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On the reaction of carboxylic acids and isonitriles with conventional heating

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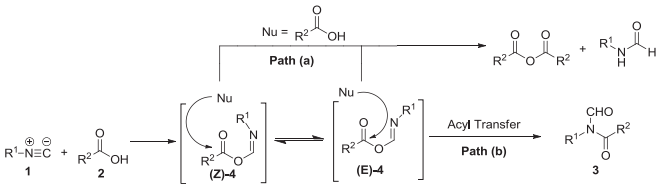
ABSTRACT

Control over the formation of *N*-formylamides versus the formation of captodative alkenes from the reaction of arylacetic acids with isonitriles has been achieved. Low temperatures and high concentrations favor alkenes, and high temperatures and low concentrations favor *N*-formylamides.

1. Introduction

In 1869, Gautier reported that isonitriles (**1**) react with carboxylic acids (**2**) to produce anhydrides and formamides.[1] Interest in the reaction of **1** and **2** in the absence of other reagents[2] remained dormant[3] until 2008, when the Danishefsky group reported *N*-formylamides (**3**) were formed under microwave conditions.[4] These two pathways can be rationalized by the mechanism in Scheme 1. The formation of a formimidate carboxylate mixed anhydride, or FCMA **4** (with interconverting (*Z*) and (*E*) isomers) from **1** and **2** has been suggested by experiments[4,5] and calculations.[6] The (*E*)-FCMA can then undergo a 1,3 O→N acyl transfer (Mumm rearrangement, path b)[7] to give **3**, or **4** can be intercepted by a nucleophile,[8] such as additional **2** (path a); which gives anhydride and formamide.



Scheme 1. Pathways for the reaction of isonitriles with carboxylic acids.

The original *N*-formylamide synthesis involved halogenated solvents with microwave heating, at or above 150 °C.[4] Recently we have shown that the reaction proceeds readily in toluene heated to 110 °C by conventional methods.[9] We now present a full account of our synthetic work on the reaction.

2. Results and discussion

2.1. Synthesis of *N*-formylamides using low concentrations of acid

On the assumption that the anhydride and formamide arose from interception of the intermediates **4** by acid **2**, the latter was added slowly via syringe pump.[10] Indeed, side product formation was suppressed, allowing isolation of **3** in good yields as shown in Table 1. Because the applications of RCO_2H/RNC coupling have largely been in peptide synthesis, no example using an aromatic isonitrile has been reported,[4,5,11] before the beginning of our work.[9] We therefore focused on the use of aromatic and simple aliphatic isonitriles (Tables 1, 2, 6, and 7). The results show high functional group tolerance from each component, e.g., of nitro, halo, cyano, pyridyl, thienyl, ether, carbomethoxy, acetyl, tertiary amino, and trifluoromethyl substituents, of unprotected indoles, and of both isolated and conjugated double bonds.

A syringe pump is impractical with acids that are not soluble in toluene at room temperature, i.e., those in Table 2. Acids with limited solubility in toluene even at 110 °C mimic the effect of slow

Table 1
Syringe pump addition of carboxylic acids to isonitriles in toluene at 110 °C[a]

Isonitrile R^1=	Acid R^2=	**3** (Yield)[b]
c-Hex (**1a**)	Ph (**2a**)	**3aa** (61%)
1a	$PhCH_2CH_2$ (**2b**)	**3ab** (72%)
n-Pent (**1b**)	**2b**	**3bb** (55%)
4-MeC_6H_4 (**1c**)	**2b**	**3cb** (68%)
2,6-Xylyl (**1d**)	**2b**	**3db** (61%)
1d	$H_2C{=}CHCH_2$ (**2c**)	**3dc** (66%)
1d	PhCH=CH (**2d**)	**3dd** (75%)
1d	2-Thiopheneacetic (**2e**)	**3de** (74%)
2-Cl−6-MeC_6H_3 (**1e**)	**2e**	**3ee** (65%)
2,6-Xylyl (**1d**)	$MeO_2C(CH_2)_6$ (**2f**)	**3df** (57%)
4-$MeOC_6H_4$ (**1f**)	$MeOCH_2CH_2OCH_2$ (**2g**)	**3fg** (72%)

[a] See Ref. 10.
[b] Isolated yields based on **2**.

