Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Facile and Versatile Room-Temperature Synthesis of N,N-Disubstituted Cyanoacetamides from Malonic Ester Chloride

Andrzej Manikowski [a] & Zofia Kolarska [a]
[a] PLIVA Kraków Pharmaceutical Company, Kraków, Poland

Available online: 08 Sep 2009

To cite this article: Andrzej Manikowski & Zofia Kolarska (2009): Facile and Versatile Room-Temperature Synthesis of N,N-Disubstituted Cyanoacetamides from Malonic Ester Chloride, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 39:20, 3621-3638

To link to this article: http://dx.doi.org/10.1080/00397910902788216

Synthetic Communications®, 39: 3621–3638, 2009

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910902788216

Taylor & Francis
Taylor & Francis Group

Facile and Versatile Room-Temperature Synthesis of N,N-Disubstituted Cyanoacetamides from Malonic Ester Chloride

Andrzej Manikowski and Zofia Kolarska
PLIVA Kraków Pharmaceutical Company, Kraków, Poland

Abstract: A general method for the synthesis of various N,N-disubstituted cyanoacetamides from readily available methyl malonyl chloride and secondary amines, including sterically demanding aliphatic and aromatic amines, is described.

Keywords: Cyanoacetamides, dehydration, malonamides, nitriles

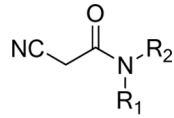
INTRODUCTION

N,N-Disubstituted cyanoacetamides (Scheme 1) have been recognized as valuable compounds and are widely used in many synthetic operations. Thanks to different features of chemical groups in their molecular backbone, cyanoacetamides can serve as building blocks for preparation of derivatives that are of interest in pharmaceutical,[1] agricultural,[2] polymer,[3] and chemical[4] industries.

Several methods have been previously reported in the literature for the preparation of N,N-disubstituted cyanoacetamides. According to the described procedures, aliphatic analogs are much easier to prepare, whereas syntheses of aromatic cyanoacetamides seem to be more problematic.

The most common methods for preparation of cyanoacetamides **4** are reactions of cyanoacetate esters with the appropriate secondary

Received September 9, 2008.
Address correspondence to Andrzej Manikowski, Research and Development, Mogilska Str. 80, Kraków 31-546, Poland. E-mail: andrzej.manikowski@yahoo.com



Scheme 1. R_1, R_2 = alkyl, alkenyl, aryl, etc.

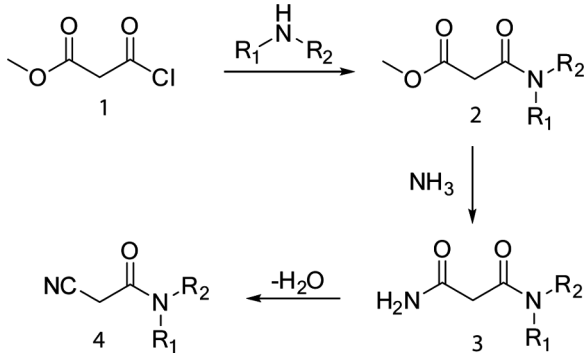
amines.[3,5,6] Yields of such reactions depend on the chemical and sterical characters of amines. The reaction usually proceeds within a few hours under elevated temperature, most often, however, under reflux conditions. For low-boiling amines, like N,N-diethylamine, a steel pressure bomb was applied to complete the reaction.[7] In the case of aromatic amines, such as N-methyl-N-phenylamine, N,N-diphenylamine, and 2-methylindoline, reactions were carried out for several hours at 180°C under nitrogen.[8] On the other hand, cyanoacetic acid ethyl ester has also been used in amidation reactions performed in a much lower temperatures.[9] The reactions of cyanoacetate ester with various secondary lithium amides at −70°C gave cyanoacetamides with good to high yield. Nevertheless, this procedure worked smoothly and rapidly for aliphatic amines but failed in the case of aromatic ones.

Another method of N,N-disubstituted cyanoacetamide synthesis is based on chloroacetic derivatives i.e., chloroacetic chloride and chloroacetic esters). Reactions of these compounds with secondary amines provide chloroacetamides,[10] which after treatment with alkali cyanide gave cyanoacetamides with satisfactory yields.[11] However, in this case a special precaution has to be taken because of the high toxicity of cyanides.

In another approach,[12] cyanoacetic chloride, prepared in the reaction of cyanoacetic acid and phosphorus pentachloride,[13] was used for synthesis of various cyanoacetamides. A few alternative methods for preparation of N,N-disubstituted cyanoacetamides has been developed, in which cyanoacetylenes,[14] phenol derivative,[15] or Meldrum's acid derivative[16] were used.

The main drawbacks of these approaches in the preparation of cyanoacetamides are the requirement of either a high or low temperature, unpredictable yields depending on the chemical character of secondary amines, usage of inert gas atmosphere, and often introduction of highly toxic reagents. Moreover, there is little information in the literature regarding preparation of N,N-disubstituted cyanoacetamides using cyanoacetic acid and a peptide coupling reagent. Although the process has been working for N-monosubstituted cyanoacetamides,[17] there is a lack of description for N,N-disubstituted analog syntheses.

We report herein a facile and high-yielding three-step synthesis of various N,N-disubstituted cyanoacetamides (Scheme 2). Our approach



Scheme 2. General procedure for N,N-disubstituted cyanoacetamides synthesis.

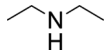
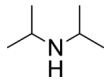
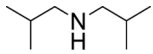
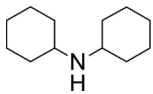
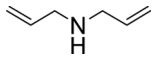
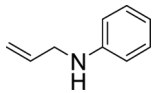
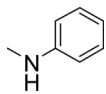
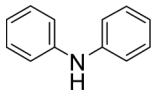
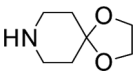
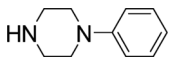
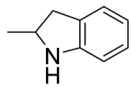
to cyanoacetamide derivative preparation is complementary to both high- and low-temperature methods, because it is carried out at room temperature. This approach can be an alternative for preparation of aliphatic cyanoacetamides **4**, and it has proved to be an excellent method for preparation of aromatic N,N-disubstituted cyanoacetamides.

We first checked our methodology using various aliphatic N,N-disubstituted amines **1** and compared physical data of synthesized cyanoacetamides **4** with those from the literature. Having obtained good results, we next applied aromatic N,N-disubstituted amines. In both cases, yields of N,N-substituted cyanoacetamides **4** were very good (65–90%) (Table 1).

