Mono Alkylation of α-Isocyano Acetamide to its Higher Homologues

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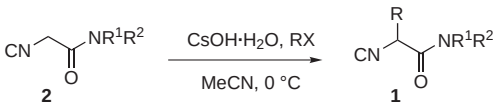
Abstract: Alkylation of α-isocyano acetamide (**2**) with alkyl halide in MeCN at 0 °C in the presence of cesium hydroxide afforded the mono-alkylated product **1** in good to excellent yield.

Key words: cesium hydroxide, isonitrile, isocyano acetamide, monoalkylation

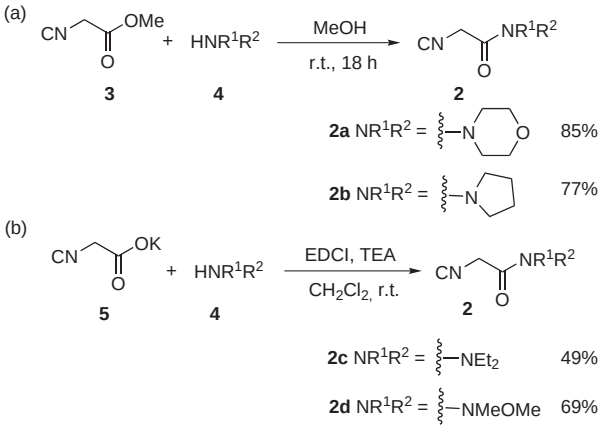
Functionalized isonitriles have found wide application in the syntheses of heterocycles.[1–3] Although less popular than α-isocyano acetate[4] and tosylmethyl isocyanide (TosMIC),[5] α-substituted α-isocyano acetamides (**1**)[6] have recently been developed into a powerful bifunctional substrate for the multicomponent syntheses of heterocycles[7,8] and macrocycles.[9] Indeed, the reactivity profile of α-isocyano acetamide (**1**) was found to be rather different from that of α-isocyano acetate under mild basic or acidic conditions. Compound **1** has previously been synthesized from the corresponding amino acid in three conventional steps via a sequence of N-formylation, amidation of carboxylic acid and dehydration.[10] Although the sequence is high-yielding for the synthesis of each individual compound, its limitation in the high-throughput synthesis of a diverse collection of this class of isonitriles is self-evident. Consequently, we were interested in developing a more efficient synthesis of **1** in order to fully exploit its synthetic potential.

Benzylation of α-isocyano acetamide (**2**) providing the corresponding α,α-bisalkylated derivative has been developed by Matsumoto in 1977.[11] To the best of our knowledge, this is the only report found in the open literature dealing with the alkylation of **2** and indeed conditions allowing the monoalkylation of (**2**) remained unknown. Similarly, alkylation of methyl α-isocyano acetate (**3**) afforded the corresponding bisalkylated product even with a substoichiometric amount of alkylating agent.[12,13] We report herein that monoalkylation of (**2**) can be realized under appropriate conditions to afford α-substituted α-isocyano acetamides (**1**) in good to excellent yield (Scheme 1).



Scheme 1 Monoalkylation of α-isocyano acetamide to its higher homologue

α-Isocyano acetamides (**2**) were synthesized as shown in Scheme 2. Stirring a methanol solution of α-isocyano acetate (**3**) with morpholine and pyrrolidine afforded the corresponding amides **2a** and **2b** in yields of 85% and 77%, respectively (Scheme 2, a). On the other hand,



Scheme 2 Synthesis of isocyano acetamides

EDCI mediated coupling of the potassium salt of α-isocyano acetic acid[14] with diethylamine provided the amide **2c** in 49% yield. The Weinreb amide **2d** was similarly prepared in 69% yield (Scheme 2, b).[15]

The benzylation of morpholino α-isocyano acetamide **2a** with benzyl bromide (**6a**) was examined as a model reaction by varying the bases, the reaction temperatures, and the solvents (Table 1). As is seen, no reaction occurred when NaOH, DBU and Cs_2CO_3 were used as bases regardless of the nature of solvents used (THF, CH_2Cl_2, biphasic solution, entries 1–4). In accord with Mastumoto's observation, performing the alkylation in THF in the presence of sodium hydride afforded **1a** in only 10% yield (entry 5). The dibenzylated compound was produced in 30% yield under these conditions. Gratifyingly, cesium hydroxide was found to be able to promote the desired monoalkylation in a variety of solvents including dichloromethane, THF, diethyl ether, toluene and acetonitrile. The optimal conditions for the alkylation of **2a** consisted of performing the reaction in acetonitrile at 0 °C with 1.05 equivalents of BnBr and 1.5 equivalents of $CsOH·H_2O$. Under these conditions, compound **1a** was isolated in 94% yield without the concurrent formation of dibenzylated compound. It has nevertheless to be emphasized that