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Table 2
Reaction of carboxylic acids with isonitriles in toluene at 110 °C

Isonitrile R^1=	Acid R^2=	**3** (Yield)[a]
c-Hex (**1a**)	4-Me(O)CC_6H_4 (**2h**)[b]	**3ah** (70%)
4-MeOC_6H_4 (**1f**)	**2h**	**3fh** (80%)
4-MeC_6H_4 (**1c**)	**2h**	**3ch** (89%)
4-$Et_2NC_6H_4$ (**1g**)	**2h**	**3gh** (79%)
c-Hex (**1a**)	4-NCC_6H_4 (**2i**)[c]	**3ai** (84%)
Ph (**1h**)	**2i**	**3hi** (83%)
4-$Et_2NC_6H_4$ (**1g**)	**2i**	**3gi** (94%)
2-Naphthyl (**1i**)	**2i**	**3ii** (65%)
c-Hex (**1a**)	4-$O_2NC_6H_4$ (**2j**)[d]	**3aj** (70%)
3-BrC_6H_4 (**1j**)	**2j**	**3jj** (67%)
2-Cl–6-MeC_6H_3 (**1e**)	2-Picolinic (**2k**)[e]	**3ek** (68%)

[a] Isolated yields based on **2**.
[b] 0.05 M, 48 h.
[c] 0.05 M, 24 h.
[d] 0.02 M, 24 h.
[e] 0.05 M, 3 d.

addition: the low acid concentrations limit FCMA interception, so yields of the *N*-formylamide are high. Examples are offered by the reaction of **2h** (0.05 M in toluene) with the isonitriles **1a**, **1c**, **1f**, or **1g** for 48 h. Likewise, the reaction of **2i** with **1a**, **1g**, **1h**, or **1i** for 24 h gives good yields.[12]

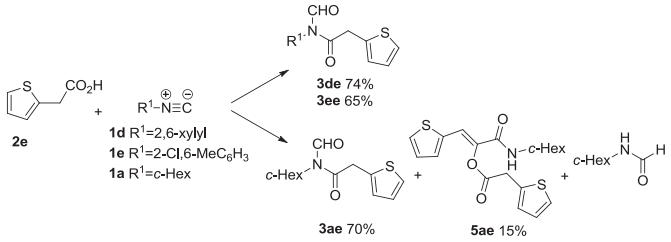
Although, 4-nitrobenzoic acid (**2j**) fully dissolves in dilute toluene at 110 °C, high yields of **3aj** and **3jj** were obtained, presumably because of the low nucleophilicity of this acid.[13] The medicinally relevant[14] 2-picolinic acid (**2k**) reacts very slowly with isonitrile **1e**, requiring 3 days, despite fully dissolving under the reaction conditions. We speculate that **2k** exists as a hydrogen-bonded dimer or as its zwitterionic tautomer,[15] thus impeding FCMA formation.

2.2. Reactivity of arylacetic acids with isonitriles

Shortly after Danishefsky's disclosure, Basso and co-workers reported another class of product—captodative alkenes **5**—from the reaction of isonitriles with arylacetic acids, also under microwave conditions.[16] They proposed the mechanism in Scheme 2, in which formation of alkenes **5** (path a) begins with (1) nucleophilic attack on the FCMA by additional isonitrile, continues with (2) carboxylate attack on the nitrilium carbon of **6** or **7**, and finishes with (3) 1,4 O→O acyl migration, as in the Passerini reaction,[2a–d] giving **5**.

