# Studies on the Synthesis of 2-Alkyl-5-aryl-1,3,4-oxadiazolines from *N*-Acylhydrazones

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**Abstract:** Reaction of *N*-acylhydrazones with benzyloxyacetyl chloride in the presence of *i*-$Pr_2EtN$ affords new 1,3,4-oxadiazolines in excellent yields (72–95%), under mild reaction conditions and in short reaction times. The structures of the products were confirmed by single-crystal X-ray diffractometry. A plausible reaction mechanism is proposed.

**Key words:** *N*-acylhydrazones, oxadiazolines, benzyloxyacetyl chloride, acylation, heterocycles

Among five-membered heterocycles, 1,3,4-oxadiazolines and derivatives have been the subject of chemical and biological studies on account of their interesting pharmacological properties, including antimicrobial,[2] anti-inflammatory,[3] antiviral,[4] and antitumor activities.[5] Selected structures **1**–**3**, are outlined in Figure 1. As a consequence of the significant biological activity, the synthesis of new and easily accessible 1,3,4-oxadiazolines seems an aim of great interest.

Previous synthetic methods reported for these compounds involve cyclization of anionic *N*-acylhydrazones under acylation conditions using acetic anhydride[6] or acetyl chloride.[7] Other methods include oxidative cyclization of aldazines using $Pb(OAc)_4$.[8] On the other hand, the formation of similar structures is described for reactions involving ketenes (generated in situ) and *N*-acylhydrazones or 2,3-diaza-1,3-dienes (azines) either with moderate to good yields or as by-products.[9] The absence of reports for the synthesis of simple 2-alkyl-5-arylderivatives is noteworthy.

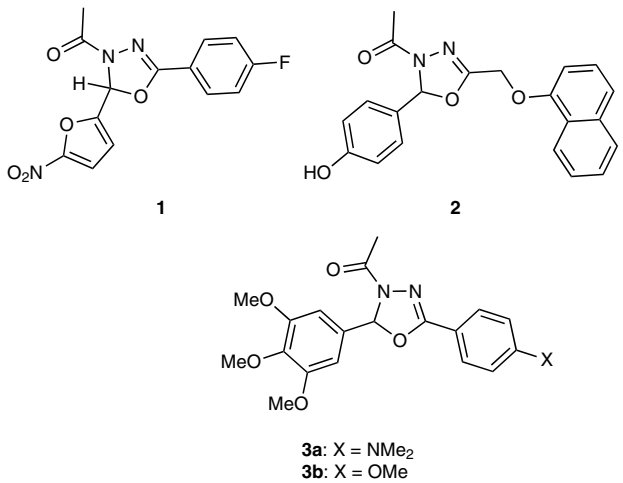
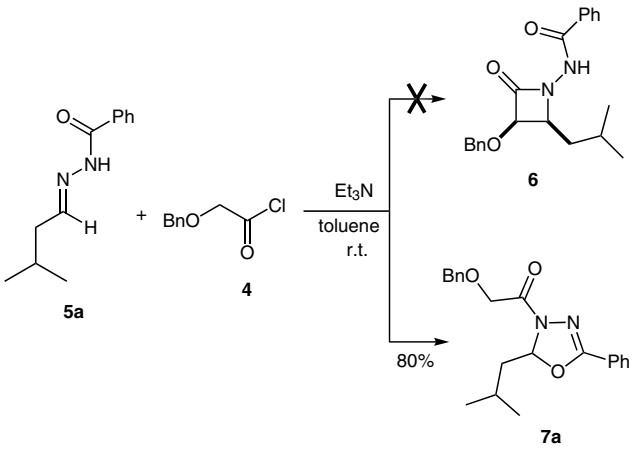



**Figure 1** Selected bioactive 1,3,4-oxadiazolines: **1** (antifungal),[2] **2** (anti-inflammatory),[3] and **3a** and **3b** (antitumor)[5a,c]