RESULTS AND DISCUSSION

We started the synthesis from methyl malonyl chloride **1**, which can be readily obtained from dimethylmalonate[18] or from commercial sources. Compound **1** reacts smoothly and rapidly with secondary amines, both aliphatic and/or aromatic, giving methyl N,N-disubstituted malonates **2** [methyl 3-(N,N-dialkylamino)-3-oxopropanoate] with good yields (89–99%). Experimentally, the acylation reactions were performed in dry dichloromethane using twofold excess of amine and were usually completed within 0.5–1 h. The reactions are often exothermic and should be cooled down. Further treatment of reaction mixture with 2% aqueous HCl solution easily removed excess of amine from the organic layer, leaving appropriate malonamides **2** pure enough to be used directly in the next step. However, aromatic amines (Table 1, entries f, h, and m) were extracted together with products and were later purified by flash column

Table 1. Reaction time and yields of compounds **2**, **3**, and **4**

Entry	Secondary amine (NHR_1R_2)	Yield (%)/reaction time (h)			Overall yield (%)	Lit. yield for **4** (%)
		2	**3**	**4**[a]		
a		99/0.5	100/2[c]	91/3[d]	90	90[9]
b		98/0.5	73[a]/72[c]	93/4[d]	67	94[9]
c		99/0.5	99/5[b]	87/2.5[d]	85	—
d		98/1	75[a]/72[c]	89/4[d]	65	—
e		99/1	100/2.5[b]	91/4[d]	90	23[3d]
f		89[a]/1	100/17[c]	89/0.5[e]	79	—
g		99/1	100/2.5[b]	83/0.5[e]	82	18[3d]
h		94/1	92/60[c]	81/5[d]	70	57[11b]
i		90/1	99/1.5[b]	91/1.5[d]	81	67[5a]
j		92[a]/1	99/1[b]	91/4[d]	83	55[5b]
k		99/1	100/19[c]	89/5[d]	88	—
l		99/1	93/7[b]	90/5.5[d]	83	—
m		91[a]/1	84[a]/24[c]	94/0.5[e]	72	n/a[8]

[a]Isolated product.
[b]NH_4OH.
[c]NH_4OH/MeOH.
[d]With TsCl.
[e]With $POCl_3$.

chromatography. All of synthesized methyl N,N-disubstituted malonates **2** were in the form of oil, except for compound **2h**, which was obtained as crystals. Mixed ester-amide derivatives of type **2** are particularly valuable organic intermediates because of their use in the synthesis of numerous biologically active compounds.[18,19]

With access to many different malonamides **2**, we examined the conditions of syntheses of bisamide derivatives **3** [3-(N,N-dialkylamino)-3-oxopropanamide] to compare the reaction times and yields. Ragan et al.[20] reported 86% yield for the amidation reaction of methyl malonamide **2** (R_1=H, R_2=H) with 2 M solution of dimethylamine in methanol for 3 days room temperature. Based on their results, we treated several compounds **2** with 2 M solution of ammonia in methanol at room temperature. Surprisingly, in all cases, the amidation reaction proceeded very slowly, and after 7 days only partial conversion was observed. Next, we turned our attention to concentrated aqueous ammonia solution. In fact, commercially available cyanoacetamide **4** (R_1=H, R_2=H) is simply prepared from cyanoacetic esters after treatment with ammonia solution.[21] Using this approach, most of methyl N,N-disubstituted malonates **2** were easily converted to an appropriate bisamide **3** with high yield at room temperature in less than 7 h. In the few cases when we used a mixture of concentrated aqueous ammonia solution and methanol, ester-to-amide exchange reactions took much longer, from 17 to 72 h.

The preparation of nitriles from their corresponding amides is a well-known process in organic synthesis.[22,23] The dehydration reaction affects only unsubstituted amides, leaving disubstituted ones intact. Monosubstituted amides can be converted to nitriles by treatment with PCl_5 (von Braun reaction). We decided to perform dehydration reactions of bisamides **3** using either $POCl_3$ or tosyl chloride in pyridine at room temperature. To our delight, the reactions worked efficiently for all cases tested, resulting in N,N-disubstituted cyanoacetamides **4** [3-(N,N-dialkylamino)-3-oxopropanenitrile] with good yields (81–95%). In our studies, we observed that when using $POCl_3$ reagent, the dehydration reactions were completed faster (0.5 h) but with slightly lower yields in comparison to reactions with longer reaction time (1.5–5.5 h) and usually higher yields for tosyl chloride. Crude cyanoacetamides **4a–c** and **4e–f** were obtained as yellow to orange oil and **4d** and **4g–m** as off-white to pale orange crystals. The purifications of compounds **4** were achieved by standard procedures (e.g., flash column chromatography, vacuum distillation, or crystallization). All new cyanoacetamides **4c–d**, **f**, **k–l**, and additional **4m** were fully characterized with infrared (IR), ^{1}H NMR, ^{3}C NMR, elemental analyses, or high-resolution mass spectra (HRMS).

CONCLUSIONS

We report a useful, versatile, three-step original synthetic route to various N,N-disubstituted cyanoacetamides. The main advantages of this method are easy implementation, commercially accessible reagents, and very good yield of final cyanoacetamides. The new process is efficient and safe. It avoids the need for either elevated or low temperature as well as an inert gas atmosphere. Considering the literature methods, our approach gives better results, especially in the case of aromatic N,N-disubstituted amines, based on yield, reaction time, and the amount of solvent used. The scope of the procedure is wide and can be applied for all sorts of secondary amines, including sterically demanding ones.