Treatment of 2,6-xylyl isonitrile (**1d**) or 2-chloro-6-methylphenyl isonitrile (**1e**) with 2-thiopheneacetic acid (**2e**) under syringe pump conditions[10] gave only the *N*-formylamides (**3de** and **3ee**), isolated in good yields as shown in Scheme 3.[9] However, treatment of cyclohexyl isonitrile (**1a**) with **2e** under the same conditions formed **5ae** (15% isolated) as well as **3ae** (71% isolated).[17] Intrigued by this finding, we decided to study more thoroughly the reactions of arylacetic acids with isonitriles and the factors that determine their outcomes.

First, we investigated the effect of reaction conditions on the product ratio (**3ae**/**5ae**) from **1a** and **2e**, as shown in Table 3. Entries 1–5 show that increasing the concentration of the reactants leads to a greater proportion of alkene **5ae**, presumably by increasing the rate of nucleophilic attack on **4** (Scheme 2, path a) relative to the rate of its rearrangement (path b). Good selectivity (entry 2) for **3ae**



Scheme 3. Preliminary reactions using syringe pump addition of 2-thiopheneacetic acid.

Table 3
The effect of conditions on the reaction of cyclohexyl isonitrile (**1a**) with 2-thiopheneacetic acid (**2e**)[a]

Entry	Conditions	**3ae** (%)	**5ae** (%)
1	Syringe pump addition of **2e**[b]	71	15
2	Syringe pump addition of **2e**[c]	80	8
3	2 equiv **1a**, 0.01 M **2e**, toluene, 110 °C	58	20
4	2 equiv **1a**, 0.02 M **2e**, toluene, 110 °C	41	33
5	2 equiv **1a**, 0.1 M **2e**, toluene, 110 °C	30[d]	65[d]
6	2 equiv **1a**, 0.1 M **2e**, Me–NO_2, 110 °C	25[d]	70[d]
7	2 equiv **1a**, 0.1 M **2e**, Me–NO_2, 90 °C	20[d]	75[d]
8	2 equiv **1a**, 0.1 M **2e**, Me–NO_2, 60 °C	7[d]	90[d]
9	2 equiv **1a**, 0.3 M **2e**, Me–NO_2, 40 °C, 2 d	—	95
10	2 equiv **1a**, 0.5 M **2e**, Me–NO_2, 40 °C, 2 d	—	95
11	2 equiv **1a**, 1 M **2e**, Me–NO_2, 25 °C, 4 d	—	91
12	2 equiv **1a**, neat, 25 °C, 4 d	—	96

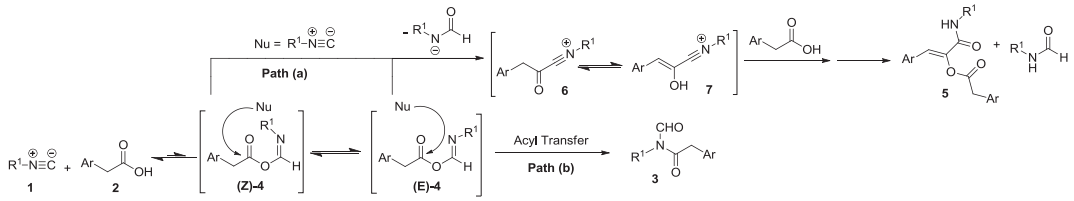
[a] Yields based on acid **2e**.
[b] See Ref. 10.
[c] See Ref. 18.
[d] Estimated from crude ^{1}H NMR analysis.

is achieved with syringe pump addition of **2e** to a solution of **1a**.[18] The more polar solvent nitromethane has little effect on the ratio (entry 6). Lower temperatures in that solvent[19] allow selective formation of **5ae** (entries 6–11), as expected: the rate of a unimolecular reaction (the formation of **3ae**) should decrease with decreasing temperature more than the rate of a bimolecular reaction (formation of **5ae**).

Next, we tested the generality of these findings with other RNC/$ArCH_2CO_2H$. At high temperatures aliphatic isonitriles generally give mixtures of **3** and **5** (Table 4).[20] From such isonitriles (**1a**, **1b**, **1k**, **1l**) we obtained significant amounts of each product with electron-deficient phenylacetic acids (**2q**–**s**) and with acids **2p** and **2e**. From the same isonitriles we obtained **3** as the major product with other acids (**2l**–**o**).