During the last few years, our research group has been interested in the asymmetric synthesis of β-lactams by a Staudinger-like reaction between aldehyde *N*,*N*-dialkylhydrazones and functionalized benzyloxyketene[10] (generated in situ from benzyloxyacetyl chloride **4** with a base) or amino ketenes.[11] Recently, we decided to explore the behavior of more reactive *N*-acylhydrazones **5** as the imine component in the [2+2] cycloaddition. Taking advantage of the high relative stability of hydrazones toward enolization, we decided to focus on aliphatic derivatives. Thus, the reaction of isovaleraldehyde benzoyl hydrazone (**5a**) as a model substrate and benzyloxyacetyl chloride (**4**) as the reagent, was chosen for preliminary experiments. However, under our previously optimized conditions (2 equiv of **4**, 4 equiv of $Et_3N$ in anhydrous toluene),[10] the reaction afforded no trace of the corresponding β-lactam **6**, instead, formation of oxadiazoline **7a** in 80% yield was observed after 24 hours at room temperature (Scheme 1).




**Scheme 1** Formation of oxadiazoline **7a**

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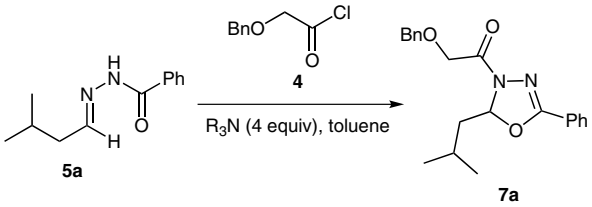
Using the same model reaction, further experiments were performed to investigate the influence of the base and/or the reaction temperature on the product distribution. To this end, reactions performed at room temperature using diisopropylethylamine and tribenzylamine were analyzed after 24 hours and compared with the triethylamine-promoted reaction. The results, collected in Table 1 (entries 1–3), indicate a slight improvement with diisopropylethylamine and a significant drop of yield in the case of the less basic tribenzylamine.[12] Finally, performing the reactions at 80 °C not only provided a slightly better yield, but also led to a significant rate acceleration, leading to virtually complete reactions in only five hours (entries 4 and 5).

**Table 1** Screening of Reaction Conditions[a]




| Entry | Base | Temp (°C) | Time (h) | Yield (%)[b] |
|---|---|---|---|---|
| 1 | $Et_3N$ | r.t. | 24 | 80 |
| 2 | *i*-$Pr_2EtN$ | r.t. | 24 | 84 |
| 3 | $Bn_3N$ | r.t. | 24 | 51 |
| 4 | *i*-$Pr_2EtN$ | 80 | 5 | 88 |
| 5 | $Bn_3N$ | 80 | 5 | 64 |

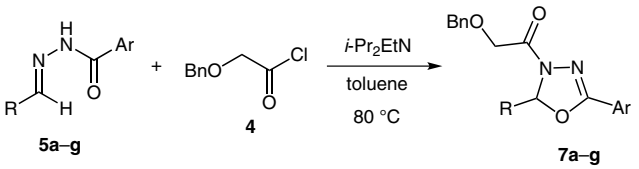
[a] Reactions performed at 0.5 mmol scale using **4** (2 equiv) and base (4 equiv).
[b] Isolated yield after column chromatography.

These optimized conditions [hydrazone (2 equiv), *i*-$Pr_2EtN$ (4 equiv), anhydrous toluene, 80 °C] were then applied to the reaction of different *N*-acylhydrazones **5a–g** with benzyloxyacetyl chloride (**4**) for the synthesis of adducts **7a–g**. The results, collected in Table 2, indicate the efficiency of the reaction for primary (entries 1, 3, 6, and 7), secondary (entries 2 and 5), and even tertiary (entry 4) aliphatic derivatives, although higher reaction temperatures and longer reaction times were required in the latter case. Examples that illustrate the compatibility with electron-withdrawing (entries 4–6) or electron-donating (entry 7) groups are included.