EXPERIMENTAL

Methyl malonyl chloride, methanolic ammonia solution, and secondary amines were purchased from Aldrich Chemical Company. Amines, except dicyclohexyl (DCHA) and diisopropyl (DIPA), as well as methyl malonyl chloride were used as received. DCHA and DIPA were freshly distilled. Reaction solvents such as dichloromethane, methanol, and concentrated aqueous ammonia solution were obtained from POCH Gliwice (Poland) and were used as received. Melting points were determined on a Büchi B-540 melting-point instrument and are uncorrected. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Varian Mercury VX spectrometer in $CDCl_3$ as a solvent. Chemical shifts are given in parts per million (ppm). Splitting patterns are designed as s, singlet; d, doublet; dd, doublet's doublet; t, triplet; q, quartet; m, multiplet; and br, broad. IR was recorded on a Fourier transform (FT)–IR Nicolet 5700 (Thermo Electron Corporation) instrument in the attenuated total reflection mode (ATR) using a Smart Performer adapter. Elemental analyses were performed on Perkin-Elmer 2400 analyzer. HRMS were obtained on a QSTAR XL Applied Biosystems (hybrid quadrupole-TOF LC/MS/MS) instrument with turbospray electrospray ionization (ESI) source in the positive ionization mode. Flash-column chromatography (FCC) was performed on Merck Kieselgel 60 (70–230 mesh ASTM), and thin-layer chromatography (TLC) was done on Merck 60 F254 silica-gel plates and visualized with UV light (254 nm) and/or iodine.

General Procedure for Preparation of Methyl 3-(N,N-Dialkylamino)-3-oxopropanoates 2

An appropriate secondary amine (2–2.1 eq) was added dropwise as a solution in dry dichloromethane (10 mL) to a precooled solution of methyl

malonyl chloride (1.0 g, 7.32 mmol, 1 eq) in dry dichloromethane (10 mL). Internal temperature was kept in the range of 10–15°C using an ice-water bath. After addition, the reaction was continued at room temperature for 0.5–1 h and was quenched with 2% aqueous HCl solution (15 mL). After being stirred for 5 min, dichloromethane was separated, and the aqueous layer was extracted with additional portions of dichloromethane (2 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The product was usually used in the next step without further purification, but if needed, product was purified on FCC using a gradient of methanol in dichloromethane (0–2%) as eluent.

Methyl 3-(N,N-Diethylamino)-3-oxopropanoate (**2a**)

Product as pale yellow oil was used directly in the next step. Yield 99%. ^{1}H NMR: 1.09 (t, 3H), 1.15 (t, 3H), 3.26 (q, 2H), 3.35 (q, 2H), 3.39 (s, 2H), 3.70 (s, 3H).

Methyl 3-(N,N-Diisopropylamino)-3-oxopropanoate (**2b**)

Product as pale yellow oil was used directly in the next step. Yield 98%. ^{1}H NMR: 1.18 (d, 6H), 1.37 (d, 6H), 3.42 (s, 2H), 3.43–3.48 (m, 1H), 3.73 (s, 3H), 3.74–3.79 (m, 1H).

Methyl 3-(N,N-Diisobutylamino)-3-oxopropanoate (**2c**)

Product as pale yellow oil was used directly in the next step. Yield 99%. ^{1}H NMR: 0.87 (d, 6H), 0.90 (m, 6H), 1.91 (m, 1H), 2.03 (m, 1H), 3.05 (d, 2H), 3.19 (d, 2H), 3.46 (s, 2H), 3.73 (s, 3H).

Methyl 3-(N,N-Dicyclohexylamino)-3-oxopropanoate (**2d**)

Hydrochloric salt of N,N-dicyclohexylamine was filtered off before extraction.

Product as pale yellow oil was used directly in the next step. Yield 98%. ^{1}H NMR: 1.05–1.34 (m, 6H), 1.44–1.84 (m, 12H), 2.41 (br s, 2H), 2.94 (br s, 1H), 3.28 (m, 1H), 3.42 (s, 2H), 3.73 (s, 3H).

Methyl 3-(N,N-Diallylamino)-3-oxopropanoate (**2e**)

Product as pale yellow oil was used directly in the next step. Yield 99%. ^{1}H NMR: 3.44 (s, 2H), 3.73 (s, 3H), 3.86 (m, 2H), 3.99 (d, 2H), 5.14–5.25 (m, 4H), 5.68–5.82 (m, 2H).

Methyl 3-(N-Allyl-N-Phenylamino)-3-oxopropanoate (**2f**)

Purification by FCC afforded pale yellow oil. Yield 89%. ^{1}H NMR: 3.19 (s, 2H), 3.65 (s, 3H), 4.30 (m, 2H), 5.06–5.13 (m, 2H), 5.79–5.92 (m, 1H), 7.15–7.19 (m, 2H), 7.32–7.43 (m, 3H).

Methyl 3-(N-Methyl-N-phenylamino)-3-oxopropanoate (**2g**)

Product as yellow oil was used directly in the next step. Yield 99%. ^{1}H NMR: 3.20 (s, 2H), 3.29 (s, 3H), 3.65 (s, 3H), 7.19–7.23 (m, 2H), 7.32–7.44 (m, 3H).

Methyl 3-(N,N-Diphenylamino)-3-oxopropanoate (**2h**)

Product as solidified yellowish oil was used directly in the next step. Yield 94%. Crystallization from toluene afforded white crystals; mp 81–83°C. ^{1}H NMR: 3.41 (s, 2H), 3.69 (s, 3H), 7.21–7.32 (m, 10H).

Methyl 3-(Pyrrolidin-1-yl)-3-oxopropanoate (**2i**)

Product as pale yellow oil was used directly in the next step. Yield 90%. ^{1}H NMR: 1.85 (quintet, 2H), 1.94 (quintet, 2H), 3.38 (s, 2H), 3.39–3.49 (m, 4H), 3.71 (s, 3H).

Methyl 3-(Morpholin-4-yl)-3-oxopropanoate (**2j**)

Purification by FCC afforded pale yellow oil of product. Yield 92%. ^{1}H NMR: 3.41–3.45 (m, 4H), 3.62–3.68 (m, 6H), 3.73 (s, 3H).

Methyl 3-(1,4-Dioxa-8-azaspiro[4,5]decan-8-yl)-3-oxopropanoate (**2k**)

Product as pale yellow oil was used directly in the next step. Yield 99%. ^{1}H NMR: 1.67–1.73 (m, 4H), 3.48–3.52 (m, 4H), 3.69–3.73 (m, 5H), 3.96 (s, 4H).

Methyl 3-(4-Phenylpiperazin-1-yl)-3-oxopropanoate (**2l**)

Product as pale yellow oil was used directly in the next step. Yield 99%. ^{1}H NMR: 3.16–3.22 (m, 4H), 3.52 (s, 2H), 3.63 (m, 2H), 3.76 (s, 3H), 3.82 (m, 2H), 6.90–6.97 (m, 3H), 7.26–7.32 (m, 2H).

