# Synthetic Studies toward 3-(Acylamino)-1*H*-indazoles and Development of a One-Pot, Microwave-Assisted, Oxadiazole Condensation/Boulton–Katritzky Rearrangement

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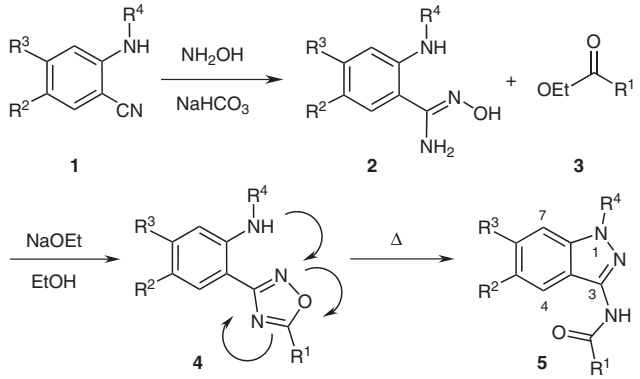
**Abstract:** Studies on the Boulton–Katritzky rearrangement of 3-(2-aminoaryl)-1,2,4-oxadiazoles have led to the identification of additional electronic factors that govern the rearrangement as well as a competitive thermal rearrangement pathway for select substrates. To circumvent the limitations of the conventional thermal conversion sequence an improved protocol that employs microwave irradiation has been devised that allows access to rearrangement products in good to excellent isolated yields. Furthermore, we have developed a two-component, one-pot sequence using a microwave-assisted oxadiazole condensation/Boulton–Katritzky rearrangement to deliver 3-(acylamino)-1*H*-indazoles from simple esters and 2-amino-*N*-hydroxy-benzamidine

**Key words:** Boulton–Katritzky rearrangement, indazole, microwave-assisted, oxadiazole condensation, substituent effects

The 3-(acylamino)-1*H*-indazole motif contains a unique array of staggered hydrogen-bond donors and acceptors. Importantly, members of this structural class have a diverse biological representation with documented activities against kinase[1] and cysteine protease[2] molecular targets as well as broader-based antifungal[3] and antiproliferative activity.[4] The Boulton–Katritzky rearrangement has been recognized as a powerful transformation for the formation of a variety of heterocycles,[5] and an elegant extension of this methodology, reported independently by Vivona and Korbonits, has led to the formation of 3-(acylamino)-1*H*-indazoles from 3-(2-aminoaryl)-1,2,4-oxadiazoles (Scheme 1, **4** → **5**).[6]




**Scheme 1**

With an interest in a varied set of 3-(acylamino)-1*H*-indazoles, this approach appeared attractive since diversity is incorporated in a highly convergent manner. Direct acylation of 3-aminoindazoles has been reported though the use of an acid chloride and/or protection of the indazole nitrogen are often required.[7] The Boulton–Katritzky methodology obviated the need for protecting groups on the indazole; the oxadiazole is generated from the condensation of simple esters **3** and oxime amides **2**, the latter prepared from 2-aminobenzonitriles **1**. The envisioned set of 3-(acylamino)-1*H*-indazoles targeted a range of functionality at the acyl position ($R^1$) as well as on the phenyl of the indazole ($R^2$, $R^3$). Our initial foray using the prescribed conditions for aryl derivatives at $R^1$ (DMF, 150 °C)[6b] revealed the limitations of this methodology for indazoles lacking N1 substitution ($R^4$ = H): extended reaction times (12–70 h) and the use of melt conditions for nonaromatic $R^1$ functionality were required. The documented electronic factors at $R^1$ also proved to be problematic for expansion of this methodology with electron-rich moieties being disfavored. Furthermore, substituent effects on the 2-aminoaryl ring ($R^2$, $R^3$), undocumented prior to this report, proved challenging. At this juncture, we decided to revisit the specifics of this rearrangement for indazoles lacking N1 substitution ($R^4$ = H). Herein, we report an expanded scope of the Boulton–Katritzky scheme to produce 3-(acylamino)-1*H*-indazoles detailing electronic factors on the 2-aminoaryl ring that govern the rearrangement as well as an improved, general protocol using microwave irradiation. This simple, effective procedure negates the use of melts, decreases reaction times to two hours or less and, importantly, allows rapid access to rearrangement products in good to excellent isolated yields. Furthermore, we have parlayed these results into a one-pot, microwave-assisted oxadiazole condensation/Boulton–Katritzky rearrangement sequence to deliver the desired indazoles from 2-amino-*N*-hydroxy benzamidine and simple esters.