In addition to the usual spectroscopic characterization (see the Supporting Information), single-crystal X-ray diffraction analysis of adduct **7e** (Figure 2)[13] unequivocally confirmed the proposed structure.

Two plausible reaction paths can be *a priori* proposed for this reaction. As is the case in reactions with *N*,*N*-dialkylhydrazones, benzyloxyacetyl chloride **4** could possibly react first with the base to form the corresponding benzyloxy ketene **8** after hydrogen chloride β-elimination. Ensuing nucleophilic addition of the $sp^2$ imine nitrogen of **5** to the electron-deficient ketene central carbon and spontaneous cyclization of the resulting zwitterionic intermediate **10** would render the product **7** (Scheme 2, blue path). A second possible path starts with the acylation of the imino nitrogen of the substrate by **4** to form acyl immonium intermediate **9** from which deprotonation by the base renders the final product **7** through the same zwitterionic intermediate **10**.

**Table 2** Synthesis of Oxadiazolines **7a–g** from *N*-Acylhydrazones **5a–g**




| Entry | 5 | Ar | R | Time (h) | 7 | Yield (%)[a] |
|---|---|---|---|---|---|---|
| 1 | **5a** | Ph | *i*-Bu | 5 | **7a** | 88 |
| 2 | **5b** | Ph | *i*-Pr | 5 | **7b** | 86 |
| 3 | **5c** | Ph | $CH_2CH_2Ph$ | 5 | **7c** | 89 |
| 4[b] | **5d** | 4-$O_2NC_6H_4$ | *t*-Bu | 16 | **7d** | 72 |
| 5 | **5e** | 4-$O_2NC_6H_4$ | *i*-Pr | 5 | **7e** | 93 |
| 6 | **5f** | 4-$O_2NC_6H_4$ | *i*-Bu | 4 | **7f** | 95 |
| 7 | **5g** | 4-$MeOC_6H_4$ | *i*-Bu | 4 | **7g** | 89 |

[a] Isolated yields after column chromatography.
[b] Reaction performed at 100 °C.

Several pieces of evidence suggest that the mechanism involving ketene **8** can be disregarded. First, previous studies[11b] indicate that the rate of ketene formation decreases in the order $Et_3N$ > *i*-$Pr_2EtN$ >> $Bn_3N$, with the latter being much slower than the observed reaction rate. Such a dependence on the base is not consistent with the observed trend. Further evidence for **9** as a reaction intermediate was obtained from the reaction of **5g** with **4** in the

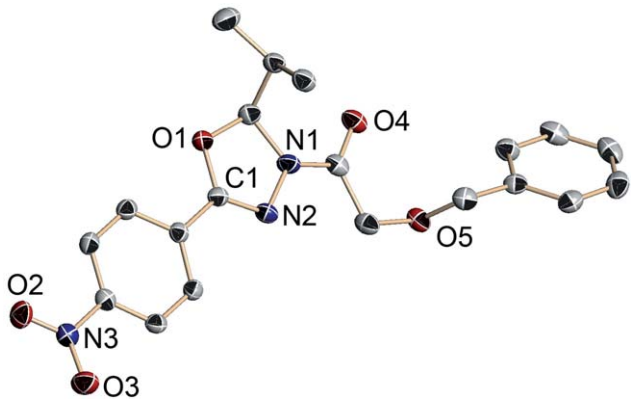
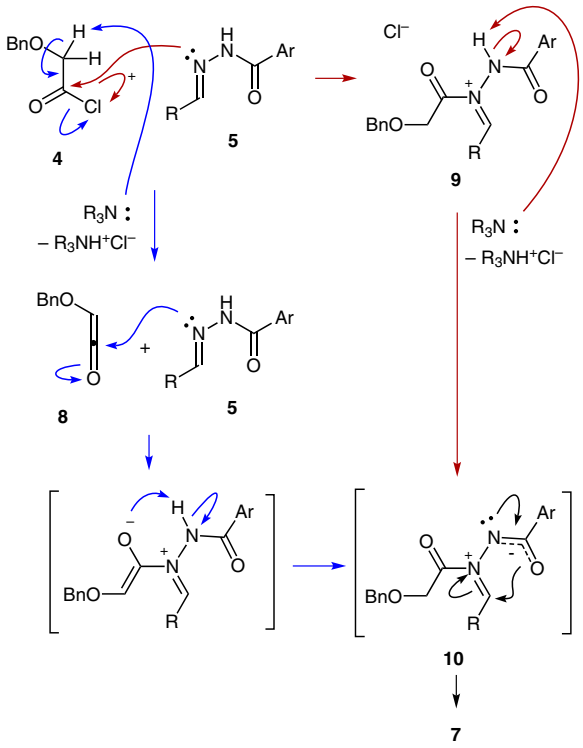