Methyl 3-(2-methylindolin-1-yl)-3-oxopropanoate (**2m**)

Purification by FCC afforded pale yellow oil. Yield 91%. ^{1}H NMR (2 rotamers): 1.27 + 1.32 (d, 3H), 2.54 + 2.67 (d, 1H), 3.32 + 3.44 (dd, 1H), 3.60 + 3.72 (dd, 2H), 3.77 (s, 3H), 4.49 + 4.73 (m, 1H), 7.00 + 8.15 (d, 1H), 7.05 (t, 1H), 7.21 (m, 2H).

General Procedure for Preparation of 3-(N,N-Dialkylamino)-3-oxopropanamides 3

Concentrated aqueous ammonia solution (10–15 mL) and methanol (0–15 mL) were added to methyl 3-(N,N-dialkylamino)-3-oxopropanoate **2** (1.0–2.0 g). Reaction was carried out at room temperature for several hours, depending on type of amides. After the reaction was completed (TLC, the mobile phase: dichloromethane–methanol 15:1), solvents were removed under vacuum to get crude product, which was used directly in the next step without further purification. However, if needed the product was purified by maceration or crystallization.

3-(N,N-Diethylamino)-3-oxopropanamide (**3a**)

Product as solidified pale yellow oil used directly in the next step. Yield 100%. ^{1}H NMR: 1.10 (t, 3H), 1.17 (t, 3H), 3.28 (s, 2H), 3.30–3.40 (m, 4H), 5.97 (br s, 1H), 7.73 (br s, 1H).

3-(N,N-Diisopropylamino)-3-oxopropanamide (**3b**)

Product as yellowish crystals after maceration in acetone/diisopropyl ether. Yield 73%. Recrystallization from acetone afforded off-white crystals; mp 156–160°C. ^{1}H NMR: 1.22 (d, 6H), 1.35 (d, 6H), 3.31 (s, 2H), 3.64 (m, 1H), 4.01 (m, 1H), 5.66 (br s, 1H), 7.53 (br s, 1H).

3-(N,N-Diisobutyl)-3-oxopropanamide (**3c**)

Product as solidified pale yellow oil was used directly in the next step. Yield 99%. Crystallization from diisopropyl ether afforded white crystals; mp: 87–88°C. ^{1}H NMR: 0.86 (d, 6H), 0.90 (d, 6H), 1.91 (m, 1H), 2.00 (m, 1H), 3.13 (d, 2H), 3.22 (d, 2H), 3.33 (s, 2H), 5.71 (br s, 1H), 7.75 (br s, 1H).

3-(N,N-Dicyclohexylamino)-3-oxopropanamide (**3d**)

Product as off-white crystals after maceration in acetone/diisopropyl ether. Yield 75%. Recrystallization from acetone afforded white crystals; mp: 166–167°C. ^{1}H NMR: 1.03–1.38 (m, 6H), 1.47–1.84 (m, 12H), 2.34 (br s, 2H), 3.03 (br s, 1H), 3.33 (s, 2H), 3.51 (br s, 1H), 5.58 (br s, 1H), 7.71 (br s, 3H).

3-(N,N-Diallylamino)-3-oxopropanamide (**3e**)

Product as solidified pale yellow oil used directly in the next step. Yield 100%. ^{1}H NMR: 3.32 (s, 2H), 3.93 (m, 2H), 3.97 (d, 2H), 5.11–5.26 (m, 4H), 5.68 (br s, 1H), 5.70–5.83 (m, 2H), 7.67 (br s, 1H).

3-(N-Allyl-N-phenylamino)-3-oxopropanamide (**3f**)

Product as pale yellow oil was used directly in the next step. Yield 100%. ^{1}H NMR: 3.06 (s, 2H), 4.31 (m, 2H), 5.06–5.19 (m, 2H), 5.78–5.91 (m, 2H), 7.11–7.17 (m, 2H), 7.32–7.44 (m, 3H), 7.75 (br s, 1H).

N-Methyl-N-phenyl malondiamide (**3g**)

Product as pale yellow oil was used directly in the next step. Yield 100%. ^{1}H NMR: 3.08 (s, 2H), 3.29 (s, 3H), 5.72 (br s, 1H), 7.14–7.20 (m, 2H), 7.33–7.46 (m, 3H), 7.76 (br s, 1H).

3-(N,N-Diphenylamino)-3-oxopropanamide (**3h**)

Product as off-white crystals was used directly in the next step. Yield 92%. Recrystallization from ethanol afforded white crystals; mp: 141–143°C (lit.[11b] 136.0°C). ^{1}H NMR: 3.30 (s, 2H), 5.67 (br s, 1H), 7.26–7.43 (m, 10H), 7.72 (br s, 1H).

3-(Pyrrolidin-1-yl)-3-oxopropanamide (**3i**)

Product as off-white crystals was used directly in the next step. Yield 99%. Recrystallization from methanol/ethyl acetate afforded white crystals; mp: 114–116.0°C. ^{1}H NMR: 1.81–2.01 (2x quintet, 4H), 3.26 (s, 2H), 3.44–3.48 (m, 4H), 5.86 (br s, 1H), 7.96 (br s, 1H).

3-(Morpholin-4-yl)-3-oxopropanamide (**3j**)

Product as solidified yellow oil was used directly in the next step. Yield 99%. Crystallization from 2-propanol afforded off-white crystals; mp 121–123°C. ^{1}H NMR: 3.33 (s, 2H), 3.52–3.68 (m, 8H), 6.10 (br s, 1H), 7.38 (br s, 1H).

3-(1,4-Dioxa-8-azaspiro[4,5]decan-8-yl)-3-oxopropanamide (**3k**)

Product as white crystals was used directly in the next step. Yield 100%. Recrystallization from methanol afforded white crystals; mp 181–184°C. ^{1}H NMR: 1.67–1.73 (m, 4H), 3.35 (s, 2H), 3.59 (t, 2H), 3.70 (t, 2H), 3.96 (s, 4H), 5.72 (br s, 1H), 7.47 (br s, 1H).

3-(4-Phenylpiperazin-1-yl)-3-oxopropanamide (**3l**)

Product as off-white crystals was used directly in the next step. Yield 93%. Recrystallization from methanol afforded white crystals; mp: 183–185°C. ^{1}H NMR: 3.16–3.22 (m, 4H), 3.40 (s, 2H), 3.72 (t, 2H), 3.81 (t, 2H), 5.65 (br s, 1H), 6.90–6.95 (m, 3H), 7.26–7.32 (m, 2H), 7.39 (br s, 1H).