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dibenzylated compound was produced as a major product if an excess of base and benzyl bromide (2.5 equiv each) were used under otherwise identical conditions.[16]

The generality of this protocol was next examined using 4 isocyano acetamides **2a**–**d** and 12 electrophiles (Figure 1). Compounds synthesized by the standard procedure (1.5 equiv of $CsOH·H_2O$, 1.05 equiv of alkylating agent, MeCN, 0 °C) were listed in Figure 2. As it is seen, the reaction turned out to be quite general. The monoalkylation took place smoothly not only with the activated halides such as benzyl bromide, allyl bromide, propargyl bromide and methyl iodide, but also with less reactive alkyl halides such as ethyl iodide (**6k**) and 1-bromobutane (**6l**). Alkylation of 4-nitrobenzylbromide (**6d**) is known to be low-yielding due to the competitive dimerization and degradation process via a radical anion mechanism,[17] it is thus interesting to note that alkylation of **2a** with **6d** proceeded smoothly to provide **1h** in 61% yield. The amide structures exerted only minor effect on the alkylation process and amide derived from cyclic amine (morpholine, pyrrolidine), acyclic amine (diethylamine) as well as the Weinreb amide can be effectively converted to the monoalkylated product.

Table 1 Survey of Conditions for Alkylation of Morpholino α-Isocyano Acetamide (**2a**) with Benzyl Bromide (**6a**)[a]

Entry	Base	Solvent	Temp (°C)	Yield of **1a** (%)[b]
1	NaOH	CH_2Cl_2–H_2O	0	0
2	DBU	CH_2Cl_2	–30	0
3	DBU	CH_2Cl_2	r.t.	0
4	Cs_2CO_3	THF	r.t.	0
5	NaH	THF	r.t.	10[c]
6	$CsOH·H_2O$	CH_2Cl_2	–25	21
7	$CsOH·H_2O$	CH_2Cl_2	0	71
8	$CsOH·H_2O$	CH_2Cl_2	r.t.	76
9	$CsOH·H_2O$	THF	r.t.	14
10	$CsOH·H_2O$	Et_2O	0	76
11	$CsOH·H_2O$	Et_2O	r.t.	56
12	$CsOH·H_2O$	MeCN	r.t.	58
13	$CsOH·H_2O$	MeCN	0	94
14	$CsOH·H_2O$	Toluene	r.t.	73

[a] General conditions: 1.5 equiv of base, 1.05 equiv of benzyl bromide, concentration 0.2 M.
[b] Yield referred to pure isolated product.
[c] Dialkylated product was isolated in 30% yield.

In summary, conditions for the efficient monoalkylation of α-isocyano acetamide to its higher homologues have been developed. This synthesis has clear advantages over