To benchmark the electronic effects we used the previously derived thermal conditions (DMF at 150 °C).[6b] Analysis of substituent effects at the $R^2$ and $R^3$ positions on the phenyl ring were explored with electron donating (OMe), electron withdrawing ($NO_2$), and halogen (Cl). Reactions were halted at the time indicated and examined for progression by both HPLC and NMR of the crude isolates. The results of these studies are depicted in Table 1. For

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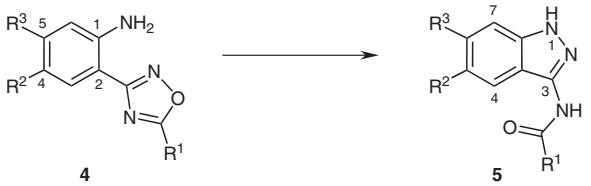
$R^1$, methyl (**4a**) and electron-rich phenyl moieties (**4c**,**d**) were disfavored as expected; conversion reached 19–36% for this subset after 48 hours of heating. Consistent with the reported paradigm, unsubstituted phenyl **4b** reached 68% conversion after 48 h, and the electron withdrawing 4-nitrophenyl derivative **4e** yielded complete consumption of the starting material, though only 64% conversion was attained due to a significant accumulation of unidentified byproducts.

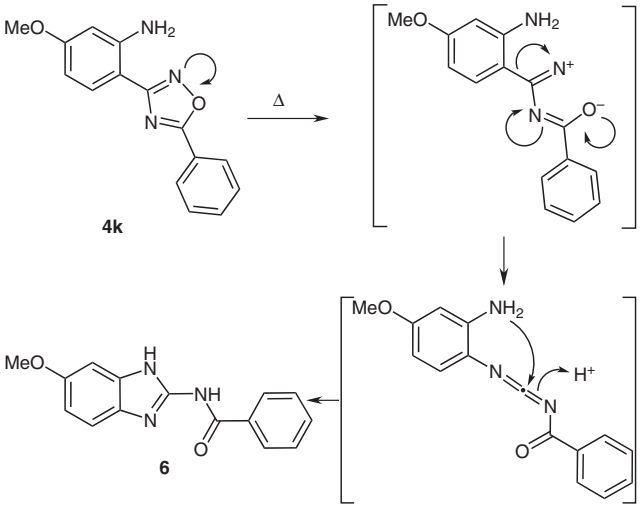
The substituent effects on the 2-aminoaryl ring were fairly pronounced. For $R^2$, an electron-withdrawing substituent decreased propensity for rearrangement, presumably due to decreased nucleophilicity of the aniline. For example, **4f** provided only 8% conversion after 96 hours. The longer reaction times indicated were necessary to provide accurate conversion numbers. In addition, when combined with an electron-rich substituent at $R^1$ scant conversion was observed even up to 120 hours (**4l**, 6%). For $R^2$, reaction rates increased from halogen (**4g**, 62% conversion, 96 h) to methoxy (**4h**, >95% conversion, 96 h). This represented the opposite inductive effect as compared to $R^1$, most likely due to increased nucleophilicity of the aniline. For $R^3$, *meta* to the aniline, electronic perturbation of the aniline nucleophilicity would be mild, though the impact on the reaction through influence on the oxadiazole was evident. The nitro group (**4i**) led to facile conversion which was predictable since, inductively, the nitrogen of the oxadiazole would be more electrophilic. The chloro (**4j**) derivative proceeded only to 38% after 96 hours, with a diminished inductive capacity to influence the oxadiazole. The methoxy derivative **4k** proved particularly interesting. Conversion into the acyl-aminoindazole over 96 hours was 48%, however, a substantial portion was converted into an alternative product with the same molecular weight in a 1.5:1 ratio of indazole/byproduct. We determined that this product was the benzimidazole derivative **6** (Scheme 2)[8] which arises through an alternative (most likely concerted) rearrangement involving cleavage of the N–O bond of the oxadiazole and then migration of the aryl to the nitrogen and formation of the *N*-acylcarbodiimide. Collapse of the aniline nitrogen forms the benzimidazole. Prior to this report, this type of rearrangement had only been observed photochemically for which a similar mechanism had been suggested.[9,10] Since this competing reaction path arises only with example **4k**, we inferred that the ensuing positive charge on the first putative intermediate is stabilized by the presence of the electron-donating methoxy group. There was no interconversion between **5k** and **6** when either was resubjected to the reaction conditions independently.