3-(2-Methylindolin-1-yl)-3-oxopropanamide (**3m**)

White crystals after crystallization from methanol. Yield 85%; mp 169–172°C.

^{1}H NMR (2 rotamers): 1.25 + 1.33 (d, 3H), 2.53 + 2.69 (d, 1H), 3.32 + 3.43 (dd, 1H), 3.50 + 3.65 (dd, 2H), 4.59 + 4.91 (m, 1H), 5.76 (br s, 1H), 7.09 (t, 1H), 7.23 (m, 2H), 7.68 (br s, 1H), 8.14 (d, 1H).

General Procedure for Preparation of 3-(N,N-Dialkylamino)-3-oxopropanenitriles 4

Phosphorus oxychloride (1.0–1.1 eq) (procedure A) or tosyl chloride (2–3 eq) (procedure B) was dropwise added to a precooled solution of 3-(N,N-dialkylamino)-3-oxopropanamide **3** (0.5–1.5 g) in pyridine (5–10 mL). Internal temperature was kept in the range of 15–20°C using an ice-water bath. After addition, dehydration was continued at room temperature untill TLC (the mobile phase: dichloromethane–methanol 15:1) showed complete conversion. The reaction was quenched with

methanol (5–10 mL) at 10–15°C, and solvents were removed under vacuum to give a residue, which was purified either on FCC using gradient of methanol in dichloromethane (0–2%) (system A), gradient of ethyl acetate in dichloromethane (6–8%) (system B), or by vacuum distillation or crystallization.

3(-N,N-Diethyl)-3-oxopropanenitrile (**4a**)

Pale yellow oil after FCC (system A). Procedure A: 86%. Procedure B: 91%. Bp 105–114°C/5 mbar. IR: 3499, 2978, 2938, 2331, 2258, 1747, 1461, 1402, 1384, 1323, 1261, 1143, 1100, 1022, 948, 894, 773; ^{1}H NMR: 1.12 (t, 3H), 1.21 (t, 3H), 3.26 (q, 2H), 3.37 (q, 2H), 3.48 (s, 2H).

3-(N,N-Diisopropyl)-3-oxopropanenitrile (**4b**)

Product as pale orange solidified oil after FCC (system B). Procedure A: 89%. Procedure B: 93%. Crystallization from diisopropyl ether afforded off-white crystals; mp: 50–51°C (lit.[9] 45–46°C). IR: 3016, 2973, 2941, 2252, 1640, 1473, 1446, 1374, 1347, 1285, 1207, 1159, 1141, 1125, 1044, 975, 917, 892. ^{1}H NMR: 1.22 (d, 6H), 1.36 (d, 6H), 3.44–3.48 (m, 1H), 3.45 (s, 2H), 3.70–3.79 (m, 1H).

3-(N,N-Diisobutyl)-3-oxopropanenitrile (**4c**)

Product as orange oil after FCC (system B). Procedure A: 84%. Procedure B: 87%. IR: 2962, 2874, 2258, 1652, 1470, 1449, 1389, 1241, 1147, 1103, 944, 924, 819. ^{1}H NMR: 0.87 (d, 6H), 0.92 (d, 6H), 1.92 (m, 1H), 2.01 (m, 1H), 3.05 (d, 2H), 3.20 (d, 2H), 3.50 (s, 2H). ^{13}C NMR: 19.95, 20.04, 25.20, 26.35, 27.67, 53.45, 56.08, 114.22, 161.83. HRMS calculated for $C_{11}H_{21}N_2O$ ($M + H^+$): 197.1648; found: 197.1654.

3-(N,N-Dicyclohexyl)-3-oxopropanenitrile (**4d**)

Off-white crystals after FCC (system B). Procedure A: 82%. Procedure B: 89%. Recrystallization from ethyl acetate afforded analytical sample as white crystals; mp: 165–168°C. IR: 2929, 2857, 2257, 1636, 1471, 1440, 1378, 1240, 1181, 1125, 996, 896, 700. ^{1}H NMR: 1.07–1.87 (m, 18H), 2.36 (br s, 2H), 2.99 (br s, 1H), 3.24 (m, 1H), 3.45 (s, 2H). ^{13}C NMR: 25.00, 25.16, 26.41, 27.18, 29.58, 31.04, 56.86, 59.48, 114.40, 160.14. Elemental analysis calculated for $C_{15}H_{24}N_2O$: C, 72.54; H, 9.74; N, 11.28. Found: C, 72.61; H, 9.90; N, 11.26.

3-(N,N-Diallyl)-3-oxopropanenitrile (**4e**)

Pale yellow oil after FCC (system B). Procedure A: 85%. Procedure B: 91%. IR: 3085, 2922, 2258, 1662, 1470, 1445, 1419, 1316, 1227, 1191, 994, 929, 819. ^{1}H NMR: 3.50 (s, 2H), 3.86 (m, 2H), 3.99 (d, 2H), 5.13–5.29 (m, 4H), 5.67–5.84 (m, 2H).

3-(N-Allyl-N-phenyl)-3-oxopropanenitrile (**4f**)

Pale yellow oil after FCC (system B). Procedure A: 89%. Procedure B: 84%. IR: 3065, 2961, 2924, 2258, 1674, 1596, 1496, 1405, 1317, 1255, 1226, 1138, 991, 928, 777, 704. ^{1}H NMR: 3.20 (s, 2H), 4.28 (t, 1H), 4.31 (t, 1H), 5.05–5.16 (m, 2H), 5.76–5.90 (m, 1H), 7.15–7.2 (m, 2H), 7.37–7.48 (m, 3H). ^{13}C NMR: 25.71, 52.85, 114.06, 119.23, 128.07, 129.16, 130.28, 131.74, 140.74. HRMS calculated for $C_{12}H_{13}N_2O$ ($M + H^+$): 201.1022; found: 201.1014.

3-(N-Methyl-N-phenyl)-3-oxopropanenitrile (**4g**)

Solidified pale orange oil after FCC (system A). Procedure A: 83%. Procedure B: 83%. Crystallization from ethyl acetate/diisopropyl ether afforded off-white crystals; mp: 76–78°C (lit.[3d] 78°C). IR: 3056, 2931, 2257, 1663, 1594, 1493, 1421, 1387, 1270, 1121, 922, 772, 670. ^{1}H NMR: 3.22 (s, 2H), 3.30 (s, 3H), 7.20–7.24 (m, 2H), 7.39–7.51 (m, 3H).

