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Oxidative C–N coupling of azoles with cycloheptatriene using an oxoammonium salt bearing the nitrate anion

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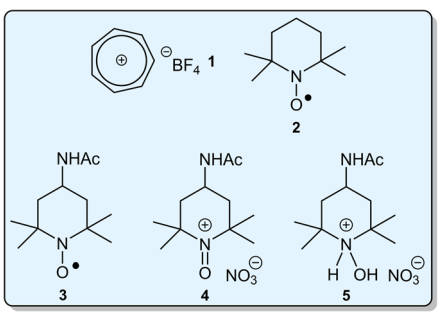
A methodology is reported for the synthesis of substituted 1,3,5-cycloheptatrienes by means of an oxoammonium salt mediated C–N coupling of azoles with cycloheptatriene. The approach does not require pre-functionalised starting materials, external bases, and excess reagents, and it proceeds under mild conditions. The reaction shows substrate compatibility across a diverse range of azole nucleophiles, and is scalable by employing microwave heating.

Introduction

Nitrogen-containing heterocycles occupy a central position in biological, medicinal, and synthetic chemistry due to their widespread occurrence in natural products, advanced materials, and pharmaceuticals.[1,2] A range of metals of catalysts such as those comprising Cu, Pd, Ir, and Cs have been developed to enable C–N bond-forming cross-coupling reactions.[3,4] However, the construction of C–N bonds can still be a challenge in organic synthesis.

Amongst nitrogen-substituted aromatic systems, derivatives such as 4-(7-cyclohepta-1,3,5-trienyl)aniline exhibit pronounced antibacterial and antimycotic activities, highlighting the medicinal relevance of cycloheptatriene-based scaffolds.[5,6] In addition to their biological significance, cycloheptatriene derivatives have attracted attention in organometallic chemistry, where they have been employed as ligands for the synthesis of catalytically active metal complexes.[7,8] Notably, the tropylium cation has been utilized as a π-ligand in sandwich type manganese complexes, commonly referred to as tromancenium salts.[9] Cycloheptatriene is a versatile coupling partner, enabled by its nonbenzenoid aromaticity and propensity for skeletal rearrangement, and has been extensively studied mechanistically.[10,11] However, despite these attractive properties and diverse applications, synthetic strategies for the efficient formation of substituted cycloheptatriene frameworks remain comparatively underexplored. Existing approaches for accessing *N*-functionalized cycloheptatriene frameworks predominantly rely on tropylium tetrafluoroborate (**1**) as the starting material.[5,12–14] The formation of **1** typically requires strong oxidizing agents and the use of a base, adding synthetic overhead and limiting practical utility.

Of the methods in the synthetic chemist's toolkit, electrochemistry has been particularly useful for the synthesis of *N*-functionalized cycloheptatriene derivatives directly from cycloheptatriene, thereby eliminating the need for pre-formed tropylium salts.[15,16] However, they tend to require a significant excess of cycloheptatriene, with a significant portion consumed as a sacrificial substrate leading to dimeric by-products.[15] In addition, they tend to operate with large solvent volumes, and involve prolonged reaction times, collectively limiting their practical utility. These issues piqued our interest in developing a methodology for the formation of nitrogen-containing substituted 1,3,5-cycloheptatriene derivatives. To achieve this goal, we turned our attention to using a derivative of 2,2,6,6-tetramethylpiperidinyloxy (TEMPO, **2**) as an electrocatalyst. Employing 4-acetamido-TEMPO (ACT, **3**), we were able to use commercially available precursors, thereby avoiding the multistep preparation of starting materials required in previous methods.[16,17] The approach also eliminates the need for excess cycloheptatriene and bases, as well as suppressing dimer formation. It proceeds efficiently under mild, scalable conditions using inexpensive electrodes and standard equipment. Having said this, issues of reaction concentration and time were still bugbears.