At lower temperatures (40 °C), with high concentrations of **2**, aliphatic isonitriles give good selectivity and high isolated yields of the alkenes **5** (Table 5).[21] Aromatic isonitriles, being less nucleophilic,[22] give no **5**, but a mixture of unreacted starting material, anhydride, formamide and **3** is observed (Basso has reported[16] one case in which **5** is formed from an aromatic isonitrile using microwave conditions.[23]).

Good selectivity for **3** is observed with syringe pump addition of **2** to aliphatic isonitriles at 110 °C, as shown in Table 6. Low concentrations and high temperatures discourage the bimolecular interception of FCMA intermediates.



Scheme 2. Pathways for the reaction of isonitriles with arylacetic acids.

Table 4
Reactions of arylacetic acids with aliphatic isonitriles[a]

Isonitrile R^1=	Acid Ar=	**3** (Yield)[b]	**5** (Yield)[b]
c-Hex (**1a**)	**2e**	**3ae** (41%)	**5ae** (33%)
n-Bu (**1k**)	**2e**	**3ke** (48%)	**5ke** (40%)
n-Pent (**1b**)	**2e**	**3be** (51%)	**5be** (48%)
i-Pr (**1l**)	**2e**	**3le** (43%)	**5le** (52%)
c-Hex (**1a**)	Ph (**2l**)	**3al** (54%)	**5al** (7%)
n-Bu (**1k**)	**2l**	**3kl** (52%)	**5kl** (<10%)
c-Hex (**1a**)	4-MeC_6H_4 (**2m**)	**3am** (65%)	**5am** (<10%)
c-Hex (**1a**)	4-$MeOC_6H_4$ (**2n**)	**3an** (60%)	Trace
n-Bu (**1k**)	**2n**	**3kn** (64%)	Trace
n-Pent (**1b**)	3,4-$(MeO)_2C_6H_3$ (**2o**)	**3bo** (71%)	Trace
c-Hex (**1a**)	Diphenylacetic (**2p**)	**3ap** (40%)	**5ap** (54%)
i-Pr (**1l**)	**2p**	**3lp** (56%)	**5lp** (41%)
c-Hex (**1a**)	4-$O_2NC_6H_4$ (**2q**)	**3aq** (45%)	**5aq** (30%)
n-Pent (**1b**)	2-$O_2NC_6H_4$ (**2r**)	**3br** (51%)	**5br** (38%)
i-Pr (**1l**)	4-ClC_6H_4 (**2s**)	**3ls** (56%)	**5ls** (24%)

[a] Toluene solution (0.02 M) of **2** heated with 2 equiv **1** at 110 °C, 24 h.
[b] Isolated yields based on acid **2**.

Table 5
Reactions of arylacetic acids with aliphatic isonitriles[a]

Isonitrile R^1=	Acid Ar=	**5** (Yield)[b]
c-Hex (**1a**)	**2e**	**5ae** (95%)
$EtCO_2CH_2$ (**1m**)	**2e**	**5me** (58%)
n-Pent (**1b**)	**2e**	**5be** (93%)
n-Bu (**1k**)	Ph (**2l**)	**5kl** (70%)
n-Bu (**1k**)	4-ClC_6H_4 (**2s**)	**5ks** (64%)
i-Pr (**1l**)	**2s**	**5ls** (97%)
i-Pr (**1l**)	Diphenylacetic (**2p**)	**5lp** (96%)
c-Hex (**1a**)	**2p**	**5ap** (86%)
n-Pent (**1b**)	2-$O_2NC_6H_4$ (**2r**)	**5br** (90%)
c-Hex (**1a**)	4-MeC_6H_4 (**2m**)	**5am** (65%)
c-Hex (**1a**)	4-$MeOC_6H_4$ (**2n**)	**5an** (56%)

[a] Nitromethane solution (0.5 M) of **2** heated with 2 equiv **1** at 40 °C, 1–2 d.
[b] Isolated yields based on **2**.

