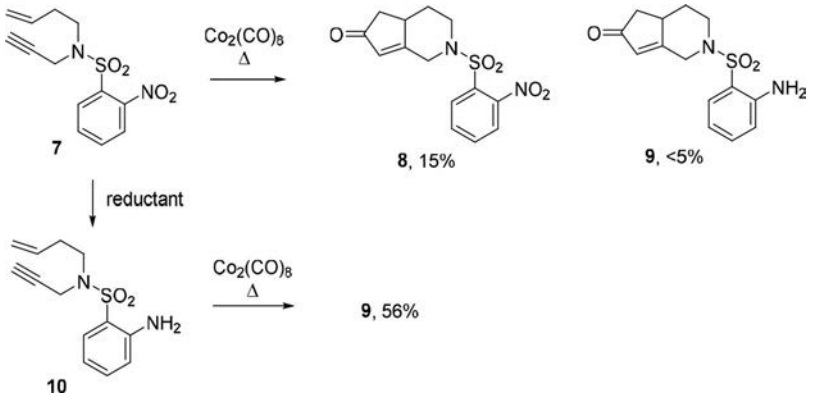
Results and discussion

The precursors for the PKR were prepared from the corresponding *N*-propargylic arylsulfonamides (**11**–**15**)[10] in one or two steps (Scheme 3).

A Mitsunobu reaction[11] using a combination of the arylsulfonamide (**11**–**15**), but-3-en-1-ol, dimethoxyethyl azodicarboxylate,[12] and triphenylphosphine (PPh_3) provided the *N*-butenylated compounds (**7, 16**–**19**) in 63–99% yield. The subsequent reduction of nitro group was performed using the Fe/NH_4Cl/EtOH/H_2O protocol[13] to give the aminoarene products (**10, 20**–**22**) in 77–93% yield.



Scheme 1. Construction of azabicyclic framework through PKR. *Note*: PKR, Pauson–Khand reaction.

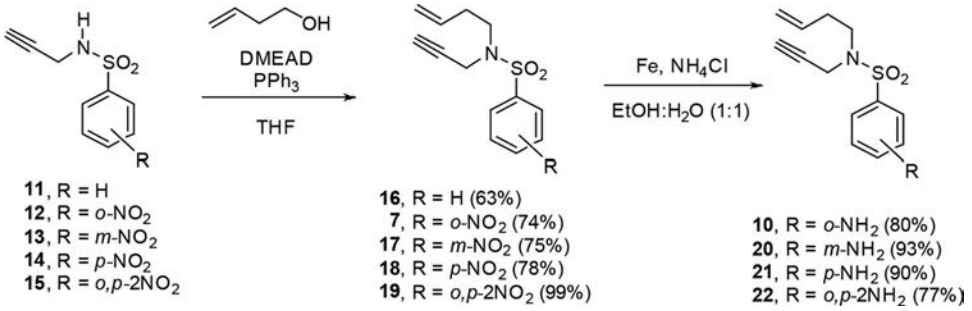


Scheme 2. Preliminary study of PKR. *Note*: PKR, Pauson–Khand reaction.

The general PKR procedure was as follows: the enyne substrate was dissolved in 1,2-dichloroethane (DCE) (0.05 mol/L solution) at room temperature under an argon atmosphere, and dicobalt octacarbonyl [$Co_2(CO)_8$] (1.05 equiv.) was added to the solution. After stirring for 2 h to generate the cobalt–alkyne complex *in situ*, the mixture was heated to 60 °C and stirred for 24 h. The reaction mixture was then filtered once and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography using a mixture of hexane and EtOAc to isolate the bicyclic product. The results of PKR with the enyne substrates **10, 16**, and **20**–**22** are summarized in Table 1.

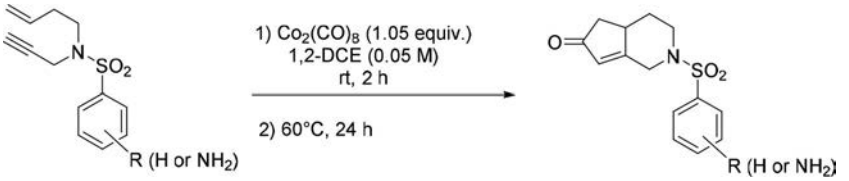
N-Butenyl *N*-propargyl benzenesulfonamide (**16**) was used as a control to assess the PKR, resulting in a 57% yield of the bicyclic compound **23** (Table 1, entry 1). The *ortho*-amino group in benzenesulfonamide **10** gave **9** in 56% yield under the same condition (Table 1, entry 2). The substrates with amine groups in the *meta*- and *para*-positions gave **24** and **25** in yields of 32 and 34%, respectively (Table 1, entries 3 and 4). In addition, substrate **22**, with *ortho*- and *para*-substituted diaminoarene, was converted to **26** in 30% yield (Table 1, entry 5).