**Table 1** Comparison of the Results of the Thermal and Microwave Rearrangement




| Entry | **4**, **5** | $R^1$ | $R^2$ | $R^3$ | Thermal conversion (%), time (h)[a] | Microwave isolated yield after 1 h (%) |
|---|---|---|---|---|---|---|
| 1 | **a** | Me | H | H | 19, 48 | 85 |
| 2 | **b** | Ph | H | H | 68, 48 | 96 |
| 3 | **c** | 4-MeO-$C_6H_4$ | H | H | 36, 48 | 93 |
| 4 | **d** | 4-$Me_2N$-$C_6H_4$ | H | H | 25, 48 | 86 |
| 5 | **e** | 4-$NO_2$-$C_6H_4$ | H | H | 64,[b] 24 | 90 |
| 6 | **f** | Ph | $NO_2$ | H | 8, 96 | 62 |
| 7 | **g** | Ph | Cl | H | 62, 96 | 91 |
| 8 | **h** | Ph | MeO | H | >95, 96 | 75 |
| 9 | **i** | Ph | H | $NO_2$ | >95, 96 | 80 |
| 10 | **j** | Ph | H | Cl | 38, 96 | 88 |
| 11 | **k** | Ph | H | MeO | 46, 96 | 53 |
| 12 | **l** | 4-MeO-$C_6H_4$ | $NO_2$ | H | 6, 120 | 76[c] |

[a] Conversion as measured by HPLC and $^1$H NMR.
[b] 100% consumption of **4e**.
[c] Reaction time: 2 h.



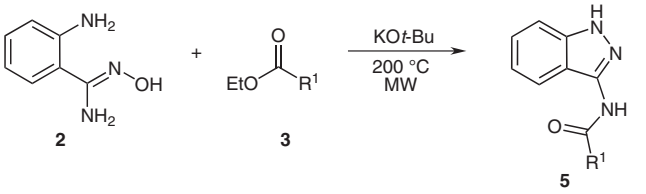

**Scheme 2**

Pursuant to establishing a general protocol, we first examined conventional heating at 200 °C in a sealed tube in the presence of the preferred solvent (DMF). Similar to the melt conditions first reported, improved rates were observed but still extended reaction times were required. For example, substrate **4b** did lead to **5b** in >95% conversion, but only after 17 hours. Since all the reactions proceeded with extended reaction times, melts, or with the use of a sealed tube, it appeared that the major constraints were the efficiency of heating and increased pressure. These specific limitations suggested that microwave irradiation would be a viable alternative.[11] With minor experimentation, we found that heating at 200 °C in DMF for one hour led to clean conversion of the oxadiazole into the indazole. We were gratified to find that this process was general for the substrates indicated in Table 2. Importantly, for an electron-rich $R^1$ group, high yields for **5a**, **5c**, and **5d** were obtained. The nitro derivative **5f** was isolated in more moderate yield (62%).

The $R^3$ methoxy derivative **4k** required only 20 minutes to give complete consumption of the starting material. The isolated yield of the desired product **5k** was 53% and, not surprisingly, we observed the presence of benzimidazole **6** in a similar ratio to that observed previously (**5k/6** = 1.5:1). Finally, we tested our newly devised conditions against the most electronically challenging substrates, namely, an electron-rich $R^1$ group (4-$MeOC_6H_4$) combined with an electron-withdrawing $R^2$ group ($NO_2$). Significantly, example **4l** gave facile rearrangement to the desired **5l** in good isolated yield (76%) though a slightly longer time (2 h) was recorded for complete conversion.