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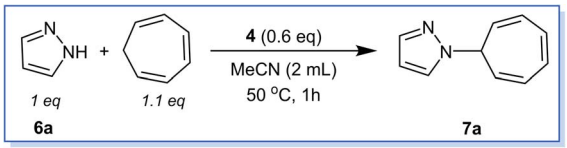
Returning to conventional approaches, over the last year, we have found success in using **4**, an oxoammonium salt bearing a nitrate counterion, as a sub-stoichiometric reagent for oxidative functionalization reactions. It is metal-free, bench-stable, and recyclable.[18,19] Based on the observed α-hydride transfer pathway associated with this salt,[20] we posited that we may be able to generate the cycloheptatrienyl cation *in situ* from 1,3,5-cycloheptatriene, thereby obviating the need to preform or isolate a stable carbocation precursor. In addition, the reduced hydroxylamine form (**5**) of the nitrate salt could feasibly function as an internal base, potentially eliminating the requirement for an external base. Furthermore, the nitrate counterion can enhances the reactivity of the oxoammonium cation significantly. The nitrate anion actively participates in the redox process, generating nitrogen oxides (NO_x) which interact with molecular oxygen, establishing a nitrogen oxide redox cycle that serves as a co-catalytic pathway for the regeneration of **4**, thereby eliminating the need for a sacrificial oxidant.[20] Guided by this rationale, we sought to access new biologically relevant cycloheptatriene derivatives through C–N bond formation using **4** and present our results here.

Results and discussion

We chose the coupling of cycloheptatriene with pyrazole as model substrates for the optimization of reaction conditions, product conversion being monitored by ^{1}H-NMR spectroscopy.

We began our study using conditions based on our successful alcohol oxidation protocol employing **4**.[18] Specifically, we used 1 eq. of pyrazole (**6a**), 1.1 eq. of cycloheptatriene, and 0.6 eq. of **4** in 2 mL of acetonitrile. We observed an 85% conversion to the desired product, **7a**, after heating at 50 °C for 1 h (Table 1, entry 1). We next performed the reaction in the presence of an external base, adding 0.12 eq. of pyridine to serve in this regard. Under these conditions, a 66% conversion to **7a** was obtained (entry 2), the remainder of the product mixture being unreacted starting materials. Reducing the loading of pyridine to 0.08 eq. led to an increase in product conversion to 85%, but reducing the pyridine loading further resulted in a concomitant drop in conversion to **7a** (entries 3 and 4). Since there was not a benefit to adding pyridine as an external base, we did not pursue this avenue further. Instead, we probed the impact of varying heating time on the outcome of the reaction. Performing the reaction at 50 °C for 10–30 min had a positive effect (entries 5–7) with optimal results being observed after 20 min (95% conversion to **7a**). Increasing the loading of **4** from 0.60 eq. to 0.65 eq. did not have a significant impact on the outcome of the reaction, but reducing the loading to 0.55 eq. did result in a noticeable drop in product conversion to **7a** (entries 8 and 9). Neither increasing or decreasing the stoichiometric quantity of cycloheptatriene significantly impacted the protocol (entries 10 and 11). We turned our attention to the solvent in which the reaction was performed. Using dichloromethane, a lower product conversion of 85% was obtained as when employing acetonitrile (entry 12). When water was used as the solvent, conversion to **7a** dropped significantly, this not being too unexpected given the solubility challenges that this poses (entry 13). Returning to acetonitrile as the solvent, increasing or decreasing the reaction concentration did not lead to any improvement in outcome (entries 14 and 15). The final parameter we probed was the temperature at which the reaction is performed. Neither increasing the temperature to 55 °C or reducing it to 45 °C had a positive impact on the outcome of the reaction. Our optimised conditions were therefore established as: pyrazole (1 mmol, 1 eq.), cycloheptatriene (1.1 eq.), and **4** (0.6 eq.) in 2 mL acetonitrile, stirred at 50 °C for 20 min.