Table 6
Syringe pump addition of arylacetic acids to aliphatic isonitriles[a]

Isonitrile R^1=	Acid Ar=	**3** (Yield)[b]
c-Hex (**1a**)	**2e**	**3ae** (80%)
n-Pent (**1b**)	**2e**	**3be** (70%)
n-Bu (**1k**)	Ph (**2l**)	**3kl** (64%)
c-Hex (**1a**)	4-MeC_6H_4 (**2m**)	**3am** (71%)
n-Pent (**1b**)	4-$MeOC_6H_4$ (**2n**)	**3bn** (65%)
c-Hex (**1a**)	Diphenylacetic (**2p**)	**3ap** (65%)

[a] See Ref. 18.
[b] Isolated yields based on **2**.

Good selectivity for **3** can also be observed with aromatic isonitriles with low concentrations and high temperatures. High isolated yields are general, as shown in Table 7. The alkene **5** is not observed in any of these cases.

3. Conclusion

N-Formylamides have been used in peptide synthesis,[4,5,11,24] and their formyl carbonyls can be used as aldehyde surrogates in the synthesis of complex amides.[25] Captodative alkenes have been employed in cycloaddition reactions,[26] polymerizations,[27] base-mediated rearrangements,[16,28] and natural product synthesis.[29] We have shown how each product can be selectively formed by the reaction of isonitriles with carboxylic acids.

4. Experimental

4.1. General remarks

Toluene and dichloromethane (DCM) were purified by a Grubbs system.[30] Diisopropylamine (DIPA) was distilled from calcium hydride. Nitromethane was purchased from Aldrich and used as received. 2-Chloro-6-methylphenyl isonitrile was dried in vacuo. Aromatic isonitriles were stored at −15 °C and aliphatic isonitriles were stored at −5 °C. *N*-Formamides were prepared by standard methods[31] or were commercially available.

MS refers to low-resolution mass spectroscopy performed on a JEOL JMS-LCmate liquid chromatography mass spectrometer using the CI^+ (MeOH) or FAB^+ technique. NMR spectra were recorded with a 300 or 400 MHz Bruker spectrometer in $CDCl_3$ and are referenced to TMS or $CHCl_3$ (^{13}C δ 77.16). IR spectra were obtained as a thin film on a NaCl salt plate.

4.2. Representative procedure for the synthesis of isonitriles

*4.2.1. 2-Trifluoromethylphenyl isonitrile (**1q**).* To a stirring 0 °C mixture of DIPA (2.7 equiv, 4.3 mL) and *N*-(2-trifluoromethylphenyl)formamide[32] (2.12 g) in DCM (0.9 M, 12.44 mL) was added $POCl_3$ (1.1 equiv, 1.15 mL) dropwise under argon. After 5 min at 0 °C and 15 min at room temperature, 3 mL water was added and mixed vigorously until the organic layer became clear. The organic layer was separated, loaded onto a short silica gel flash column, and eluted with DCM to give 1.7 g (89%) of a foul-smelling off-white solid, which melts near room temperature to a blue liquid.

^1H NMR (300 MHz, $CDCl_3$): δ=7.53–7.62 (m, 3H, Ar), 7.72–7.74 (m, 1H, Ar) ppm.

IR (cm^{-1}): 2126.

