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A CONVENIENT SYNTHESIS OF *N*-(α-AMINOBENZYL)FORMAMIDES

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Abstract: Three-component condensation of benzaldehyde, formamide, and morpholine or piperidine, results in an expeditious synthesis of the *N*-(α-dialkylaminobenzyl)-formamides.

The synthetic usefulness of isocyanides has led to the development of a number of routes to their precursors, the *N*-substituted formamides. A recent paper[1] describing the preparation of *N*-(α-morpholinobenzyl)formamide (**1a**) from the corresponding *N*-[α-(1-benzotriazolyl)benzyl]formamide (**2**) appears to present a particularly versatile synthesis of formamides of this class. Here, we disclose a simpler and more direct approach which is applicable to some, but not all, cases.

We find that mixing benzaldehyde, morpholine and formamide in a 1:1:1 molar ratio, in ethanol, leads to the separation of a crystalline product (**1a**) in good yield. The ethanol may be omitted, but then the product should be recrystallised: when the solvent is used in the synthesis the product is sufficiently pure to pass on to the dehydration stage (if the objective is the isocyanide).

A crystalline product is also formed using piperidine in place of morpholine, but pyrrolidine failed to yield any isolable product. The reaction also failed using anisaldehyde and *p*-chlorobenzaldehyde. When furfuraldehyde is used a crystalline compound could be isolated when the reaction was carried out at 0 °C, but it proved to be 2-(dimorpholinomethyl)furan (**3**), a compound which, to our surprise, seems not to have been reported in the literature until now.

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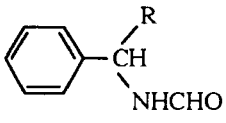
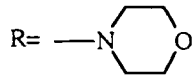
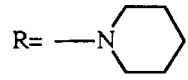
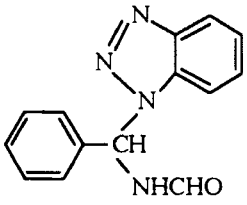
Although the reaction appears to lack general applicability, we feel that the method is worth trying in terms of simplicity, and in particular by those who may be allergic to benzotriazoles.



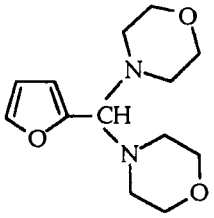
(1)

(a) R= 

(b) R= 



(2)



(3)

In a typical experiment, the aldehyde and formamide were mixed in 1:1 molar ratio, and ethanol was added to increase the volume by *ca* 50%. The amine (1 mole) was added, and crystals began to appear within 30 min. After being allowed to stand for two hours the mixture was cooled to *ca* 5 °C and kept overnight. Filtration yielded the product.

When the reaction was repeated using furfural and morpholine, taken in dry ether at 0 °C, a small amount of a yellowish product was produced. By omitting the formamide a purer, white but otherwise identical, product, 2-(di-morpholinomethyl)furan (**3**), was obtained.

N-(α-morpholinobenzyl)formamide (**1a**), m.p. 141-142 °C (lit.[1] 141-142 °C); yield 80%.

I.R.: strong absorption bands at ν 3310 (NH), and at 1660cm^{-1} (C=O)

^{1}H NMR ($CDCl_3$, 90MHz): δ- 8.56 (1H), 8.30 (1H), 7.41-7.30 (5H), 5.37 (1H), 3.37 (4H), 2.28 (4H)

Analysis: $C_{12}H_{16}N_2O_2$ Calc. C 65.43, H 7.32, N 12.72
Found C 65.31, H 7.24, N 12.62

N-(α-piperidinobenzyl)formamide (**1b**), m.p. 111-112 °C; yield 67%.
I.R. ν 3300 and 1650 cm^{-1}
^1H NMR ($CDCl_3$, 90MHz), δ- 8.43 (1H), 8.26 (1H), 7.41-7.27 (5H), 5.20 (1H), 2.50 (4H), 1.54 (6H)
Mass: m/z at 218 (M^+), 173, 133, 104 (100%), 84, 77
Analysis: $C_{13}H_{18}N_2O$ Calc. C 71.55, H 8.25, N 12.84
Found C 71.45, H 8.12, N 12.74

2-(dimorpholinomethyl)furan (**3**), m.p. 122-123 °C (from pet. ether-dichloromethane), yield 50%.
I.R.: ν 1600, 1520, and 1500 cm^{-1}.
^1H NMR ($CDCl_3$, 90MHz), δ 7.20 (d, 1H), 6.5-6.2 (m, 2H), 4.0-3.6 (m, 8H), 2.8-2.4 (br m, 8H). The aminal proton signal was not seen, and probably was buried among the morpholine proton signals, which were broadened presumably due to slow conformational exchange.
Mass: m/z at 252 (M^+), 165, 140, 81 (100%), 57, 29
Analysis: Calc. C 61.90, H 7.93, N 11.11
Found C 62.03, H 8.10, N 11.00

Reference

1. Katritzky A. R., Xie L. -H., Fan W. -Q.; *Synthesis*, **1993**, 45

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