Thus, the substrates with *ortho*-substituted NH_2 groups showed enhanced yields of the PKR product compared to those substituted in the *meta* or *para* positions. We suggest that an intramolecular coordination of the amino group to the cobalt moiety (**TS1**) during the ring formation process (**10** to **9** in Scheme 4) could be responsible for these enhanced yields, in accordance with the previous proposal by Sugihara and Yamaguchi groups.[9]



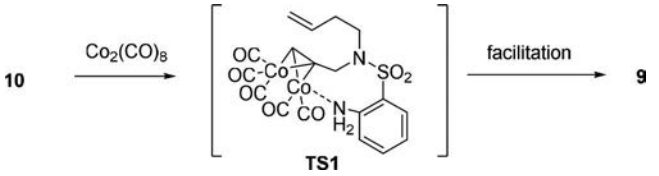
Scheme 3. Preparation of various enyne-arylsulfonamides.

Table 1. PKR of enyne-substrates.



Entry	Substrate	Product yield (%)
1	**16**, R=H	**23** (57)
2	**10**, R = *o*-NH_2	**9** (56)
3	**20**, R = *m*-NH_2	**24** (32)
4	**21**, R = *p*-NH_2	**25** (34)
5	**22**, R = *o*,*p*-$2NH_2$	**26** (30)

PKR, Pauson–Khand reaction.

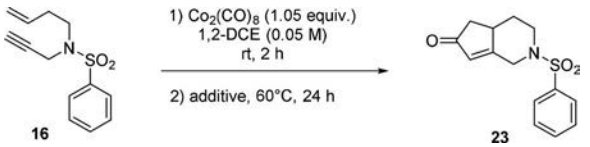


Scheme 4. Possible mechanism through transition state (**TS1**).

We next investigated the ability of aniline and its derivatives to exert an intermolecular effect during the PKR of **16**, and the results are summarized in Table 2.

The addition of 1 equiv. of aniline increased the yield of PKR from 57 to 82% (Table 2, entry 6). We varied the amount of aniline from 0.1 to 10 equiv., which showed that the addition of excess aniline resulted in further yield improvements, with 10 equiv. providing an almost quantitative conversion (Table 2, entries 7–9). The addition of *N*-methylaniline and *N*,*N*-dimethylaniline had no effect on the yield (Table 2, entries 10 and 11). A primary aromatic amine (aniline) additive provided the greatest yield improvement compared to secondary or tertiary amines, and adding either a stoichiometric or excess amounts of the amine each provided an effective yield increase.

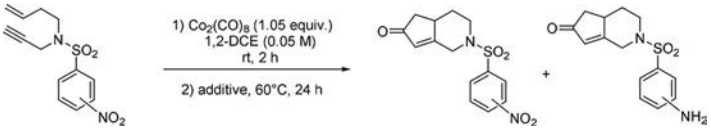
Table 2. PKR of **16** with aminoarene additives.



Entry	Additive (equiv.)	Yield of **23** (%)
6	Aniline (1)	82
7	Aniline (0.1)	51
8	Aniline (3)	81
9	Aniline (10)	96
10	*N*-methylaniline (1)	62
11	*N*,*N*-dimethylaniline (1)	51

PKR, Pauson–Khand reaction.

Table 3. PKR of enyne-nitroarene with the addition of aniline and nitrobenzene.



Entry	Substrate	Additive (equiv.)	Product nitro/amino yields (%)
12	**7**, *o*-NO_2	Aniline (1)	**8/9** (16/34)
13	**7**, *o*-NO_2	Nitrobenzene (10)	**8/9** (21/5)
14	**7**, *o*-NO_2	Aniline (10) + nitrobenzene (10)	**8/9** (50/8)
15	**17**, *m*-NO_2	Aniline (10) + nitrobenzene (10)	**27/24** (54/trace)
16	**18**, *p*-NO_2	Aniline (10) + nitrobenzene (10)	**28/25** (55/trace)
17	**19**, *o,p*-$2NO_2$	Aniline (10) + nitrobenzene (20)	**29/26** (43/trace)

PKR, Pauson–Khand reaction.

