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Photoinduced synthesis of benzo[*c*]isoxazoles from 2-azidobenzaldehydes

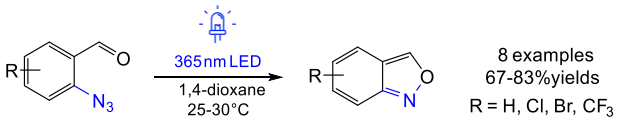
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A photochemical method for synthesis of benzo[*c*]isoxazoles (anthranils) from 2-azidobenzaldehydes is reported. A significantly faster rate of the photochemical initiation compared to the thermal initiation is demonstrated.



Keywords: photochemistry, aryl azides, benzo[*c*]isoxazole, anthranil, 2-azidobenzaldehyde.

The swift progress in organic photochemistry and photocatalysis over the last decade has greatly enriched the arsenal of synthetic methods at chemists' disposal. Modern monochromatic light sources allow for strict control of the excitation wavelength and provide fine-tuning of photochemical processes.[1,2] Photochemistry is effectively combined with flow chemistry[3,4], electrosynthesis,[5] enantioselective catalysis,[6] and biocatalysis.[7] Since light is a traceless and "green" reagent,[8] photochemistry holds great potential for widespread application in synthesis.[9] For the chemical industry, light may become a fine alternative to traditional thermal methods for molecule activation.[10]

Herein, we report the photochemical transformation of 2-azidobenzaldehydes to benzo[*c*]isoxazoles (anthranils). This reaction has been studied under thermal conditions[11] and proceeds *via* nitrogen elimination and nitrene formation.[12-15] However, to the best of our knowledge, the preparative photochemical synthesis of anthranils from 2-azidobenzaldehydes has not been reported. In this study, we demonstrate that the photochemical transformation of 2-azidobenzaldehyde to benzo[*c*]isoxazole proceeds significantly faster than the thermal reaction. The use of light can be effectively applied to the synthesis of anthranil derivatives. Anthranil and its derivatives are valuable synthetic building blocks. For example, anthranils have been effectively used to synthesize anticancer azaindoles[16] and 2-acylacridines with anti-inflammatory activity.[17]

During a systematic study of the *ortho*-substituted benzaldehydes photochemistry,[18,19] we observed the transformation of 2-azidobenzaldehyde **1a** into benzo[*c*]isoxazole **2a** upon irradiation with 365 nm light in DMSO. Solvent optimization (see Online Supplementary Materials, part 2) identified 1,4-dioxane as the best medium for this transformation. The photoreaction proceeded with similar efficiency in other polar aprotic solvents (DMF, DMAc, NMP).

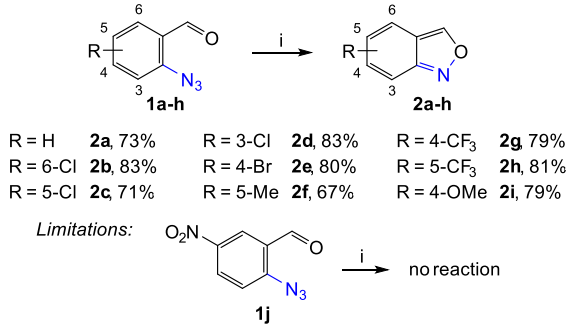
We compared the photochemical and thermal activation of 2-azidobenzaldehyde **1a** in 1,4-dioxane at different temperatures (Table 1, see Online Supplementary Materials, part 3). Irradiation at room temperature resulted in almost complete conversion of **1a** to **2a** within two hours. In contrast, without irradiation, the transformation occurred only to a small extent near the boiling point and upon reflux. Thus, irradiation with 365 nm light in dioxane at room temperature proved to be more efficient and was chosen as the optimal conditions for preparative synthesis.

Table 1 Conditions screening for **1a** to **2a** conversion in 1,4-dioxane (Online Supplementary Materials, part 3).

Entry	Conditions	**2a**, %	Remained **1a**, %
1	365 nm LED irradiation, r. t.[a]	78	3
2	r. t.[a]	0	90
3	40°C	0	90
4	60°C	0	90
5	80°C	2	88
6	101.5°C[b]	6	83

[a] Room temperature. [b] Reflux.

The phototransformation was extended to nine examples (Scheme 1). Products **2a–i** were obtained in good yields (67–83%). The higher yields for anthranils **2b** and **2d** may be attributed to the halogen orienting effect to the formyl group[20] or the «buttressing» effect of the substituent.[21] At the same time, the method is limited by the nitro group-containing substrate **1j**. The lack of phototransformation for **1j** may be a consequence of a significant change in the excited state induced by the strong electron-withdrawing substituents.[22]



Scheme 1 *Reagents and conditions* i, 1,4-dioxane, 365 nm LED, 25-30°C.

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In summary, a photochemical method for the synthesis of benzo[*c*]isoxazoles (anthranils) from 2-azidobenzaldehydes is proposed. Irradiation with a 365 nm LED was found to be significantly more efficient than the thermal reaction. This approach can be applied to the preparation of benzo[*c*]isoxazoles, which are valuable synthetic building blocks[23,24] and precursors of biologically active compounds.[16,17,25]

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.8128.

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