**Figure 2** X-ray crystal structure of oxadiazoline **7e**. Hydrogen atoms omitted for clarity. Thermal ellipsoids drawn at the 50% probability level.

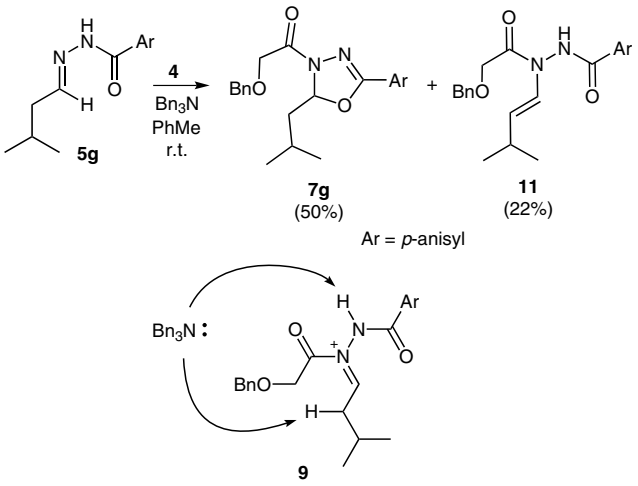




**Scheme 2** Plausible reaction mechanisms

presence of a large excess of tribenzylamine (8 equiv) as the base. Under these conditions, a moderate (50% yield) amount of product **7g** was obtained, along with a small amount (22%) of enhydrazine by-product **11** (Scheme 3), which is presumed to form by competitive deprotonation of the acidic α-methylene from the same intermediate **9**.



**Scheme 3**

In summary, use of diisopropylethylamine as the base enables a mild and efficient synthesis of 5-alkyl-1,3,4-oxadiazolines **7a–g** from *N*-acylhydrazones **5a–g** and benzyloxyacetyl chloride **4**. Experimental evidence suggests that the reaction proceeds through *N*-acyliminium intermediates resulting from direct acylation of the hydrazone N(sp$^2$) atom by acyl chloride **4**.

**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

## Acknowledgment

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(13) Crystal data for **7e** (CCDC 850772): $C_{20}H_{21}N_3O_5$; *M* = 383.40; monoclinic; *a* = 33.9831 (8) Å, *b* = 6.14820

(10) Å, $c$ = 20.2932 (5) Å, $\alpha$ = 90.00°, $\beta$ = 118.3420 (10)°, $\gamma$ = 90.00°; $V$ = 3731.71 (14) Å$^3$; $T$ = 100 (2) K; space group $C2/c$; $Z$ = 8; $\mu(\mathrm{Mo_{K\alpha}})$ = 0.100 mm$^{-1}$; 34754 reflections measured, 5690 independent reflections ($R_{int}$ = 0.0436). The final $R_1$ values were 0.0474 ($I > 2\sigma(I)$). The final $wR(F^2)$ values were 0.1106 ($I > 2\sigma(I)$). The final $R_1$ values were 0.0941 (all data). The final $wR(F^2)$ values were 0.1314 (all data); goodness-of-fit: 1.030.



 