4.3. Representative procedure for compounds in Table 1

*4.3.1. N-(2,6-Dimethylphenyl)-N-formyl-2-(thiophen-2-yl)acetamide (**3de**).* 2,6-Dimethylphenyl isonitrile (94 mg, 2 equiv) in 1 mL dry toluene was passed through a short plug (ca. 0.5 cm in a 5 inch glass pipette) of silica gel (for drying) into a flame-dried 50 mL round-bottom flask. The plug was flushed with an additional milliliter of toluene. The reaction vessel was sealed with a septum, blanketed under argon, fitted with an argon-purged deflated balloon, and immersed in a 110 °C oil bath. 2-Thiopheneacetic acid in toluene (18 mL, 0.02 M stock solution, 0.36 mmol) was added via syringe pump to the reaction at a rate of 0.4 mL/h (extra solution was taken up to account for the dead volume in the syringe). Pressure from the balloon was released periodically. Heating was maintained for an additional 3 h (48 h total reaction time). Volatile residues were removed in vacuo; purification by silica gel flash chromatography using 4:1 hexanes/ethyl acetate gave 73 mg (74%).[9]

4.4. Representative procedure for compounds in Table 2

*4.4.1. N-(3-Bromophenyl)-N-formyl-4-nitrobenzamide (**3jj**).* 4-Nitrobenzoic acid (55 mg, 0.33 mmol) was heated with the silica dried (see Section 4.3) isonitrile **1j** (2 equiv, 120 mg) in 22 mL dry toluene for 24 h in a sealed flame-dried round-bottom flask. After cooling to room temperature and removing volatiles, a brown solid was obtained. Most of the brown color and the isonitrile odor were removed by washing the solid with toluene (2×3 mL). The solid was

Table 7
Reaction of arylacetic acids with aromatic isonitriles[a]

Isonitrile R^1=	Acid Ar=	**3** (Yield)[b]	Isonitrile R1=	Acid Ar=	**3** (Yield)[b]
2-Cl-6-MeC_6H_3 (**1b**)	Ph (**2l**)	**3bl** (64%)	2-Naphth (**1i**)	**2e**	**3ie** (72%)
2,6-Xylyl (**1d**)	**2l**	**3dl** (76%)	Ph (**1h**)	**2e**	**3he** (97%)
4-$MeOC_6H_4$ (**1f**)	**2l**	**3fl** (75%)	2,6-Xylyl (**1d**)	**2e**	**3de** (91%)
Ph (**1h**)	**2l**	**3hl** (78%)	2-Cl–6-MeC_6H_3 (**1e**)	**2e**	**3ee** (73%)
4-$Et_2NC_6H_4$ (**1g**)	1-Naphth (**2t**)	**3gt** (90%)	2-$CF_3C_6H_4$ (**1q**)	**2e**	**3qe** (81%)
Ph (**1h**)	4-$O_2NC_6H_4$ (**2q**)	**3hq** (67%)	3-$CF_3C_6H_4$ (**1p**)	**2e**	**3pe** (63%)
4-ClC_6H_4 (**1n**)	4-$MeOC_6H_4$ (**2n**)	**3nn** (78%)	3-BrC_6H_4 (**1j**)	**2e**	**3je** (83%)
4-$MeOC_6H_4$ (**1f**)	3-$MeOC_6H_4$ (**2u**)	**3fu** (77%)	4-BrC_6H_4 (**1o**)	**2e**	**3oe** (80%)
4-BrC_6H_4 (**1o**)	4-ClC_6H_4 (**2s**)	**3os** (70%)	4-ClC_6H_4 (**1n**)	**2e**	**3ne** (78%)
4-$MeOC_6H_4$ (**1f**)	2-$O_2NC_6H_4$ (**2r**)	**3fr** (88%)	4-MeC_6H_4 (**1c**)	**2e**	**3ce** (94%)
3-$CF_3C_6H_4$ (**1p**)	4-MeC_6H_4 (**2m**)	**3pm** (68%)	4-$Et_2NC_6H_4$ (**1g**)	**2e**	**3ge** (83%)
2,6-Xylyl (**1d**)	3,4-$(MeO)_2C_6H_3$ (**2o**)	**3do** (68%)	4-$MeOC_6H_4$ (**1f**)	**2e**	**3fe** (88%)
2,6-Xylyl (**1d**)	4-FC_6H_4 (**2v**)	**3dv** (84%)	4-$O_2NC_6H_4$ (**1r**)	**2e**	**3re** (75%)
2,6-Xylyl (**1d**)	Indole-3-acetic (**2w**)	**3dw** (65%)			
4-$MeOC_6H_4$ (**1f**)	**2w**	**3fw** (73%)			
4-MeC_6H_4 (**1c**)	**2w**	**3cw** (88%)			
4-MeC_6H_4 (**1c**)	Diphenylacetic (**2 p**)	**3cp** (93%)			