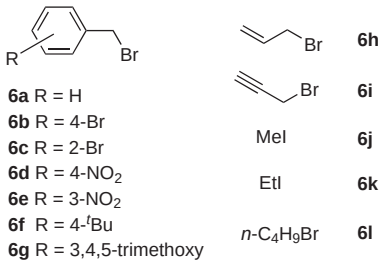

Figure 1 Structure of alkyl halides

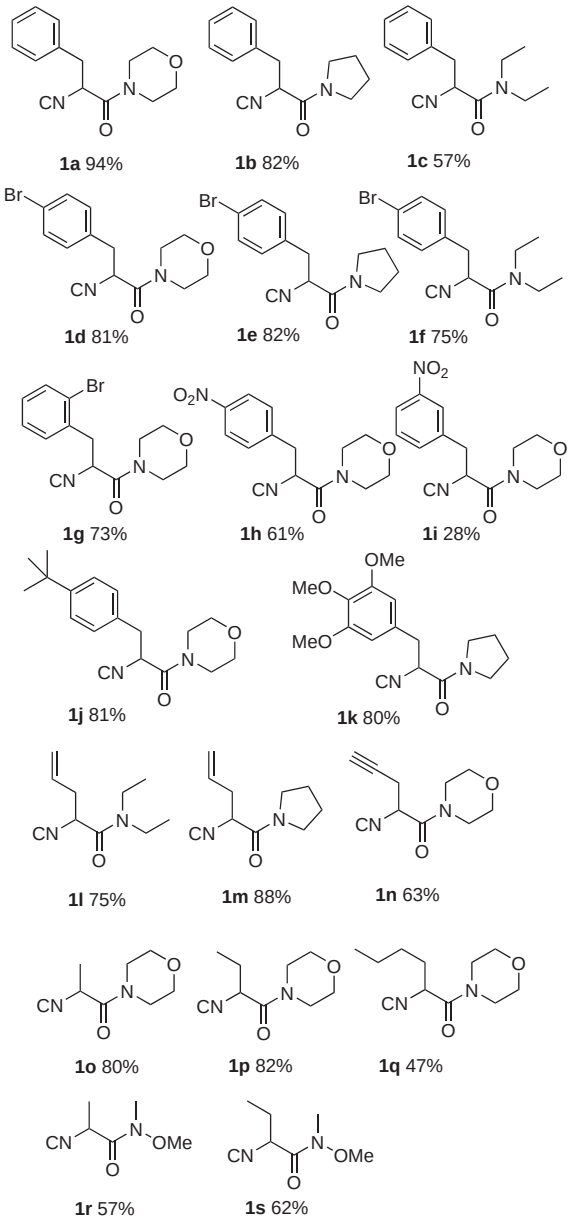

Figure 2 α-Substituted α-isocyano acetamide

the previously reported three-step synthesis especially if the starting amino acid is not commercially available. The present protocol should thus facilitate the further exploitation of this unique class of isonitrile and enhance its application scope in heterocycle synthesis.

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(15) **Synthesis of Compound 2a.**
To a solution of methyl α-isocyanoacetate (4.4 mmol) in dry MeOH (3.0 mL) was added morpholine (10.3 mmol, 2.3 equiv) and the reaction mixture was stirred at r.t. for 18 h. The volatile was removed under reduced pressure and the crude material was purified by flash chromatography (SiO_2, EtOAc–heptane = 2:1) to afford **2a** in 85% yield, mp 77–78 °C. IR ($CHCl_3$): 2163, 1658, 1462, 1422, 1274, 1236, 1111, 992 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.31 (s, 2 H), 3.63 (m, 4 H), 3.54 (m, 2 H), 3.30 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.3, 160.7, 66.5, 66.1, 45.6, 44.3, 42.6. MS (ES, positive mode): *m*/*z* = 177.1 $[M + Na]^+$.
Synthesis of Compound 2d.
To a suspension of potassium salt of α-isocyano acetic acid (4.4 mmol) in dry CH_2Cl_2 (22 mL) were added Et_3N (5.7 mmol), EDCI (5.3 mmol) and hydrochloride salt of MeNH(OMe) (4.8 mmol). After being stirred at r.t. for 20 h, the reaction mixture was quenched with H_2O (2 mL) and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried and evaporated under reduced pressure. The crude material was purified by flash chromatography (Al_2O_3, EtOAc–heptane = 2:1) to afford **2d** as a brown solid (69%), mp 72–73 °C. IR ($CHCl_3$): 2162, 1681, 1410, 1317, 1179, 963 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.39 (s, 2 H), 3.69 (s, 3 H), 3.19 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.9, 160.7 (141.9), (62.3) 61.7, (52.3) 43.8, (40.7) 32.7. MS (ES, positive mode): *m*/*z* = 151.1 $[M + Na]^+$.

(16) **Monoalkylation of α-Isocyanoacetamide – A General Procedure.**
To a dry test tube containing $CsOH·H_2O$ (0.34 mmol, 1.7 equiv) were added, under argon atmosphere, a solution of isocyano acetamide (0.20 mmol) in MeCN (1.0 mL) and alkylating agent (0.21 mmol) at 0 °C. The resulting reaction mixture was stirred at 0 °C. When the reaction was deemed complete by TLC analysis (typically 24 h), the volatile was removed under reduced pressure. Purification of the crude product by either preparative TLC (silica gel) or flash chromatography (silica gel) afforded the desired product. Compound **1a**: yield 94%. IR ($CHCl_3$): 2928, 2863, 2142, 1668, 1496, 1456, 1116 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.26–7.36 (m, 5 H), 4.54 (dd, *J* = 7.7, 7.0 Hz, 1 H), 3.20–3.69 (m, 10 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 163.5, 159.8, 135.0, 129.4 (2 C), 128.8 (2 C), 127.7, 66.4, 65.9, 55.0, 46.2, 42.9, 39.1. MS (EI): *m*/*z* = 244 $[M]^+$. Anal. Calcd for $C_{14}H_{16}N_2O_2$ (%): C, 68.83; H, 6.60; N, 11.47. Found: C, 68.71; H, 6.60; N, 11.47.

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