Table 1 Screening of reaction conditions[a]



Entry	Deviation from above	7a [a] (%)
1	None	85
2	Addition of 0.12 eq. pyridine	66
3	Addition of 0.08 eq. pyridine	85
4	Addition of 0.06 eq. pyridine	78
5	Heating for 30 min	94
6	Heating for 20 min	95
7	Heating for 10 min	90
8	**4** (0.65 eq.), heating for 20 min	88
9	**4** (0.55 eq.), heating for 20 min	71
10	Cycloheptatriene (1 eq.), heating for 20 min	91
11	Cycloheptatriene (1.2 eq.), heating for 20 min	81
12	Dichloromethane (2 mL), heating for 20 min	85
13	Water (2 mL), heating for 20 min	58
14	Acetonitrile (1.5 mL), heating for 20 min	75
15	Acetonitrile (2.5 mL), heating for 20 min	93
16	Heating at 55 °C for 20 min	92
17	Heating at 45 °C for 20 min	82

[a] Conversion determined by ^{1}H-NMR spectroscopy.

With optimised conditions in hand, we investigated the substrate scope of the methodology (Fig. 1). The coupling of a variety of substituted pyrazoles with cycloheptatriene was successful. The protocol proved effective for electron-rich, electron-poor, and sterically encumbered pyrazoles bearing substituents at either the 3- or 4- position, as well as for a di-substituted example (Fig. 1, **7a–7g**). Representative triazoles, indazoles, and imidazoles were also successfully transformed in acceptable yields (Fig. 1, **7h–7k**). In some cases, isolation of the desired product was challenging. With 1,2,3-triazole, we obtained 100% conversion (as determined by NMR) and a 75% isolated yield of the desired product, **7h**. In contrast, 1,2,4-triazole afforded a 75% conversion to **7i**, but we were unable to isolate the product. This was likely due to the strong interaction of **7i** to silica gel during purification, because of the non-consecutive arrangement of the nitrogen atoms in the heterocycle ring. When using imidazole as a coupling partner, only a 20% conversion to the desired product, **7j**, was obtained but when using maleimide, no product formation was observed. To expand the remit of the methodology, we screened a number of

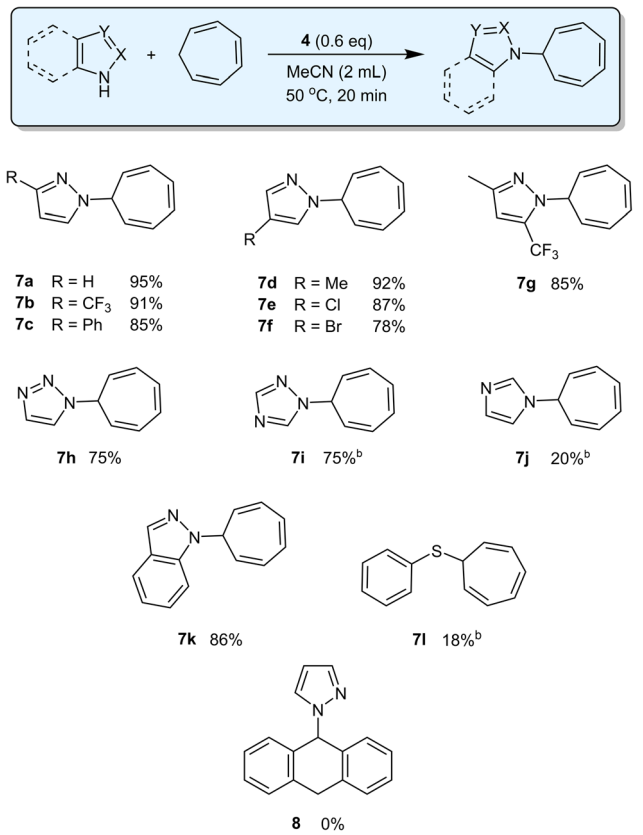


Fig. 1 Scope of the coupling of azoles and cycloheptatriene using **4**.[a] [a]Using azole (1.0 mmol), cycloheptatriene (1.1 mmol), and **4** (0.6 mmol) in 2 mL of acetonitrile; heating for 20 min at 50 °C. [b]Product conversion determined by ^{1}H-NMR spectroscopy.