Finally, the PKR of nitroarene substrates **7** and **17**–**19** was investigated and the results are summarized in Table 3.

The PKR of **7** in the presence of 1 equiv. of aniline resulted in the formation of both the nitro- and amino-bicyclic compounds (**8**/**9**), which were obtained in a ~1:2 ratio (Table 3, entry 12) with a total yield of 50%. Although the mechanism by which the nitro group is reduced during the PKR is unclear,[14] the addition of 10 equiv. of nitrobenzene as a sacrificial reagent was found to prevent the formation of aminoarene **9** (Table 3, entry 13). Thus, the PKR of **7** in the presence of 10 equiv. of both aniline and nitrobenzene improved the ratio in which the nitro and amino products were formed (Table 3, entry 14). This protocol was found to be applicable to a range of other nitroarenes (**17**–**19**), which gave bicyclic nitro products (**27**–**29**) in moderate yield (Table 3, entries 15–17).

Conclusion

We investigated the effect of aromatic amine groups on the PKR and found that the use of a primary aromatic amine as an additive provided increased yield. Furthermore, we found that the use of an excess of both aniline and nitrobenzene could improve the efficiency of PKR-based synthesis of *N*-Ns azabicyclic compound **8**. These results allow the syntheses of bioactive alkaloids and related compounds to be carried out using milder deprotection conditions. Further optimization of the solvent, concentration, temperature, and reaction time of the PKR is currently being investigated in our group.

Experimental

Representative procedures and selected characterization data are as follows:

Mitsunobu reaction (11 to 16, Scheme 3)

Dimethoxyethyl azodicarboxylate (95% purity, 456 mg, 1.85 mmol) was added to a mixture of *N*-propargyl benzenesulfonamide **11** (300 mg, 1.54 mmol), but-3-en-1-ol (0.15 mL, 1.69 mmol), and PPh_3 (485 mg, 1.85 mmol) in anhydrous THF (8 mL) under an argon atmosphere at room temperature. After stirring for 24 h at room temperature, the solution was evaporated under reduced pressure. The residue was dissolved in H_2O (8 mL) and Et_2O

(8 mL) and the mixture was stirred for 10 min. The Et_2O was separated from H_2O layer, washed with brine, and dried with $MgSO_4$. The dried solution was filtered, and the filtrate was evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography by eluting with hexane:EtOAc (3:1) to give **16** (244 mg, 63% yield) as a colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 (d, $J = 7.6$ Hz, 2H), 7.56 (t, $J = 7.6$ Hz, 1H), 7.49 (dd, $J = 7.6$, 7.6 Hz, 2H), 5.76 (ddt, $J = 6.9$, 10.3, 17.2 Hz, 1H), 5.11 (d, $J = 17.2$ Hz, 1H), 5.06 (d, $J = 10.3$ Hz, 1H), 4.15 (s, 2H), 3.28 (t, $J = 7.6$ Hz, 2H), 2.34 (dt, $J = 6.9$, 7.6 Hz, 2H), 1.99 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.0, 134.5, 132.8, 128.9, 127.7, 117.4, 76.5, 73.8, 45.8, 36.5, 32.3; IR (neat, cm^{-1}): 3290, 1447, 1348, 1332, 1161; HR-MS (CI): *m/z* $[M]^+$ calcd for $C_{13}H_{15}NO_2S$: 249.0823; found, 249.0802.

Reduction of nitroarene (18 to 21, Scheme 3)

Iron powder (95% purity, 2.16 g, 36.7 mmol) was added to a mixture of the nitroarene **18** (1.08 g, 3.67 mmol) and NH_4Cl (1.98 g, 36.7 mmol) in EtOH (36.5 mL) and H_2O (36.5 mL) at room temperature. After stirring for 72 h at room temperature, the mixture was filtered through a celite pad. The organic solvents were removed from the filtrate under reduced pressure. The remaining H_2O layer was extracted with EtOAc (36.5 mL × 2) and the combined EtOAc fractions were washed with brine and dried with $MgSO_4$. The solution was then filtered and the filtrate was evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography by eluting with hexane:EtOAc (3:1) to give **21** (0.88 g, 90% yield) as a white solid; mp 63–65 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 (d, $J = 8.9$ Hz, 2H), 6.65 (d, $J = 8.9$ Hz, 2H), 5.75 (ddt, $J = 6.9$, 10.3, 17.2 Hz, 1H), 5.09 (d, $J = 17.2$ Hz, 1H), 5.04 (d, $J = 10.3$ Hz, 1H), 4.12 (br s, 2H), 4.09 (d, $J = 2.8$ Hz, 2H), 3.22 (t, $J = 7.2$ Hz, 2H), 2.32 (dt, $J = 6.9$, 7.2 Hz, 2H), 2.04 (t, $J = 2.8$ Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 150.7, 134.8, 129.9, 127.1, 117.2, 114.0, 77.0, 73.7, 45.8, 36.4, 32.3; IR (neat, cm^{-1}): 3463, 3369, 3268, 1663, 1596, 1504, 1433, 1336, 1303, 1139, 1122; HR-MS (CI): *m/z* $[M+H]^+$ calcd for $C_{13}H_{17}N_2O_2S$: 265.1011; found, 265.1009.