3-(N,N-Diphenyl)-3-oxopropanenitrile (**4h**)

Pale orange crystals after FCC (system B). Procedure A: 80%. Procedure B: 81%. Recrystallization from methanol afforded off-white crystals; mp: 151–153°C (lit.[11b] 151–152°C). IR: 3088, 2957, 2926, 2264, 1675, 1591, 1491, 1392, 1365, 1270, 1176, 1002, 920, 868, 764, 751, 706, 695. ^{1}H NMR: 3.42 (s, 2H), 7.26–7.46 (m, 10H).

3-(Pyrrolidin-1-yl)-3-oxopropanenitrile (**4i**)

Solidified pale yellow oil after FCC (system A). Procedure A: 89%. Procedure B: 91%. Crystallization from ethyl acetate afforded off-white crystals; mp: 70–72°C (lit.[5a] 71°C). IR: 2984, 2944, 2888, 2256, 1645, 1632, 1450, 1402, 1341, 1285, 1168, 953, 912, 797, 707. ^{1}H NMR: 1.89 (quintet, 2H), 2.00 (quintet, 2H), 3.42 (s, 2H), 3.44–3.51 (m, 4H).

3-(Morpholin-1-yl)-3-oxopropanenitrile (**4j**)

Solidified pale yellow oil after FCC (system A). Procedure A: 83%. Procedure B: 91%. Crystallization from ethyl acetate/diisopropyl ether afforded white crystals, mp 85–87°C (lit.[5b] 87°C). IR: 2972, 2929, 2873, 2265, 1652, 1467, 1452, 1390, 1319, 1279, 1243, 1107, 1068, 1034, 977, 929, 842. ^{1}H NMR: 3.43 (t, 2H), 3.51 (s, 2H), 3.59 (m, 2H), 3.66–3.72 (m, 4H).

3-(1,4-Dioxa-8-azaspiro[4,5]decan-8-yl)-3-oxopropanenitrile (**4k**)

Off-white crystals after FCC (system A). Procedure A: 82%. Procedure B: 89%. Recrystallization from acetone/diisopropyl ether afforded white crystals; mp 119–120°C. IR: 2947, 2889, 2259, 1651, 1637, 1437, 1361, 1226, 1146, 1102, 1034, 945, 919, 792. ^{1}H NMR: 1.69 (t, 2H), 1.75 (t, 2H), 3.50 (m, 4H), 3.69 (t, 2H), 3.96 (s, 4H). ^{13}C NMR: 24.99, 34.47, 35.16, 40.70, 44.52, 64.53, 106.27, 114.06, 159.92. Elemental analysis calculated for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.33. Found: C, 57.18; H, 6.76; N, 13.15.

3-(4-Phenylpiperazin-1-yl)-3-oxopropanenitrile (**4l**)

Off-white crystals after FCC (system A). Procedure A: 88%. Procedure B: 90%. Recrystallization from ethyl acetate afforded white crystals; mp 132–134°C. IR: 2917, 2813, 2261, 1648, 1595, 1495, 1446, 1334, 1276, 1223, 1154, 982, 900, 768, 699. ^{1}H NMR: 3.19 (t, 2H), 3.25 (t, 2H), 3.54 (s, 2H), 3.63 (t, 2H), 3.80 (t, 2H), 6.91–6.96 (m, 3H), 7.27–7.33 (m, 2H). ^{13}C NMR: 24.97, 42.40, 46.29, 49.17, 49.42, 114.08, 116.81, 120.88, 129.32, 150.58, 160.21. Elemental analysis calculated for $C_{13}H_{15}N_3O$: C, 68.10; H, 6.59; N, 18.33. Found: C, 68.17; H, 6.65; N, 18.28.

3-(2-Methylindolin-1-yl)-3-oxopropanenitrile (**4m**)

Off-white crystals after FCC (system A). Procedure A: 94%. Procedure B: 91%. Recrystallization from diisopropyl ether afforded white crystals; mp 154–156°C. IR: 2981, 2963, 2923, 2256, 1659, 1598, 1478, 1416, 1375, 1271, 1112, 998, 919, 752, 710. ^{1}H NMR (2 rotamers): 1.26 + 1.33 (d, 3H), 2.57 + 2.70 (d, 1H), 3.34 + 3.47 (dd, 1H), 3.67 + 3.80 (dd, 2H), 4.43 + 4.92 (m, 1H), 6.93 + 8.09 (d, 1H), 7.09 (t, 1H), 7.21 (m, 2H). ^{13}C NMR (2 rotamers): 19.91 + 21.81, 26.45 + 27.08, 35.11 + 36.52,

56.39 + 57.09, 113.96 + 114.60, 118.08, 125.06 + 126.76, 125.17 + 126.79, 127.71, 130.26, 140.65, 158.86. Elemental analysis calculated for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99; found: C, 71.95; H, 6.06; N, 13.95.