phenols and thiols. In the case of thiophene, an 18% conversion to the product, **7l**, was obtained and we did not have success in the case of phenols. Returning to pyrazole, using 9,10-dihydroanthracene in place of cycloheptatriene was also unsuccessful, none of the coupling product **8** being obtained. This outcome could be due to the steric hindrance around the benzylic positions or the inability of the substrate to form a stable carbocation intermediate when oxidized by **4**.

To evaluate further the practicality of this methodology, we attempted to scale up the coupling of pyrazole and cycloheptatriene. Performing the reaction on the 5 mmol scale was not as efficient as when operating at 1 mmol. Only a 45% conversion to the desired product, **7a**, was observed, the remaining material being unreacted cycloheptatriene and protonated pyrazole. We posited that this outcome could be due to the fact that using an oil-bath resulted in non-uniform heating of the reaction mixture and also less effective stirring as compared to the smaller-scale example. These factors could potentially reduce the efficiency of the productive C–N bond formation and instead favour off-target acid–base protonation of pyrazole, thereby lowering the overall conversion to **7a**. We have had success in scaling up the transformation by using microwave heating instead of the traditional approach. It is not that there are any special effects associated with microwave irradiation; this method simply can affect rapid, homogeneous heating in solution-phase reactions. Using our optimised conditions for oil-bath heating, we performed an abbreviated optimisation of the coupling of pyrazole and cycloheptatriene using microwave irradiation (Table 2, entry 1). We probed reaction time (Table 2, entries 2 and 3), temperature (entries 4 and 5), stoichiometry (entries 6–8), and concentration (entry 9). The best outcome was observed when performing the coupling using pyrazole (1 mmol, 1 eq.), cycloheptatriene (1.1 eq.), and **4** (0.6 eq.) in 2 mL acetonitrile, stirred at 45 °C for 30 min. Using this approach we successfully scaled up the coupling to the 5 mmol level, obtaining a 79% isolated yield of **7a** (Fig. 2).

A plausible mechanism for the reaction is shown in Fig. 3. The process proceeds *via* an initial hydride transfer from cycloheptatriene to **4**, generating a cycloheptatrienyl cation. This highly stabilized cationic species subsequently undergoes nucleophilic attack by the azole, leading to formation of the desired C–N coupled product. Hydroxylamine (**5**) functions as an internal base, facilitating proton transfer in the bond-forming event and thereby obviating the need for an external base.

Experimental section

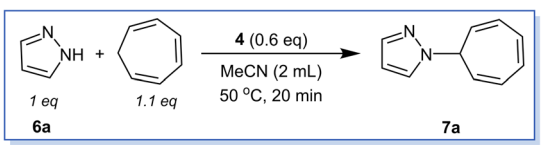
General considerations

Reactions performed using microwave heating were performed in a CEM Discover microwave unit. NMR spectra (^{1}H-, ^{13}C-, and ^{19}F-) were performed at 300 K using either a 300 MHz, or 400 MHz spectrometer. ^{1}H-NMR spectra were referenced to residual $CHCl_3$ (7.26 ppm) in $CDCl_3$. ^{13}C-NMR spectra were referenced to $CDCl_3$ (77.16 ppm). ^{19}F-NMR spectra were referenced to hexafluorobenzene (−161.64 ppm).[21] Reactions were monitored by a gas chromatograph attached to a mass spectrometer and/or thin-layer chromatography.