The results presented thus far led us to consider expanding the utility of this microwave-assisted reaction. Recently, Wang and co-workers have documented the use of microwaves to assist in the synthesis of 1,2,4-oxadiazoles.[12] In light of our own data, we envisioned that if an *ortho*-aniline is incorporated into this scheme, we could effect a two-component oxadiazole condensation/Boulton–Katritzky sequence to provide the desired indazole in one pot. Towards this end, the various conditions required for the condensation reported by Wang, which involved carboxylic acid activation or in situ acid chloride formation, were effective for oxadiazole condensation but also led to concomitant acylation of the aniline, providing complex mixtures. Alternatively, Adib and co-workers demonstrated that Meldrum's acid derivatives are effective partners for the condensation to oxadiazoles using solvent-free conditions, though the extent of their findings was limited to Meldrum's acid or the monomethyl derivative.[13] For ease and utility, we decided to use the ester functionality as the condensation partner, and in DMF we were unable to effect condensation even at elevated temperatures (200 °C). We then surveyed a series of bases including Hünig's base, MP-carbonate, sodium ethoxide and potassium *tert*-butoxide. With minor experimentation we found that treating a mixture of the oxime amide and the ester in DMF with 0.3 equivalent of potassium *tert*-butoxide using microwave heating at 200 °C the reaction could be effected, albeit with significant formation of the 2-aminobenzonitrile, resulting from loss of hydroxylamine from the oxime amide. We could achieve higher yields by increasing the stoichiometry of the oxime amide and by running the reaction first at 160 °C to induce the condensation and then heating to 200 °C to promote the rearrangement. Alternatively, to suppress this side reaction, we followed Adib's solvent-free protocol which led to clean conversion into the oxadiazole followed by rearrangement to the indazole upon further heating. In instances where incomplete conversion of the oxadiazole into the indazole was observed, DMF could be added, and then the reaction was resubjected to microwave heating to result in a complete transformation.

**Table 2** One-Pot Microwave-Assisted Reaction




| Entry | **3**, **5** | $R^1$ | Time (h) | Yield of **5** (%) |
|---|---|---|---|---|
| 1 | **a** | Me | 2 | 67 |
| 2 | **b** | Ph | 2 | 71 |
| 3 | **c** | 4-MeO-$C_6H_4$ | 2 | 58 |
| 4 | **e** | 4-$NO_2$-$C_6H_4$ | 2 | 48 |

This procedure appeared general for the substitution on the ester (Table 2), encompassing alkyl ($R^1$ = Me), aryl ($R^1$ = Ph), electron-rich ($R^1$ = 4-MeO-$C_6H_4$) and electron-poor aryl derivatives ($R^1$ = 4-$NO_2$-$C_6H_4$). Albeit, moderate isolated yields (48–71%) were obtained following this protocol, the rapid generation of pharmacologically relevant structures using commercially available or readily obtained starting materials demonstrates the usefulness of

this sequence. Extension to substituted 2-amino-*N*-hydroxy-benzamidines did, however, complicate the one-pot sequence and a general protocol for these substrates is currently under development.

In conclusion, we have further documented electronic factors that govern the Boulton–Katritzky rearrangement of 3-(2-aminoaryl)-1,2,4-oxadiazoles to 3-(acylamino)-1*H*-indazoles. Specifically, the propensity for the thermal rearrangement of 3-(2-aminoaryl)-1,2,4-oxadiazole substrates bearing substituents at the 4-position ($R^2$) follows the paradigm methoxy > halogen > nitro. In addition, a competing rearrangement pathway for substrates with an electron-donating substituent (MeO) at the 5-position ($R^3$) of the substrate has been demonstrated that, prior to this report, has only been observed photochemically. Furthermore, we have devised microwave-irradiation conditions which rely on an improved efficiency in heating with increased pressure that negate the use of melt or conventional sealed-tube conditions, decrease reaction times to two hours or less and offer the rearrangement products in good to excellent isolated yields. Finally, we have devised a two-component, one-pot protocol using a microwave-assisted oxadiazole condensation/Boulton–Katritzky rearrangement to deliver 3-(acylamino)-1*H*-indazoles from esters and 2-amino-*N*-hydroxy-benzamidine.