REFERENCES

1. (a) Manikowski, A.; Kolarska, Z.; Jerkovic, J. A process for preparing entacapone. WO Patent Application 2008007093. *Chem. Abstr.* 2008, *148*, 168462; (b) Ferreira, J. J.; Almeida, L.; Cunha, L.; Ticmeanu, M.; Rosa, M. M.; Januario, C.; Mitu, C.-E.; Coelho, M.; Correia Guedes, L.; Morgadinho, A.; Nunes, T.; Wright, L. C.; Falcao, A.; Sampaio, C.; Soares-de-Silva, P. Effects of nebicapone on levodopa pharmacokinetics; catechol-O-methyltransferase activity, and motor fluctuations in patients with Parkinson disease. *Clin. Neuropharmacol.* **2008**, *31*, 2–18; (c) Nadkarni, S.; Vaya, N.; Karan, R. S.; Gupta, V. K. Novel drug delivery system. IN Patent Application 2005MU01012. *Chem. Abstr.* 2007, *148*, 503081; (d) Foster, J. E.; Sheng, Q.; McClain, J. R.; Bures, M.; Nicas, T. I.; Henry, K.; Winkler, M. E.; Gilmour, R. Kinetic and mechanistic analyses of new classes of inhibitors of two-component signal transduction systems using a coupled assay containing HpkA-DrrA from *Thermotoga maritima*. *Microbiology* **2004**, *150*, 885–896; (e) Yang, D.-P.; Ji, H.-F.; Tang, G.-Y.; Ren, W.; Zhang, H.-Y. How many drugs are catecholics? *Molecules* **2007**, *12*, 878–884.
2. (a) Dipierro, G.; Giannos, S. A. Transdermal delivery techniques for drugs, nutraceuticals, and other active substances. WO Patent Application 2008054788. 2008; *Chem. Abstr. 148*, 523656; (b) Kajita, S.; Ohmura, H.; Akashi, M.; Kojima, S.; Satoh, A.; Tomida, K. Preparation of benzoyl derivatives having sulfoximine group as herbicides. WO Patent Application 2004052849. *Chem. Abstr.* 2004, *141*, 54066; (c) Jablonkai, I. Alkylating reactivity and herbicidal activity of chloroacetamides. *Pest Management Sci.* **2003**, *59*, 443–450.
3. (a) Kharas, G. B.; Tian, X.; Alegarbes, J.; Bartosik, A. T.; Hadziahmetovic, M.; Hai, A. K.; Ibarra, I.; Hua, P. Novel copolymers of styrene and some ring-substituted 2-cyano-N,N-dimethyl-3-phenyl-2-propenamides. *J. Macromol. Sci. A: Pure Appl. Chem.* **2007**, *44*, 565–568; (b) Schenker, G. Compositions containing cyanoacetylurea and tetrafluoroborate for stabilization of halogen-containing organic plastics. DE Patent 10230423. 2004; *Chem. Abstr. 140*, 94981; (c) Friedrich, H. H.; Wehner, W. Cyanoacetylurea stabilization of chlorinated polymers. EP Patent Application 962491. *Chem. Abstr.* **1999**, *132*, 23513; (d) Werner, T. N,N-Disubstituierte α-cyanacrylsäureamide und deren Herstellung. DE Patent 2307156. *Chem. Abstr.* 1974, *82*, 43995.
4. (a) Yokoyama, Y.; Suzuki, S.; Furihata, H.; Takahi, S.; Nomura, M.; Kajitani, M. The development of a novel synthetic method for cyanofluoroamides using a cobaltadithiolene complex. *Synthesis* 2004, *5*, 701–705; (b) Shi, Y.; Zhang, J.; Grazier, N.; Stein, P. D.; Atwal, K. S.; Traeger, S. C.;

Callahan, S. P.; Malley, M. F.; Galella, M. A.; Gougoutas, J. Z. One-pot synthesis and conformational features of *N,N′*-dusubstituted ketene aminals. *J. Org. Chem.* **2004**, *69, 188–191; (c) Vyas, S. G.; Kulkarni, A. B. 2,2-Dibromo-2-cyano-N,N-dimethylacetamide as a new brominating agent. Ind. J. Chem.* **1979**, *17B, 305–306; (d) Suzuki, J.; Suzuki, K.; Sekiya, M. Monobromination of cyanoacetamides and amidinoacetamide with molecular bromine. Chem. Pharm. Bull.* **1974**, *22, 965–966.*

5. (a) Osdene, T. S.; Santilli, A. A.; McCardle, L. E.; Rosenthale, M. E. Pteridinecarboxamide diureties, II: Reaction of 4,6-diamino-5-nitrosopyrimidines with N-substituted cyanoacetamides. *J. Med. Chem.* **1967**, *10*, 165–171; (b) Whitehead, C. W.; Traverso, J. J. Synthesis of cytosines. *J. Am. Chem. Soc.* **1955**, *77*, 5867–5872; (c) Tkachenko, V. V.; Tregub, N. G.; Knyazev, A. P.; Mezheritskii, V. V. 1,8-Substituted naphthalenes, XX: New naphth[1,8-bc]oxepin derivatives. *Zh. Org. Khim.* **1990**, *26*, 638–649.
6. McCall, J. M.; TenBrink, R. E.; Ursprung, J. J. A new approach to triamino-pyrimidine *N*-oxides. *J. Org. Chem.* **1975**, *40*, 3304–3306.
7. (a) Cossey, A. L.; Harris, R. L.; Huppatz, J. L.; Philips, J. N. Pyridines and pyridinium salts from cyanoacetamides. *Aust. J. Chem.* **1976**, *29*, 1039–1050; (b) Cossey, A. L.; Harris, R. L.; Huppatz, J. L.; Philips, J. N. The synthesis of tetrasubstituted pyridines from *N,N*-dialkylcyanoacetamides. *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 1098–1099.
8. Harnish, H. Oxazolyl-essigsäurederivate und Oxyzolyl-cumarine. DE Patent 2030507. *Chem. Abstr.* **1972**, *76*, 128826.
9. Bhawal, B. M.; Khanapure, S. P.; Biehl, E. R. Rapid, low-temperature amidation of ethyl cyanoacetate with lithium amides derived from primary and secondary amines. *Synth. Commun.* **1990**, *20*, 3235–3243.
10. Concellon, J. M.; Bardales, E. Synthesis of Aromatic (*E*)- or (*Z*)-α,β-unsaturated amides with total or very high selectivity from α,β-epoxyamides and samarium diiodide. *J. Org. Chem.* **2003**, *68*, 9492–9495.
11. (a) Seguin, H.; Gardette, D.; Moreau, M. F.; Madelmont, J. C.; Gramain, J. C. A general method for the synthesis of *N,N*-dialkylaminobutylamines. *Synth. Commun.* **1998**, *28*, 4257–4272; (b) Lafon, L. Acetamide derivatives. US Patent 4177290. *Chem. Abstr.* **1979**, *93*, 7872; (c) Seeger, Q.; Juergen, H. Verfahren zur Herstellung von Cyanacetamiden. DE Patent 2538254. *Chem. Abstr.* **1977**, *87*, 22442; (d) Schwarz, M.; Bodenstein, O. F.; Fales, J. H. Compounds related to cyanoacetic acid as repellents for cockroaches, II. *J. Econ. Entomol.* **1971**, *64*, 576–578.
12. (a) Andreev, S. A.; Lebedev, B. A.; Tselinskii, I. V.; Shokhor, I. N. N-Nitration of amides, VI: Mechanism of the nitrolysis of N,N-dialkylamides of carboxylic acids by nitronium tetrafluoroborate in acetonitrile. *Zh. Org. Khim.* **1980**, *16*, 1353–1360; (b) Andreev, S. A.; Lebedev, B. A.; Tselinskii, I. V. N-Nitration of amides, VII: Kinetics of the nitrolysis of N,N-dialkylamides of carboxylic acids by nitronium tetrafluoroborate in acetonitrile. *Zh. Org. Khim.* **1980**, *16*, 1360–1365.
13. (a) Mansour, T. S. Selective carbon formylation of cyanoacetanilides. *Synth. Commun.* **1987**, *17*, 1315–1322; (b) Bianchi, M.; Butti, A.; Rossi, S. New

investigations on the chemical behavior of 4-keto-1H-4,5-dihydro-1,2,5-benzotriazepines. *Tetrahedron* **1974**, *30*, 2765–2771; (c) Ireland, R. E.; Chaykovsky, M. *t*-Butyl cyanoacetate. *Org. Synth. Coll.* **1973**, *5*, 171–175.