Pauson–Khand reaction (7 to 8/9, Table 3, entry 14)

$Co_2(CO)_8$ (95% purity, 50.0 mg, 0.125 mmol) was added to a solution of **7** (35.0 mg, 0.119 mmol) in anhydrous 1,2-DCE (2.40 mL) under an argon atmosphere at room temperature. After stirring for 2 h at room temperature, thin layer chromatography (TLC) analysis confirmed the generation of a di-cobalt–alkyne complex ($R_f = 0.45$ in hexane:EtOAc 1:1). Aniline (0.108 mL, 1.19 mmol) and nitrobenzene (0.122 mL, 1.19 mmol) were then added to the complex and the mixture was heated to 60 °C in an oil bath. After stirring for 24 h at 60 °C, the mixture was cooled to room temperature and filtered through a celite pad. The filtrate was added to HCl (1 M, 5 mL) and stirred for 10 min. The organic layer was separated from the aqueous layer, washed with H_2O (5 mL) and brine, and dried with $MgSO_4$. The solution was then filtered and the solvent was removed from the filtrate under reduced pressure. The resulting residue was purified by silica gel column chromatography by eluting with hexane:EtOAc (1:2) to give **9** (2.8 mg, 8% yield) as a pale yellow oil, or with hexane:EtOAc (0:1) to give **8** (19.3 mg, 50% yield) as a colorless oil.

Compound **8**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.03 (d, $J = 7.6$ Hz, 1H), 7.76–7.67 (m, 2H), 7.64 (d, $J = 7.6$ Hz, 1H), 6.03 (s, 1H), 4.79 (d, $J = 14.4$ Hz, 1H), 4.00 (d, $J = 11.7$ Hz, 1H),

3.72 (d, $J = 14.4$ Hz, 1H), 3.03 (ddd, $J = 2.1$, 12.4, 13.1 Hz, 1H), 2.81–2.73 (m, 1H), 2.62 (dd, $J = 6.2$, 19.3 Hz, 1H), 2.20–2.13 (m, 1H), 2.04 (d, $J = 18.6$ Hz, 1H), 1.54–1.45 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.1, 171.7, 148.2, 134.1, 131.9, 131.8, 131.1, 129.1, 124.4, 47.2, 45.7, 41.5, 39.4, 32.8; IR (thin film, cm^{-1}): 1705, 1633, 1541, 1356, 1163; HR-MS (EI): *m/z* $[M]^+$ calcd for $C_{14}H_{14}N_2O_5S$: 322.0623; found, 322.0624.

Compound **9**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 (d, $J = 8.3$ Hz, 1H), 7.31 (dd, $J = 6.9$, 8.3 Hz, 1H), 6.76 (dd, $J = 6.9$, 8.3 Hz, 1H), 6.72 (d, $J = 8.3$ Hz, 1H), 5.98 (s, 1H), 5.03 (s, 2H), 4.72 (d, $J = 13.8$ Hz, 1H), 3.98–3.93 (m, 1H), 3.44 (d, $J = 13.8$ Hz, 1H), 2.75 (dd, $J =$ 12.4, 12.4 Hz, 1H), 2.69–2.63 (m, 1H), 2.58 (dd, $J = 6.9$, 18.6 Hz, 1H), 2.14–2.07 (m, 1H), 1.99 (d, $J = 18.6$ Hz, 1H), 1.50–1.42 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.3, 172.4, 146.4, 134.7, 130.4, 129.1, 117.9, 117.8, 117.6, 47.4, 45.7, 41.5, 39.4, 32.2; IR (thin film, cm^{-1}): 3475, 3370, 1702, 1618, 1483, 1452, 1322, 1140; HR-MS (CI): *m/z* $[M+H]^+$ calcd for $C_{14}H_{17}N_2O_3S$: 293.0960; found, 293.0930.

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