**General Procedure for Microwave Rearrangements**

The 1,2,4-oxadiazole (0.50 mmol) in DMF (2.0 mL) was heated at 200 °C for 1 h. After cooling, the contents of the reaction were poured into $H_2O$ (25 mL) and extracted with EtOAc (3 × 25 mL). The combined organics were washed with brine and dried over $MgSO_4$ and then concentrated under reduced pressure to remove all residual solvent. The remaining residue was triturated and recrystallized in $CH_2Cl_2$–hexanes, and the resulting solids were filtered.

**Representative Procedure for the One-Pot Condensation–Rearrangement**

2-Amino-*N*-hydroxybenzimidamide (106 mg, 0.701 mmol), ethyl benzoate (126 mg, 0.841 mmol), and KO*t*-Bu (10 mg, 0.0891 mmol) were combined and heated in the microwave reactor for 60 min at 200 °C (with optional addition of DMF (1.5 mL) after 30 min followed by the remaining 30 min of heating at 200 °C). The reaction mixture was then brought up in 20 mL of $H_2O$ and extracted with EtOAc (3 × 25 mL). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated to afford a yellow oil. The crude product was purified by flash chromatography (30–60% EtOAc–hexanes) to give 118 mg of **5b** as a white solid (71%) which was spectroscopically equivalent to that reported in the literature.[6b]

**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett. Experimental procedures, spectral data and copies of $^1H$, $^{13}C$ NMR and HRMS for all new compounds are included.

## Acknowledgment

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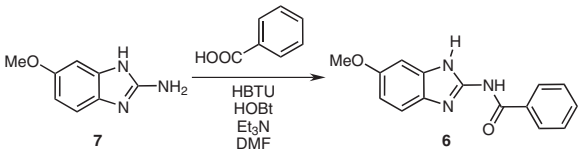
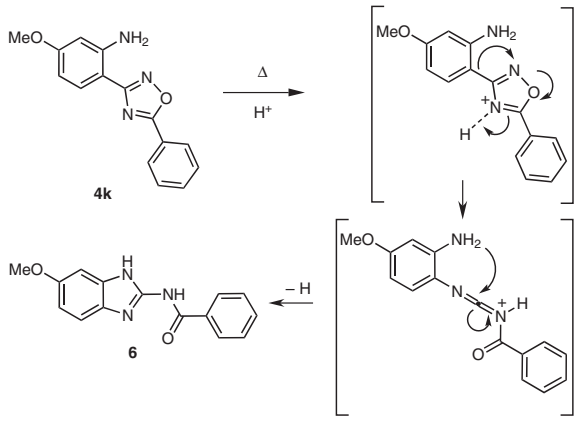
(8) The structure was confirmed by independent synthesis. Coupling 6-methoxy-1*H*-benzoimidazol-2-ylamine with benzoic acid provided **6**, spectroscopically equivalent to the material from the rearrangement (Scheme 3). For a similar procedure, see: Hasegawa, M.; Nishigaki, N.; Washio, Y.; Kano, K.; Harris, P. A.; Sato, H.; Mori, I.; West, R. I.; Shibahara, M.; Toyoda, H.; Wang, L.; Nolte, R. T.; Veal, J. M.; Cheung, M. *J. Med. Chem.* **2007**, *50*, 4453.




**Scheme 3**

(9) Buscemi, S.; Vivona, N.; Caronna, T. *J. Org. Chem.* **1996**, *61*, 8397.

(10) An alternative mechanism suggested by a reviewer involves protonation of the oxadiazole which promotes the observed rearrangement as shown below (Scheme 4).




**Scheme 4**

(11) Heating was performed in a CEM Discover® microwave for organic synthesis at 300 W for the time indicated with a ramp time of 2 min with a vertically focused IR temperature sensor.

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