[a] Toluene solution (0.02 M) of **2** heated with 2 equiv **1** at 110 °C, 24 h.
[b] Isolated yields based on **2**.

washed further with Et_2O (2×3 mL) and hexanes (2×3 mL). Drying in vacuo gave 77 mg (67%) as an off-white solid.[9]

4.5. Representative procedure for compounds in Tables 4 and 7

*4.5.1. N-(2-Chloro-6-methylphenyl)-N-formyl-2-(thiophen-2-yl) acetamide (**3ee**).* 2-Chloro-6-methylphenyl isonitrile (104 mg, 2 equiv) was added to a flame-dried 50 mL round-bottom flask containing 2-thiopheneacetic acid (49 mg) in toluene (17.25 mL, 0.02 M). The flask was sealed with a wire-secured septum, blanketed under argon, and heated as a sealed tube in a 110 °C oil bath overnight (18–24 h). Volatile residues were removed in vacuo; purification by silica gel flash chromatography using 5:1 hexanes/ethyl acetate gave 74 mg (73%) as an off-white solid.[9]

Note: The very polar isonitriles **1e**, **1g**, **1n**, **1o**, and **1r** were added to the reaction mixture without passing them through silica gel. Yields are based on carboxylic acid.

4.6. Representative procedure for compounds in Table 5

*4.6.1. (Z)-3-(Butylamino)-1-(4-chlorophenyl)-3-oxoprop-1-en-2-yl 2-(4-chlorophenyl)acetate (**5ks**).* *n*-Butyl isonitrile (69 μL, 2 equiv) was added to a nitromethane solution (0.66 mL, 0.5 M) of 4-chlorophenylacetic acid (56 mg, 0.33 mmol) in an oven dry screw cap vial. After stirring 24 h at 40 °C as a sealed tube, volatiles were removed in vacuo; purification by silica gel flash chromatography using 3:1 hexanes/ethyl acetate gave 43 mg (64%).[16]

Note: Removal of essentially all of the nitromethane was crucial for successful chromatographic separation.

4.7. Representative procedure for compounds in Table 6

*4.7.1. (Z)-3-(Cyclohexylamino)-3-oxo-1-(thiophen-2-yl)prop-1-en-2-yl 2-(thiophen-2-yl)acetate (**3ae**).* Following the procedure in Section 4.3, 2-thiopheneacetic acid in toluene (20 mL, 0.02 M stock solution, 0.4 mmol) was added at a rate of 1.0 mL/h, and heating was maintained for an additional 2–4 h (22–24 h total reaction time). Volatile residues were removed in vacuo; purification by silica gel flash chromatography using 4:1 hexanes/ethyl acetate gave 81 mg (80%) as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ=1.15–2.1 (m, 10H, Cy-ring), 4.23 (s, 2H, Ar–CH_2), 4.28–4.37 (m, 1H, N–$CH_{Cy\text{-}ring}$), 6.89–6.97 (m, 2H, Ar), 7.22–7.24 (m, 1H, Ar), 9.10 (s, 1H, CHO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=25.26, 26.35, 29.82, 37.92, 54.03, 125.64, 126.94, 127.15, 134.52, 163.11, 171.58 ppm.

MS: 251.79 (M+1), 223.85 (M–27). IR (cm^{-1}): 1672 (br).

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Supplementary data

Full experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR of all new compounds. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.09.068.

References and notes

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18. A 0.02 M toluene solution of the acid was added over the course of 24 h to 2 equiv isonitrile in 0.02 M toluene at 110 °C.
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