14. Sasaki, T.; Kojima, A. The chemistry of cyanoacetylenes VII: The reaction of hydrogen chloride with diethylaminocyanoacetylene. *Tetrahedron Lett.* **1969**, *41*, 3639–3642.
15. Eliel, E. L. The structure of the guaiacol "Mannich bases." *J. Am. Chem. Soc.* **1951**, *73*, 43–45.
16. Cheikh, A. B.; Chuche, J.; Manisse, N.; Pommelet, J. C.; Netsch, K. P.; Lorencak, P.; Wentrup, C. Synthesis of α-cyano carbonyl compounds by flash vacuum thermolysis of (alkylamino)methylene derivatives of Meldrum's acid: Evidence for facile 1,3-shifts of alkylamino and alkylthio groups in imidoylketene intermediates. *J. Org. Chem.* **1991**, *56*, 970–975.
17. (a) Sutherland, K. W.; Feigelson, G. B.; Boschelli, D. H.; Blum, D. M.; Strong, H. L. Process for preparation of 4-amino-3-quinolinecarbonitriles. US Patent Application 2005/0043537. *Chem. Abstr.* **2005**, *142*, 261413; (b) Sjogren, E. B.; Rider, M. A.; Nelson, P. H.; Bingham, S.; Poulton, A. L.; Emanuel, M. A.; Komuniecki, R. Synthesis and biological activity of a series of diaryl-substituted α-cyano-β-hydroxypropenamides, a new class of anthelmintic agents. *J. Med. Chem.* **1991**, *34*, 3295–3301.
18. Box, V. G. S.; Marinovic, N.; Yiannikouroa, P. The synthesis of β-lactones and β-lactams from malonates and malonamides. *Heterocycles* **1991**, *32*, 245–251.
19. (a) Wu, Z.; Ede, N. J.; Mathieu, M. N. Solid-phase synthesis of benzimidazole *N*-oxides on SynPhase lanterns. *Tetrahedron Lett.* **2003**, *44*, 2293–2296; (b) Njoroge, F. G.; Vibulbhan, B.; Pinto, P.; Strickland, C. L.; Bishop, W. R.; Kirschmeir, P.; Girijavallabhan, V.; Ganguly, A. K. Trihalobenzocycloheptapyridine analogues of Sch 66336 as potent inhibitors of farnesyl protein transferase. *Bioorg. Med. Chem.* **2003**, *11*, 139–143; (c) Clark, A. J.; Dell, C. P.; McDonagh, J. M.; Geden, J.; Mawdsley, P. Oxidative 5-*endo* cyclization of enamides mediated by ceric ammonium nitrate. *Org. Lett.* **2003**, *12*, 2063–2066; (d) Henke, B. R.; Aquino, C. J.; Birkemo, L. S.; Croom, D. K.; Dougherty, R. W.; Ervin, G. N.; Grizzle, M. K.; Hirst, G. C.; James, M. K.; Johnson, M. F.; Queen, K. L.; Sherrill, R. G.; Sugg, E. E.; Suh, E. M.; Szewczyk, J. W.; Unwalla, R. J.; Yingling, J.; Willson, T. M. Optimization of 3-(1*H*-indazol-3-ylmethyl)-1,5-benzodiazepines as potent, orally active CCK-A agonists. *J. Med. Chem.* **1997**, *40*, 2706–2725; (e) Wee, A. G.; Liu, B. The nafion-H catalysed cyclization of α-carbomethoxy-α-diazoacetanilides. synthesis of 3-unsubstituted-2-indolinones. *Tetrahedron* **1994**, *50*, 609–626; (e) Svoboda, J.; Paleta, O.; Liska, F.; Dedek, V. Fluorinated 3-diethylaminopropenoates and their reactions. *Collect. Czech. Chem. Commun.* **1981**, *46*, 1389–1396; (f) Frincke, J. M.; Henderson, G. L. The major metabolite of fentanyl in the horse. *Drug Metab. Dispos.* **1980**, *8*, 425–427; (g) Takei, H.; Fukuda, Y.; Sugaya, K.; Taguchi, T.; Kawara, T. Reaction of α-bromo-α,β-unsaturated esters and butenolides with malonamic esters. *Chem. Lett.* **1980**, 1307–1310; (h) Coppola, G. M.; Hardtmann, G. E. The

chemistry of 2*H*-3,1-benzoxazine-2,4(1*H*)dione (isatoic anhydride), 7: Reactions with anions of active methylenes to form quinolines. *J. Heterocycl. Chem.* **1979**, *16*, 1605–1610; (i) Gais, H. J.; Hafner, K.; Neuenschwander, M. Acetylene mit Elektronendonator- und Elektronenakzeptorgruppen. *Helv. Chim. Acta* **1969**, *52*, 2641–2657.

20. Ragan, J. A.; Burmaster, M.; Hill, P. D. Synthesis of *N,N*-dimethylpropanediamide and its utility for the preparation of 2-(acetamidomethyl)-4-aryloxazoles. *Synlett* **2004**, *8*, 1334–1338.
21. Henecka, H.; Kurtz, P. Funktionelle N-Derivate der Carboxylgruppe. *Methoden der Organischen Chemie*, Houben-Weyl, Stuttgart, Germany, 1952; vol. 8, p. 658.
22. Smith, M. B.; March, J. *March's Advanced Organic Chemistry,* 5th Ed., Wiley Interscience, 2001; p. 1350.
23. Maffioli, S. I.; Marzorati, E.; Marazzi, A. Mild and reversible dehydration of primary amides with $PdCl_2$ in aqueous acetonitrile. *Org. Lett.* **2005**, *7*, 5237–5239.