General procedure for coupling azoles and cycloheptatriene

Conventional heating. To a 4-dram reaction vial equipped with a stir bar were added 4-acetamido-2,2,6,6-tetramethyl-oxo-

Table 2 Screening of reaction conditions using microwave heating[a]



Entry	Deviation from above	7a [a] (%)
1	None	91
2	Heating for 30 min	96
3	Heating for 35 min	80
4	Heating at 55 °C for 30 min	86
5	Heating at 45 °C for 30 min	96
6	Cycloheptatriene (1 eq.)	89
7	**4** (0.65 eq.), heating for 30 min	92
8	**4** (0.55 eq.), heating for 30 min	77
9	Acetonitrile (1 mL)	56

[a] Conversion determined by ^{1}H-NMR spectroscopy.

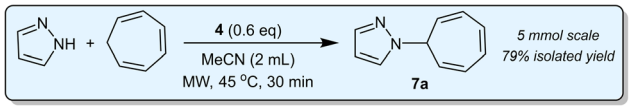


Fig. 2 Coupling of pyrazole and cycloheptatriene using microwave heating.

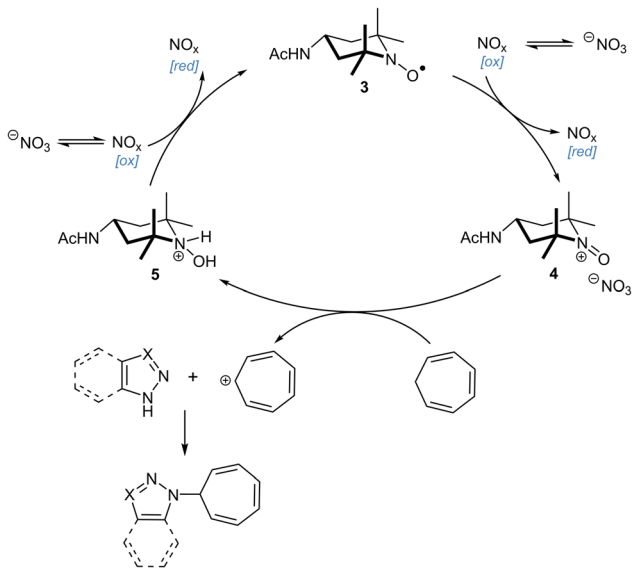


Fig. 3 Proposed mechanism for the coupling of azoles and cycloheptatriene using **4**.

piperidinium nitrate (**4**, 165 mg, 0.6 eq.), nucleophile (1 mmol, 1 eq.), cycloheptatriene (1.1 mmol, 1.1 eq.) and acetonitrile (2 mL) The vial was closed tightly and the contents heated at 50 °C for 20 min in an oil bath. Upon completion of the heating step, the contents of the vial was filtered through a pad of silica, and then the silica washed with an 85 : 15 mixture of hexanes and ethyl acetate to elute the product. The solvent was removed from the filtrate under vacuum, affording the pure product.

Microwave heating. To a 10 mL capacity microwave vial equipped with a stir bar were added 4-acetamido-2,2,6,6-tetramethyl-oxo-piperidinium nitrate (**4**, 165 mg, 0.6 eq.), nucleophile (1 mmol, 1 eq.), cycloheptatriene (1.1 mmol, 1.1 eq.), and acetonitrile (2 mL). The vial was sealed and the contents heated at 45 °C for 30 min. Upon completion of the heating step, the contents of the vial was filtered through a pad of silica, and then the silica washed with an 85 : 15 mixture of hexanes and ethyl acetate to elute the product. The solvent was removed from the filtrate under vacuum, affording the pure product.

Conclusions

In summary, we have developed a methodology for the efficient coupling of azoles with cycloheptatriene in which a sub-stoichiometric quantity of oxoammonium salt **4** serves as the oxidant. This strategy provides a simple, robust, and readily reproducible approach to accessing substituted cycloheptatriene frameworks. Importantly, pre-functionalised starting materials, external bases, and excess reagents are not required. The reaction shows substrate compatibility across a diverse range of azole nucleophiles, proceeds under mild conditions, and is scalable by employing microwave heating.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: experimental details and spectral characterisation. See DOI: https://doi.org/10.1039/d6ra02034h.

Acknowledgements

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